### Title
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# Comparing PET imaging and CSF measurements of Aβ

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## Abstract

**Objective—**We examined agreement and disagreement between two biomarkers of Aβ deposition (amyloid PET and CSF $A\beta_{1-42}$) in normal aging and dementia in a large multicenter study.

**Methods—**Concurrently acquired florbetapir-PET and CSF Aβ were measured in cognitively normal, mild cognitive impairment (MCI), and Alzheimer's disease (AD) participants (N=374) from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We also compared Aβ measurements in a separate group with serial CSF measurements over 3.1 +/− 0.8 yrs that preceded a single florbetapir session. Additional biomarker and cognitive data allowed us to further examine profiles of discordant cases.

**Results—**Florbetapir and CSF Aβ were inversely correlated across all diagnostic groups, and dichotomous measurements were in agreement in 86% of subjects. Among subjects showing the most disagreement, the two discordant groups had different profiles: the florbetapir+/CSF Aβ− group was larger (N=13) and was made up of only normal and early MCI subjects; while the florbetapir−/CSF Aβ+ group was smaller (N=7), had poorer cognitive function and higher CSF tau, but no ApoE4 carriers. In the longitudinal sample, we observed both stable longitudinal CSF

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JQ Trojanowski may accrue revenue in the future on patents submitted by the University of Pennsylvania wherein he is co-inventor and he received revenue from the sale of Avid to Eli Lily as co-inventor on imaging related patents submitted by the University of Pennsylvania.

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Aβ trajectories and those actively transitioning from normal to abnormal, but the final CSF Aβ measurements were in good agreement with florbetapir cortical retention.

**Interpretation—**CSF and amyloid-PET measurements of Aβ were consistent in the majority of subjects in the cross-sectional and longitudinal populations. Based on our analysis of discordant subjects, the available evidence did not show that CSF Aβ regularly becomes abnormal prior to fibrillar Aβ accumulation early in the course of disease.

The beta-amyloid (Aβ) peptide is the primary component of neuritic plaques in Alzheimer's disease (AD) and can be quantified in humans using cerebrospinal fluid (CSF) and PET imaging measurements. A number of recent studies have reported that greater fibrillar Aβ in cortex, which has been measured previously with amyloid PET imaging using the tracer $^{11}$C-Pittsburgh Compound B (PiB), is associated with low concentrations of CSF $A\beta_{1-42}$ in normal aging and dementia[1–7]. While this inverse relationship is consistent at the group level, there is not perfect agreement between the two markers, since some individuals with abnormal CSF $A\beta_{1-42}$ have normal amyloid PET and vice versa[3]. Specifically, some studies have suggested that when there is a discrepancy, CSF $A\beta_{1-42}$ may be more likely than amyloid PET to be abnormal in cognitively normal older individuals, leading to the possibility that CSF Aβ abnormalities precede fibrillar Aβ aggregation in cortex[2, 8, 9]. However, conflicting findings have also been reported[6, 10], indicating that further research is needed to understand how often and under what circumstances discordance between the two Aβ markers occurs.

The goal of this study was to examine the agreement between Aβ markers in normal aging, MCI, and AD. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a large multisite study that includes a number of biomarkers including CSF and amyloid PET imaging with the $^{18}$F-labeled radioligand florbetapir. We evaluated two samples of ADNI participants: a large sample (N=374) with concurrent florbetapir and CSF measurements, and a separate smaller sample (N=60) with serial CSF measurements over approximately a 3 year period and ending prior to a single florbetapir scanning session. Based on previous studies, we expected to find evidence that abnormal Aβ can be detected in CSF prior to amyloid PET imaging, particularly in individuals with minimal or no cognitive deficits. We further predicted that other CSF, neuroimaging, genetic, and cognitive data in discordant cases would provide additional support for potentially differing roles of Aβ markers at different stages of disease severity.

## Methods

### ADNI

Our study samples were drawn from different phases of the Alzheimer's Disease Neuroimaging Initiative, a longitudinal multisite study supported by the NIH, private pharmaceutical companies, and nonprofit organizations with approximately 50 medical center and university sites across the United States and Canada (www.loni.ucla.edu/ADNI). Subjects in this report are ADNI participants with either cross-sectional CSF and florbetapir measurements, or longitudinal CSF measures with a single florbetapir timepoint.

Full inclusion/exclusion criteria are described in detail at www.adni-info.org. Briefly, all subjects were between ages 55 and 90 years, had completed at least 6 years of education, were fluent in Spanish or English, and were free of any other significant neurologic diseases. Participants with MCI, now referred to as late MCI (LMCI) had a subjective memory complaint, a Clinical Dementia Rating (CDR) of 0.5, and were classified as single- or multi-domain amnestic[11]. An early MCI group (EMCI) differed from LMCI only based on education-adjusted scores for the delayed paragraph recall subscore on the WMS-R Logical

Memory II such that EMCI subjects were intermediate to normals and LMCI. Normal subjects had CDR scores of 0, and patients with AD met standard diagnostic criteria[12].

