Comparison of Visual and Quantitative Florbetapir F 18 Positron Emission Tomography Analysis in Predicting Mild Cognitive Impairment Outcomes

Stefanie Schreiber, MD; Susan M. Landau, PhD; Allison Fero, BSc; Frank Schreiber, MSc; William J. Jagust, MD; for the Alzheimer’s Disease Neuroimaging Initiative

**IMPORTANCE** The applicability of β-amyloid peptide (Aβ) positron emission tomography (PET) as a biomarker in clinical settings to aid in selection of individuals at preclinical and prodromal Alzheimer disease (AD) will depend on the practicality of PET image analysis. In this context, visual-based Aβ PET assessment seems to be the most feasible approach.

**OBJECTIVES** To determine the agreement between visual and quantitative Aβ PET analysis and to assess the ability of both techniques to predict conversion from mild cognitive impairment (MCI) to AD.

**DESIGN, SETTING, AND PARTICIPANTS** A longitudinal study was conducted among the Alzheimer’s Disease Neuroimaging Initiative (ADNI) sites in the United States and Canada during a 1.6-year mean follow-up period. The study was performed from September 21, 2010, to August 11, 2014; data analysis was conducted from September 21, 2014, to May 26, 2015. Participants included 401 individuals with MCI receiving care at a specialty clinic (219 [54.6%] men; mean [SD] age, 71.6 [7.5] years; 16.2 [2.7] years of education). All participants were studied with florbetapir F 18[18F] PET. The standardized uptake value ratio (SUVR) positivity threshold was 1.11, and one reader rated all images, with a subset of 125 scans rated by a second reader.

**MAIN OUTCOMES AND MEASURES** Sensitivity and specificity of positive and negative [18F] florbetapir PET categorization, which was estimated with cerebrospinal fluid Aβ1-42 as the reference standard. Risk for conversion to AD was assessed using Cox proportional hazards regression models.

**RESULTS** The frequency of Aβ positivity was 48.9% (196 patients; visual analysis), 55.1% (221 patients; SUVR), and 64.8% (166 patients; cerebrospinal fluid), yielding substantial agreement between visual and SUVR data (κ = 0.74) and between all methods (Fleiss κ = 0.71). For approximately 10% of the 401 participants in whom visual and SUVR data disagreed, interrater reliability was moderate (κ = 0.44), but it was very high if visual and quantitative results agreed (κ = 0.92). Visual analysis had a lower sensitivity (79% vs 85%) but higher specificity (96% vs 90%), respectively, compared with SUVR. The conversion rate was 15.2% within a mean of 1.6 years, and a positive [18F] florbetapir baseline scan was associated with a 6.91-fold (SUVR) or 11.38-fold (visual) greater hazard for AD conversion, which changed only modestly after covariate adjustment for apolipoprotein ε4, concurrent fludeoxyglucose F 18 PET scan, and baseline cognitive status.

**CONCLUSIONS AND RELEVANCE** Visual and SUVR Aβ PET analysis may be equivalently used to determine Aβ status for individuals with MCI participating in clinical trials, and both approaches add significant value for clinical course prognostication.

Published online August 17, 2015.
Increased brain β-amyloid peptide (Aβ) seen with positron emission tomography (PET) and decreased Aβ1-42 measured in cerebrospinal fluid (CSF) allow in vivo detection of Aβ, with substantial agreement.1-4 These biomarkers have therefore been proposed as indicators of Alzheimer disease (AD) neuropathology, aiding the selection and monitoring of individuals with mild cognitive impairment (MCI) due to AD or prodromal AD in clinical trials.5,6 In MCI, Aβ load assessment may be additionally useful for prognostication since Aβ PET positivity predicts a higher risk of cognitive decline and AD conversion.7-15 With the exception of a few studies of relatively small samples,7,13,16 most MCI studies evaluating the prognostic value of Aβ PET5,9,11,14,37 and the agreement between Aβ PET with Aβ CSF markers2-4 have used semiquantitative image assessments of standardized uptake value ratios (SUVRs). Although visual Aβ PET rating is relatively simple and is the standard in clinical practice, there is a lack of knowledge about its significance for prognostication in large MCI cohorts and its agreement with CSF Aβ1-42 data and more quantitative PET measures. In terms of participant selection for clinical trials, further research is needed to evaluate whether MCI due to AD could be equivalently identified by visual PET ratings.

The goals of our study were to investigate the concordance between visual and quantitative Aβ PET analysis and evaluate how each of those image assessments agrees with CSF Aβ1-42 data in MCI. We further aimed to examine the effect of visual and quantitative image categorization as Aβ PET negative or positive to predict longitudinal cognitive function and AD conversion risk. Our methodologic design intentionally corresponds to the setting of large clinical trials including a large MCI sample derived from various sites or centers using different PET scanners and performing Aβ imaging with florbetapir F18 [18F], a tracer approved for clinical use by the US Food and Drug Administration and European Medicines Agency.