## Participants

Our cross-sectional sample was made up of 374 subjects (103 Normal, 187 Early MCI, 62 Late MCI, 22 AD at the time of the florbetapir scan; see Table 1) who each had a single lumbar puncture (LP) and a florbetapir session between May 2010 and March 2012. LPs and florbetapir scans occurred within 2 weeks of each other (see Table 1).

Our longitudinal sample was made up of the 60 ADNI subjects (29 Normal, 31 MCI at enrollment) who underwent an average of 3.5 LPs (min = 2, max = 5) at approximately yearly intervals between October 2005 and November 2010, and subsequently underwent florbetapir scanning an average of 1.4 +/− 0.6 yrs after the last LP. The majority of subjects had concurrent structural MRI and FDG scans, CSF tau and p-tau measurements, and cognitive function (e.g. mini-mental state examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)).

Over the approximately 5 year followup period, 5/29 (17%) of Normal subjects converted to MCI, while 16/31 (52%) of MCI subjects converted to AD and 3/31 (10%) of MCI subjects reverted to Normal (see Table 4).

All participants gave written informed consent that was approved by the Internal Review Board (IRB) of each participating institution.

## Florbetapir Imaging and Analysis

Florbetapir image data were acquired from a variety of PET scanners and sites nationwide. Data preprocessing information is available online (adni.loni.ucla.edu/about-data-samples/image-data/). Briefly, image data was acquired in four 5 min frames 50–70 minutes after injection of approximately 10 mCi, the four frames were coregistered to one another, averaged, interpolated to a uniform image and voxel size (160×106×96, 1.5mm$^3$), and smoothed to a uniform resolution (8mm FWHM) to account for differences between scanners[13].

In order to quantify cortical Aβ, preprocessed florbetapir image data and coregistered structural magnetic resonance images (MRI) were analyzed using Freesurfer v4.5.0 (surfer.nmr.mgh.harvard.edu/) as described elsewhere[14, 15] and online (adni.loni.ucla.edu/research/pet-post-processing/). We used one or, in most cases, two T1 structural 1.5 T or 3T MRI scans that were acquired as close as possible to the florbetapir scan to define cortical regions of interest that were averaged together, coregistered to the florbetapir images to extract mean cortical retention and then normalized to a cerebellar reference region as a summary measure of florbetapir retention for each subject.

## CSF Data Analysis

LPs were carried out at ADNI sites as described in the online ADNI protocol (http://adni.loni.ucla.edu/research/protocols/biospecimens-protocols/). The CSF $A\beta_{1\text{-}42}$, total tau (t-tau), and tau phosphorylated at threonine 181 (p-$tau_{181p}$) were measured using the multiplex xMAP Luminex platform with Innogenetics immunoassay kit–based reagent as described and validated previously[16–18]. Additional analysis details and quality control procedures appear online (http://adni.loni.ucla.edu/).

All longitudinal and cross-sectional CSF aliquots were anchored to the same baseline assay in order to use the cutoff values for abnormal and normal $A\beta_{1\text{-}42}$, t-tau, and p-$tau_{181p}$ status

that were established and validated for that assay[17]; details are provided in Supplementary Materials.

### Additional biomarkers and cognitive tests

Information about measurement of additional biomarkers (ApoE4, hippocampal volume, FDG-PET) and neuropsychological testing appears in the Supplementary Materials.

### Biomarker cutoffs

Subjects were categorized as abnormal (+) or normal (−) on florbetapir using a cortical retention ratio cutoff value of 1.11[15]. This value is based on the upper limit of the 95% confidence interval for the distribution of florbetapir values for young healthy controls[19] and is consistent with a separate autopsy-validated sample[20]. The CSF cutoffs from the autopsy-validated baseline assay used in this study were $A\beta_{1\text{-}42}$=192 pg/mL, t-tau=93 pg/ML, and p-$tau_{181p}$=23 pg/mL[17]; low $A\beta_{1\text{-}42}$ and high tau values were abnormal (+). Finally, to categorize subjects as abnormal (+) and normal (−) on FDG, we used a cutoff of 1.21 that was derived from an ROC analysis of normal and AD subjects in a separate ADNI population[21].

### Statistical Methods

All statistical tests were performed with SPSS v19.0 and carried out at $\alpha = 0.05$. Associations that included continuous CSF and florbetapir measurements were assessed using Spearman rank correlation coefficients ($\rho$) in order to account for the non-normally distributed nature of these amyloid measurements. Associations between ApoE4 carrier status and other dichotomous measurements were assessed with chi-square ($\chi^2$) tests. The kappa ($\kappa$) statistic was used to quantify agreement between dichotomous (+/−) measurements (CSF, florbetapir, FDG) relative to what would be expected by chance.

## Results

### Descriptive information and biomarker associations in the cross-sectional population

Demographic information for the 374 normal, EMCI, LMCI, and AD participants in the cross-sectional sample is summarized in Table 1. Age, education, and sex were similar across diagnostic groups, while MMSE and ADAS-cog performance declined across groups as diagnostic severity increased. The percent of ApoE4 allele carriers and the percent of subjects categorized as abnormal (+) on each biomarker (florbetapir, CSF $A\beta_{1\text{-}42}$, t-tau, and p-$tau_{181p}$, and FDG) also increased with diagnostic severity. Of these markers, FDG status was most consistent with diagnosis, with 17% of normals and 100% of AD patients categorized as abnormal.

Across all individuals, age was associated with continuous forms of biomarkers (florbetapir, CSF Aβ, t-tau, and p-tau, hippocampal volume, and FDG) while education was weakly correlated with FDG (p=0.04) not CSF t-tau, p-tau, $A\beta_{1\text{-}42}$, hippocampal volume, or age.

### Cross-sectional associations between CSF Aβ and florbetapir

The inverse relationship between continuous forms of concurrent CSF Aβ and florbetapir measurements for all diagnostic groups is plotted in Figure 1a, as well as cutoffs for abnormal and normal status (+/−) for each biomarker.

Using continuous measures, florbetapir was more closely correlated with CSF Aβ ($\rho$ =−0.74) than with t-tau ($\rho$ =0.51) or p-tau ($\rho$ =0.55) across the entire sample. Similarly, within individual diagnostic groups, florbetapir associations were stronger with CSF Aβ (Normal, $\rho$

=−0.67; EMCI, ρ= −0.72; LCMI ρ= −0.61; AD, ρ = −0.41) than with t-tau (Normal, ρ =0.23; EMCI, ρ =0.55; LCMI ρ=0.57; AD, ρ=0.17) or p-tau (Normal, ρ=0.28; EMCI, ρ=0.60; LCMI ρ=0.55; AD, ρ=0.30).

We also evaluated dichotomous forms of these biomarkers. The majority (62%) of normals were negative for both florbetapir and CSF Aβ and the majority of AD patients (77%) were positive for both (Figure 1c). The proportion of subjects with agreement was stable across diagnostic groups (83–91%) and κ=0.72 overall (Table 2).

Agreement between florbetapir status (+/−) and status on other biomarkers (CSF t-tau and p-tau, FDG) was moderate (CSF t-tau, κ=0.42; CSF p-tau, κ=0.52; FDG, κ=0.26 for the total sample) but this was variable across diagnostic groups (Table 2; also see Supplementary Figure).

The proportion of ApoE4 carriers was highest for subjects who were positive for both markers, lowest for subjects negative for both, and intermediate for the 2 discordant groups (Figure 1d).

## CSF Aβ and florbetapir disagreement

Across all diagnostic groups, 9–17% of subjects (52 subjects total; 31 florbetapir+/CSF Aβ −, 21 florbetapir−/CSF Aβ+) were discordant (Figure 1c).

Visual inspection of florbetapir−/CSF Aβ+ indicated that the quantitative florbetapir estimates plotted in the figure are consistent with qualitative interpretation (Figure 1b).

To identify subjects who were considerably discordant, as opposed to those with one or both Aβ measurements close to the cutoffs, we created +/− 5% confidence intervals around each cutoff (Figure 2). Out of the original 52 discordant subjects, 20 discordant subjects remained (13 florbetapir+/CSF Aβ− and 7 florbetapir−/CSF Aβ+). The diagnoses, cognitive measurements, and imaging and fluid biomarker profiles of these remaining discordant subjects are listed in Table 3. 100% (13/13) subjects in the florbetapir+/CSF Aβ − group were in the two most cognitively intact groups (cognitively normal or early MCI). The florbetapir−/CSF Aβ+ group, on the other hand, had more cognitive impairment (5/7 subjects had a diagnosis of LMCI and AD) and higher CSF tau (p=0.01) than the other discordant group, but a lower proportion of ApoE4 carriers (0/7 subjects, compared with 6/13 (46%) in the florbetapir+/CSF Aβ− group; Chi-square test; p=0.03). Group differences between the other biomarkers were not significant (p > 0.10).

## Longitudinal CSF Aβ trajectories for florbetapir +/− individuals

Demographic information for the longitudinally followed subjects is shown in Table 4. A number of subjects had changes in diagnosis during followup: 52% of MCI subjects converted to AD and 17% of normal individuals progressed to MCI prior to the florbetapir scan.