Methods

Participants

Our analysis was performed on participants in the Alzheimer’s Disease Neuroimaging Initiative (ADNI), a multisite study supported by the National Institutes of Health, private pharmaceutical companies, and nonprofit organizations, with a goal of using multimodal imaging, CSF, and cognitive measurements in elderly controls as well as patients with MCI or AD to standardize and validate biomarkers in AD clinical trials. Additional methodologic information on participants, image acquisition, CSF, and data analysis, is provided in eAppendix 2 in the Supplement. All participants provided written informed consent. The institutional review board of each participating institution approved this study. Provision of financial compensation depended on the local policies of the individual study sites. The study was performed from September 21, 2010, to August 11, 2014; data analysis was conducted from September 21, 2014, to May 26, 2015.

The study included 401 ADNI participants with one baseline [18F] florbetapir and one concurrent fludeoxyglucose F 18 (FDG)-PET scan who were categorized at baseline PET into 2 groups: early MCI (EMCI) or late MCI (LMCI). Participants were monitored for at least 12 months after the baseline scan, with the final follow-up occurring on August 11, 2014. All MCI cases were single-domain or multidomain amnestic, had a subjective memory problem, had a Mini-Mental State Examination score between 24 and 30, and had a Clinical Dementia Rating of 0.5.18 Assignment to the EMCI or LMCI group was based on the individuals’ educational level-adjusted scores on the Logical Memory II subscale (Delayed Paragraph Recall, paragraph A only) from the Wechsler Memory Scale–Revised.23 Conversion to probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association criteria20 was determined at each center. Participants with AD conversion were censored at the first visit during which dementia was diagnosed; the remaining MCI cases were censored at their most recent follow-up. Longitudinal cognitive function was assessed every 6 to 12 months from the baseline [18F] florbetapir scan.

[18F] Florbetapir Analysis

Preprocessed florbetapir scans and coregistered structural magnetic resonance images were analyzed as described previously.11,37 [18F] Florbetapir SUVRs were created from a volume-weighted average of the mean [18F] florbetapir uptake from cortical gray matter (lateral and medial frontal, anterior and posterior cingulate, lateral parietal, and lateral temporal) normalized to the cerebellum (white and gray matter).

[18F] florbetapir scans were also rated by 2 neurologists: reader 1 (S.S.), an inexperienced scan reader, and reader 2 (W.J.J.), an experienced scan reader; both were blinded to all clinical and other imaging characteristics of each participant. Reader 1 rated the [18F] florbetapir scans of all 401 participants with MCI. Reader 2 subsequently rated the scans of a subsample (n = 125) including (1) the images of 72 randomly chosen participants with MCI whose [18F] florbetapir scan assessments were discordant between visual analysis (reader 1) and SUVRs and (2) all 53 participants whose [18F] florbetapir scan assessments were discordant between visual analysis (reader 1) and SUVRs. The ratings of reader 1 were used for statistical analysis.

Additional Biomarkers

For statistical analysis, CSF Aβ1-42 data for 256 of all 401 MCI participants (63.8%) were available. Dichotomized apolipoprotein E (APOE) ε4 carrier status and dichotomized FDG data of all 401 participants with MCI were included as covariates in Cox proportional hazards regression models.

The threshold values were 1.11 for [18F] florbetapir SUVR,4,11 192 pg/mL for CSF Aβ1-42,21 and less than or equal to 1.21 for an abnormal FDG-PET scan.22