CSF Aβ trajectories for the longitudinally-followed, separate sample are plotted in Figure 3a. Subjects are divided by florbetapir status and by diagnosis at the time of florbetapir (end of CSF followup) so all AD subjects in Figure 3a were diagnosed as MCI at enrollment, and several Normal and MCI subjects had a different diagnosis at enrollment as well (see Table 4). Unlike the cross-sectional population, the CSF Aβ measures occurred more than a year before florbetapir scans. Nonetheless, kappa values reflecting agreement between the last CSF Aβ +/− status and florbetapir +/− status were similar to the cross-sectional dataset (Normal, κ= 0.67; MCI, κ=0.65; AD, κ= 0.82). There were fluctuations in CSF Aβ over the course of followup for many subjects, but florbetapir+ individuals (top panel, Figure 3a) had

primarily downward CSF Aβ trajectories. Four subjects had normal CSF Aβ at enrollment and declines throughout the six-year followup, ending with abnormal -- or near abnormal -- measurements that preceded abnormal florbetapir status. While the gap between the last CSF measurement and the florbetapir scan leaves some uncertainty, the direction of change for these actively transitioning subjects suggests good agreement between coinciding CSF Aβ and florbetapir.

There were, however, several discordant subjects whose florbetapir scans appear in Figure 3 b–d (see Supplementary Materials for additional demographic and biomarker characteristics).

## Discussion

We found that CSF $A\beta_{1-42}$ and amyloid PET imaging measurements were inversely associated in the majority of subjects, and that dichotomous classification was in substantial agreement. There was no evidence from cross-sectional or longitudinal analyses that abnormal CSF Aβ precedes abnormal florbetapir early in the course of disease.

We observed good agreement between CSF Aβ and amyloid PET measurements across several comparisons: with continuous or dichotomous forms of the variables, using cross-sectional and longitudinal CSF measurements, and across diagnostic groups. Overall, the association between CSF Aβ and florbetapir explains approximately 55% of the variance in these measurements, which is comparable to previous studies with PiB[2–7]. As expected, the proportion of subjects who were abnormal on both markers increased with severity of diagnosis, but the overall proportions of subjects who had concordant (both normal or both abnormal) and discordant Aβ measurements was stable across diagnostic groups (83–91% concordant, 9–17% discordant). In the longitudinal CSF sample, there was considerable change in CSF Aβ from the beginning to end of the followup period for some subjects, with most change occurring in a decreasing direction. Consistent with the cross-sectional sample, there was good agreement between the final CSF Aβ and the subsequent florbetapir measurement.

Our data did not support the hypothesis that a decline in CSF Aβ precedes aggregation of fibrillar Aβ[2, 8]. In fact, among discordant subjects whose measurements were not close to the cutoffs, normal and EMCI subjects made up 100% of the CSF Aβ−/florbetapir+ group but only 29% of the CSF Aβ+/florbetapir− group (Figure 2). Because active accumulation of amyloid is most likely to occur prior to the onset of significant cognitive decline[22, 23], our findings support the possibility that fibrillar Aβ can be detected first in some individuals, which has been reported[6, 10], or that there is a complex relationship between different species of Aβ and the progression of disease. For example, although decreasing CSF Aβ measurements in AD are generally thought to reflect the accumulation of soluble forms of Aβ in neuritic plaques [24, 25], this process may be altered by comorbid pathology or other etiologies that influence the production or clearance of different Aβ species. Specifically, low CSF Aβ in the absence of neuritic plaques has been reported in other disorders such as amyotrophic lateral sclerosis and Creuzfeldt-Jacob syndrome [26]. Detection may play an important role as well; a recent case study reported low CSF Aβ in the presence of diffuse plaques detected at autopsy but not with PiB-PET imaging[27]. Although more longitudinal studies are needed, the existing evidence suggests that there may be considerable variability in the temporal dynamics and pattern of soluble and fibrillar Aβ.

Nonetheless, the combination of florbetapir and CSF marker information provided useful insight into diagnostic status for some subjects. For example, 3/22 subjects in the cross-sectional sample were diagnosed with AD at enrollment but were negative for both markers,

indicating that their dementia is likely due to non-AD pathology. Similarly, in the longitudinal sample, 4/31 MCI subjects converted to AD during the followup period but were negative for both markers (Figure 3a; one was borderline positive for CSF Aβ). Misdiagnosis in AD patients with normal CSF Aβ and amyloid PET has been suggested previously[28] and may account for some amyloid negative AD subjects in this study. Furthermore, comorbidities may have influenced the accuracy of the biomarker cutoffs themselves, and may account for inaccuracies in both clinical diagnoses and biomarker classifications. Of subjects who have come to autopsy, 5/9 ADNI MCI and AD subjects (not in this study) had comorbid pathologies such as alpha-synuclein pathology and tauopathy[29]. Furthermore, in a recent study of dementia patients that included individuals with comorbidities, the sensitivity and specificity of CSF biomarker measurements was lower for clinical compared with neuropathological diagnosis[30], providing additional evidence that both misdiagnosis and non-AD pathology influence biomarker accuracy.

The longitudinal sample provided additional insight into the relationship between the two markers and the time course of the accumulation of amyloid pathology. While minimal longitudinal change in serial CSF Aβ measurements in normal or AD individuals has been reported previously[1, 31], we observed a combination of stable trajectories and considerable variability and declines for some individuals. CSF Aβ trajectories were variable over time for those who were florbetapir negative at the end of followup, but there was minimal net change. Among those who were ultimately florbetapir positive, we observed several individuals whose CSF Aβ actively declined throughout the 5 to 6 year followup period to levels that were abnormal or close to abnormal, and this status was ultimately reflected by their abnormal florbetapir scan as well. We note that there is ambiguity about whether CSF Aβ became abnormal before florbetapir or vice versa due to the approximately one year delay between the final CSF measurement and the florbetapir scan; however, the downward trajectory of CSF measurement appears to be informative.

Older age in our sample may account for why we did not find evidence that CSF Aβ becomes abnormal prior to amyloid PET measurements. Previous cross-sectional PiB studies suggesting a possible offset in the time course of Aβ abnormality had subjects as young as 43 (and a mean age in the mid 60s)[2, 8]. Studies that did not report a pattern that was consistent with CSF Aβ becoming abnormal prior to amyloid PET had mean ages of approximately 65[10] and 71[6], while the subjects in the current study had a mean age of 73. Since Aβ aggregation may begin earlier than 50 years of age[32], our subjects may have passed a critical time period where the offset would be most clearly observed. Older age in our population may also explain why we did not find any evidence for an initial increase in CSF Aβ followed by a subsequent decline, although to our knowledge this has only been reported in autosomal dominant AD[22, 33] and not in late-onset AD[34].

Several other methodological factors may have contributed to our findings. Although we had a large sample overall, the relatively small numbers of discordant subjects (particularly in the longitudinal sample) made it difficult to draw conclusions about the cause of the discordance. Disagreement between CSF Aβ and florbetapir measurements may have been due to measurement problems such as errors introduced by PET image processing, the use of cutoffs with differing sensitivities and specificities, and standardizing CSF assays to the same set of cutoffs. Establishing standardization across laboratories for LP collection and CSF assay analysis is a significant challenge that is currently being addressed[18, 35]. In addition, the cutoffs and distributions CSF Aβ and florbetapir differ in a way that influences the shape and linearity of their association. Both markers have an approximately bimodal distribution across the entire sample, but for florbetapir the broadest part of the distribution relative to the cutoff is in the abnormal range of values, whereas for CSF Aβ the broadest

part of the distribution is in the normal range of values, resulting in a nonlinear inverse relationship when they are plotted against each other.

Overall, we found good agreement between florbetapir and CSF Aβ, and we did not find any evidence that CSF Aβ is more likely to become abnormal prior to the accumulation of fibrillar Aβ early in the course of disease. Furthermore, disagreement between Aβ measurements was not uncommon. One in seven individuals in this study (or one in twenty after applying cutoff confidence intervals) had discordant Aβ markers and are therefore considered ambiguous cases according to recently revised AD diagnostic criteria[36]. Understanding discrepancies between in vivo Aβ measurement is important since the new criteria treat these markers as interchangeable in terms of diagnostic utility. In addition, in vivo Aβ measurement to aid in development and testing of pharmaceutical treatments targeting Aβ is underway, making accurate measurement an essential component of subject enrichment and evaluation of drug efficacy in clinical trials. Future research may address remaining questions about the relationship between different species of Aβ. Forthcoming longitudinal data in the current sample will be critical for determining the clinical relevance of these imbalances.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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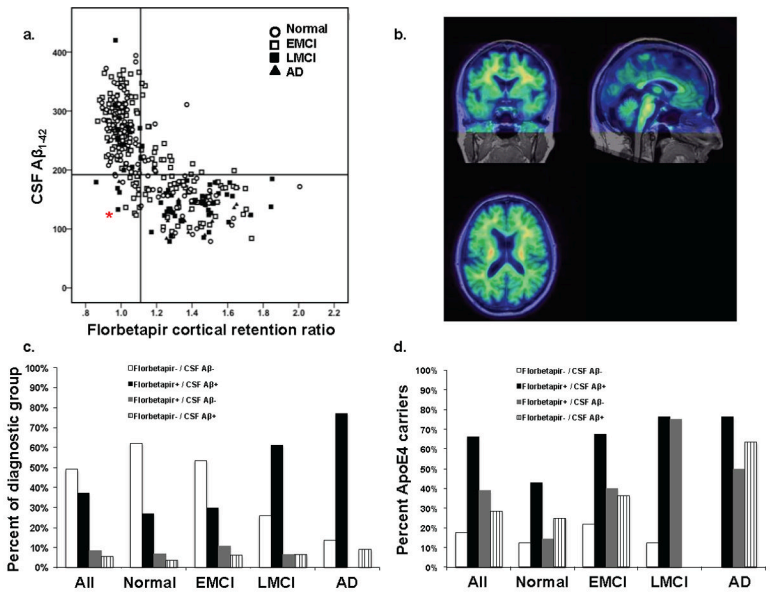


**Figure 1.**

The inverse association between florbetapir cortical retention ratios and CSF $A\beta_{1-42}$ is shown for normal, EMCI, LMCI, and AD individuals (a). Predefined cutoffs are shown each marker (CSF $A\beta_{1-42}$ =192 pg/mL; florbetapir = 1.11) that were derived from independent samples (see Methods). Subjects with concordant florbetapir and CSF $A\beta_{1-42}$ are in the upper left (florbetapir−/CSF Aβ−) and bottom right (florbetapir+/CSF Aβ+) quadrants while subjects with discordant florbetapir and CSF $A\beta_{1-42}$ are in the upper right (florbetapir+/CSF Aβ−) and bottom left (florbetapir−/CSF Aβ+) quadrants. A florbetapir scan for an example discordant LMCI subject (florbetapir−/CSF Aβ+) is shown (b; see asterisk on scatterplot in A), indicating that the visual read is consistent with the qualitative florbetapir measurement (florbetapir cortical retention ratio = 0.98) despite abnormal CSF status. The percent of individuals from each diagnostic group in each of the 4 scatterplot quadrants is shown in the bar graph (c). The proportion of subjects who are abnormal on both markers (black bars) increases as diagnostic severity increases, but the proportions of discordant subjects (grey and striped bars) is similar across diagnostic groups and between the two types of discordance. The proportion of ApoE4 allele carriers who are concordant on both markers increases with diagnostic severity (d; black bars), the proportion of ApoE4 carriers is moderate for the two discordant groups (grey and striped bars) in the Normal and EMCI subjects.

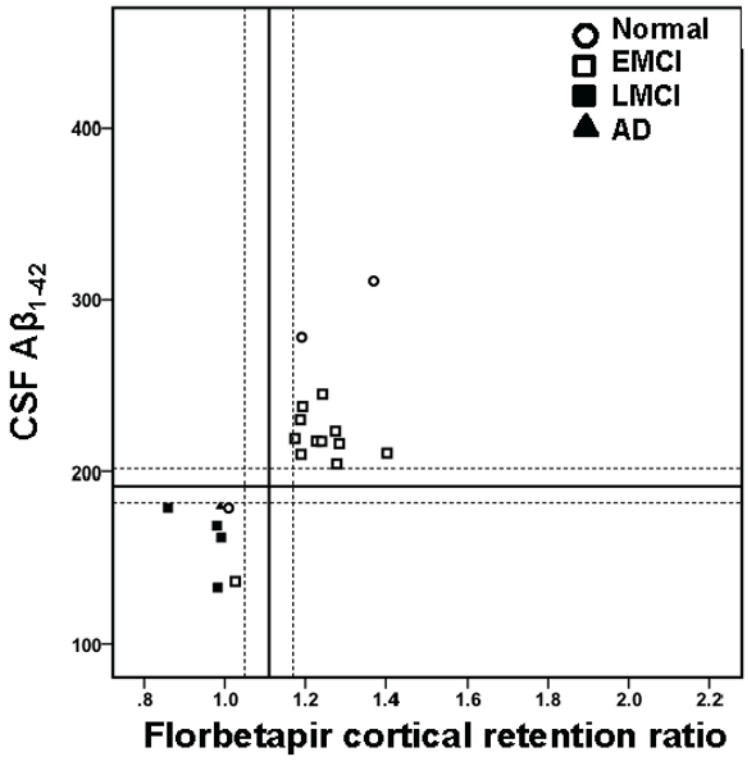


**Figure 2.**
Subjects who remain discordant after applying a +/− 5% confidence interval to each cutoff.

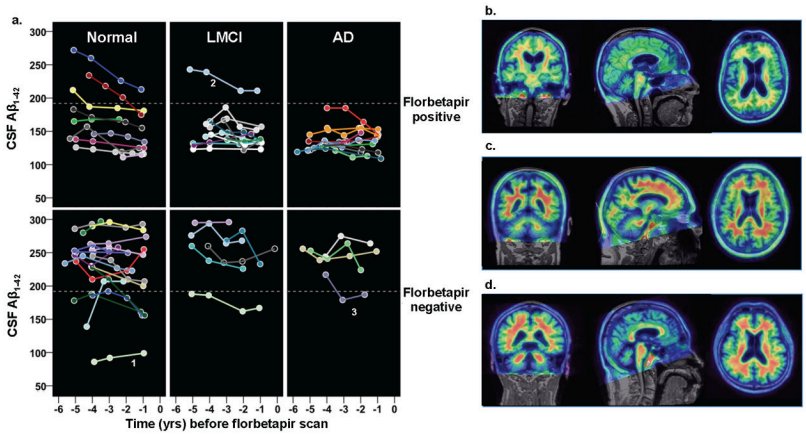


**Figure 3.**

Longitudinal CSF $A\beta_{1\text{-}42}$ data is plotted against time for each subject in the longitudinal sample (a), with florbetapir+ individuals in the top row and florbetapir− subjects in the bottom row. Subjects are plotted separately by diagnosis at the time of florbetapir (left column, 27 Normal; middle column, 17 MCI; right column, 16 AD). Time of zero corresponds to the florbetapir scan, each colored line corresponds to an individual subject, and each point on the line corresponds to a CSF $A\beta_{1\text{-}42}$ value from a single LP. Dotted lines in each panel represent the CSF $A\beta_{1\text{-}42}$ cutoff value (192 pg/mL) that divides abnormal values (below line) from normal values (above line). In the top panel, CSF Aβ values that are concordant with florbetapir appear below the dotted line (both abnormal), while in the bottom panel CSF Aβ values that are concordant with florbetapir appear above the dotted line (both normal). Representative florbetapir scans are shown for three discordant subjects: (b) a CSF Aβ+/florbetapir− normal 80 yo male (florbetapir = 1.06, labeled “1” on plot); (c) a CSF Aβ−/florbetapir+ 84 yo MCI male (florbetapir cortical retention ratio = 1.12, labeled “2” on plot); and (d) a CSF Aβ+/florbetapir− 81 yo AD male (florbetapir = 0.99, labeled “3” on plot). All longitudinal CSF samples for an individual subject were included in the same immunoassay analytical run to minimize variance due to run to run and reagent lot to lot variabilities.

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**Table 1**

Demographic and descriptive biomarker information for the cross-sectional study population.

| | Total cross-sectional sample | Diagnosis at florbetapir | | | |
|---|---|---|---|---|---|
| | | Normal | Early MCI | Late MCI | AD |
| **Subject characteristics** | | | | | |
| **N** | 374 | 103 | 187 | 62 | 22 |
| **Time from LP to florbetapir (months)** | 0.4 (0.6) | 0.3 (0.5) | 0.4 (0.7) | 0.3 (0.4) | 0.3 (0.4) |
| **Age at florbetapir (yrs)** | 72.7 (7.4) | 74.9 (5.5) | 71.3 (7.6) | 72.5 (7.2) | 74.6 (10.7) |
| **Sex, female** | 45% | 47% | 44% | 48% | 36% |
| **Education (yrs)** | 16.2 (2.7) | 16.6 (2.6) | 15.8 (2.6) | 16.5 (2.6) | 15.9 (2.7) |
| **MMSE at florbetapir (range: 0–30)** | 27.9 (2.3) | 29 (1.1) | 28.2 (1.6) | 27.4 (2.1) | 21.8 (2.8) |
| **ADAS-cog at florbetapir (range: 0–70)** | 8.9 (5.1) | 6.3 (3) | 8 (3.7) | 12.1 (4.8) | 19.6 (6.3) |
| **Abnormal biomarkers** | | | | | |
| **ApoE4 carriers** | 38% | 21% | 39% | 55% | 64% |
| **Abnormal florbetapir** | 46% | 34% | 41% | 68% | 77% |
| **Abnormal CSF $A\beta_{1\text{-}42}$** | 43% | 31% | 36% | 68% | 86% |
| **Abnormal CSF tau** | 31% | 23% | 25% | 50% | 68% |
| **Abnormal CSF p-$tau_{181p}$** | 44% | 36% | 38% | 68% | 68% |
| **Abnormal FDG** | 32% | 17% | 26% | 49% | 100% |

**Table 2**

Kappa (κ) statistics representing agreement in +/− status between florbetapir and the other biomarkers in the cross-sectional sample.

| | Total cross-sectional sample | Diagnosis at florbetapir | | | |
|---|---|---|---|---|---|
| | | Normal | Early MCI | Late MCI | AD |
| **CSF $A\beta_{1-42}$** | 0.72 | 0.76 | 0.65 | 0.71 | 0.70 |
| **CSF tau** | 0.42 | 0.27 | 0.46 | 0.39 | 0.09 |
| **CSF p-$tau_{181p}$** | 0.52 | 0.45 | 0.52 | 0.48 | 0.32 |
| **FDG** | 0.26 | 0.21 | 0.11 | 0.33 | * |

* κ was invalid since all AD subjects were FDG+

**Table 3**

Demographic, cognitive, and biomarker profiles of discordant subjects who survived the 5% cutoff confidence interval.

| | Dx | Age | Sex | Edu (yrs) | ApoE4 | ADAS-cog | MMSE | AVLT | HV/ICV (*$10^{-3}$) | Florbeta pir | CSF $A\beta_{1-42}$ | CSF tau | CSF ptau | FDG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Florbetapir+/CSF−(N=13)** | N | 71 | F | 20 | 0 | 5 | 28 | 52 | 4.60 | 1.37 + | 311 | 80 | 17 | |
| | | 78 | M | 14 | 0 | 6 | 30 | 44 | 4.88 | 1.19 + | 278 | 81 | 37 | 1.39 |
| | EMCI | 81 | M | 20 | 0 | 8 | 27 | 41 | 4.60 | 1.28 + | 204 | 58 | 20 | |
| | | 63 | F | 20 | 0 | 6 | 29 | 50 | 5.10 | 1.17 + | 219 | 79 | 22 | 1.51 |
| | | 73 | F | 12 | 1 | 5 | 30 | 46 | 5.87 | 1.40 + | 211 | 139 + | 53 | 1.19 (+) |
| | | 66 | M | 18 | 1 | 5 | 30 | 50 | 5.35 | 1.28 + | 216 | 77 | 21 | 1.20 (+) |
| | | 62 | F | 20 | 1 | 8 | 29 | 55 | 4.40 | 1.19 + | 230 | 50 | 22 | 1.39 |
| | | 71 | M | 20 | 0 | 5 | 29 | 36 | 5.36 | 1.24 + | 217 | 90 | 19 | 1.35 |
| | | 68 | F | 14 | 1 | 7 | 27 | 41 | 4.50 | 1.19 + | 238 | 85 | 22 | 1.45 |
| | | 75 | M | 20 | 1 | 9 | 29 | 31 | 5.66 | 1.19 + | 210 | | 23 (+) | 1.18 (+) |
| | | 82 | F | 14 | 0 | 7 | 29 | 26 | 5.06 | 1.28 + | 223 | 111 + | 26 + | 1.24 |
| | | 74 | F | 13 | 0 | 6 | 28 | 37 | 5.64 | 1.24 + | 245 | 42 | 19 | 1.35 |
| | | 64 | M | 18 | 1 | 9 | 27 | 34 | 3.36 | 1.23 + | 218 | 81 | 24 (+) | 1.11 + |
| **Florbetapir−/CSF+ (N=7)** | N | 86 | F | 12 | 0 | 6 | 26 | 35 | 4.94 | 1.01 | 179 + | 120 + | 26 + | 1.18 (+) |
| | EMCI | 70 | M | 18 | 0 | 6 | 28 | 30 | 4.03 | 1.03 | 137 + | 38 | 25 + | 1.40 |
| | LMCI | 72 | M | 19 | 0 | 8 | 30 | 42 | 5.14 | 0.98 | 133 + | 60 | 20 | 1.47 |
| | | 67 | M | 17 | 0 | 11 | 30 | 35 | 5.01 | 0.99 | 162 + | 140 + | 31 + | 1.44 |
| | | 80 | F | 16 | 0 | 10 | 26 | 36 | 3.76 | 0.98 | 169 + | 47 | 24 (+) | 1.11 + |
| | | 91 | M | 20 | 0 | 13 | 27 | 36 | 3.77 | 0.86 | 179 + | 38 | 11 | 1.18 (+) |
| | AD | 76 | M | 16 | 0 | 26 | 18 | 19 | 4.25 | 0.99 | 180 + | 146 + | 27 + | 1.13 + |

Subjects whose PET and CSF measurements were abnormal based on previously derived cutoffs are indicated (abnormal: +, borderline: (+)); see methods

**Table 4**

Demographic and descriptive biomarker information for the longitudinal study population.

| | | Diagnosis at Enrollment | |
|---|---|---|---|
| | **Total longitudinal sample** | **Normal** | **MCI** |
| **Subject characteristics** | | | |
| **N** | 60 | 29 | 31 |
| **Age at florbetapir (yrs)** | 80.1 (6.0) | 82.1 (4.4) | 78.3 (6.8) |
| **Time between first and last LP (yrs)** | 3.1 (0.8) | 3.2 (0.8) | 3.1 (0.8) |
| **Number of LP samples** | 3.5 (0.7) | 3.5 (0.6) | 3.5 (0.8) |
| **Time between last LP and florbetapir (yrs)** | 1.4 (0.6) | 1.4 (0.6) | 1.3 (0.6) |
| **Sex, % female** | 42% | 48% | 35% |
| **Education (yrs)** | 16.0 (3.0) | 16.1 (3.3) | 15.9 (2.7) |
| **ApoE4 carriers (%)** | 38% | 52% | 24% |
| **MMSE at florbetapir (range: 0–30)** | 26.4 (4.2) | 28.7 (1.6) | 24.3 (4.7) |
| **ADAS-cog at florbetapir (range: 0–70)** | 12.1 (9.2) | 6.3 (3.8) | 17.5 (9.5) |
| **Abnormal biomarkers** | | | |
| **ApoE4 carriers** | 38% | 24% | 52% |
| **Abnormal florbetapir** | 55% | 41% | 68% |
| **Abnormal CSF $A\beta_{1\text{-}42}$** | 62% | 55% | 68% |
| **Abnormal CSF tau** | 32% | 24% | 39% |
| **Abnormal CSF p-$tau_{181p}$** | 68% | 72% | 65% |
| **Abnormal FDG** | 51% | 31% | 70% |
| **Diagnosis at florbetapir scan** | | | |
| **Normal** | 27 | 24 | 3 |
| **MCI** | 17 | 5 | 12 |
| **AD** | 16 | 0 | 16 |