Statistical Analysis

Dichotomous variables were dummy coded as 0 if they were negative ([18F] florbetapir, APOE e4) or normal (FDG) and as 1 if they were positive or abnormal. Intermethod agreement between any 2 Aβ biomarkers was determined using Cohen κ, and
Table 1. Descriptive Statistics of the Participants’ Demographic Data, Cognitive Function, and Biomarkers*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All MCI</th>
<th>EMCI</th>
<th>LMCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants*</td>
<td>401</td>
<td>256</td>
<td>145</td>
</tr>
<tr>
<td>Age at [18F] florbetapir scan, y</td>
<td>71.6 (7.5)</td>
<td>71.4 (7.4)</td>
<td>72.9 (7.9)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>219 (54.6)</td>
<td>146 (57.0)</td>
<td>73 (50.3)</td>
</tr>
<tr>
<td>Educational level, y</td>
<td>16.2 (2.7)</td>
<td>16 (2.7)</td>
<td>16.6 (2.5)</td>
</tr>
<tr>
<td>APOE ε4 carriers, No. (%)</td>
<td>198 (49.4)</td>
<td>114 (44.5)</td>
<td>84 (57.9)</td>
</tr>
<tr>
<td>MMSE closest to [18F] florbetapir scan</td>
<td>28.1 (1.7)</td>
<td>28.3 (1.6)</td>
<td>27.6 (1.8)</td>
</tr>
<tr>
<td>ADAS-cog closest to [18F] florbetapir scan, baseline</td>
<td>9.4 (4.4)</td>
<td>8.1 (3.5)</td>
<td>11.6 (4.9)</td>
</tr>
<tr>
<td>Aβ plaque and tangle, No. (%)</td>
<td>221 (55.1)</td>
<td>123 (48.0)</td>
<td>98 (67.6)</td>
</tr>
<tr>
<td>[18F] florbetapir positive, No. (%)</td>
<td>196 (48.9)</td>
<td>104 (40.6)</td>
<td>92 (63.4)</td>
</tr>
<tr>
<td>[18F] florbetapir positive, No. (%), visual reads</td>
<td>221 (55.1)</td>
<td>123 (48.0)</td>
<td>98 (67.6)</td>
</tr>
<tr>
<td>[18F] florbetapir positive among converters, No. (%)</td>
<td>54 (88.5) [61]</td>
<td>11 (78.6) [14]</td>
<td>43 (91.5) [47]</td>
</tr>
<tr>
<td>Mean FDG</td>
<td>1.27 (0.13)</td>
<td>1.28 (0.12)</td>
<td>1.23 (0.14)</td>
</tr>
<tr>
<td>CSF Aβ1-42 level, pg/mL</td>
<td>170.81 (51.42)</td>
<td>176.48 (52.17)</td>
<td>163.04 (51.42)</td>
</tr>
<tr>
<td>CSF Aβ1-42 positive, No. (%)</td>
<td>166 (64.8) [256]</td>
<td>88 (59.5) [148]</td>
<td>78 (62.2) [108]</td>
</tr>
<tr>
<td>CSF Aβ1-42 positive among converters, No. (%)</td>
<td>33 (89.2) [61]</td>
<td>6 (85.7) [7]</td>
<td>27 (90.0) [30]</td>
</tr>
<tr>
<td>Interval between [18F] florbetapir and FDG scan, d</td>
<td>8.3 (11.3)</td>
<td>8.5 (11.9)</td>
<td>7.9 (10.2)</td>
</tr>
<tr>
<td>Interval between [18F] florbetapir and LP, d</td>
<td>25.6 (100.9)</td>
<td>36.7 (129.6)</td>
<td>9.4 (13.1)</td>
</tr>
<tr>
<td>Interval between [18F] florbetapir scan and ADAS-cog baseline, d</td>
<td>11.3 (15.2)</td>
<td>12.6 (16.6)</td>
<td>9.0 (12.2)</td>
</tr>
<tr>
<td>Follow-up time from [18F] florbetapir scan on for non-converters and converters, y</td>
<td>1.6 (0.7)</td>
<td>1.8 (0.8)</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>Follow-up time from [18F] florbetapir scan for nonconverters, y</td>
<td>1.6 (0.7)</td>
<td>1.8 (0.8)</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>Follow-up time from [18F] florbetapir scan for converters, y</td>
<td>1.5 (0.5)</td>
<td>1.6 (1.0)</td>
<td>1.3 (0.7)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, β-amyloid peptide; AD, Alzheimer disease; ADAS-cog, Alzheimer’s Disease Assessment Scale-Cognitive Subscale; MMSE, Mini-Mental State Examination; SUVR, [18F] florbetapir standardized uptake values ratio.

* Data are reported as mean (SD) unless otherwise indicated.

Fleiss κ was applied to indicate intermethod agreement between all 3 Aβ biomarkers (visual, quantitative PET, and CSF) simultaneously.

Age-, sex-, and educational level–adjusted linear regression models were used to examine the main effect of a visual or quantitative positive [18F] florbetapir baseline scan (dichotomous variable) on longitudinal cognitive function. Age-, sex-, and educational level–adjusted Cox proportional hazards regression models were examined to calculate the MCI conversion hazard ratio for a positive [18F] florbetapir compared with a negative [18F] florbetapir scan at baseline (performed separately for visual and SUVR analysis). Analysis was related to time to censoring. Additional models included APOE4, FDG-PET scan data (dichotomous variable), or cognitive function as the baseline Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-cog) score (continuous variable).

In the presence of these covariates, the positive [18F] florbetapir to negative [18F] florbetapir scan hazard ratio refers to APOE4 positivity, abnormal mean FDG value, and 1-unit per score baseline ADAS-cog increase.

All analyses were performed using SPSS, version 22.0 (SAS Institute Inc). Statistical significance was defined as P ≤ 0.05.

Results

Participants

Descriptive statistics of the participants are given in Table 1. The overall conversion rate was 15.2% over a mean of 1.6 years; the rates for EMCI and LMCI were 5.5% and 32.4%, respectively. Nonconverters and converters differed on baseline cognition and several biomarkers (eAppendix 2 in the Supplement).

Agreement Between Aβ Biomarkers

At baseline, visual readings among all 401 participants were [18F] florbetapir positive for 196 patients (48.9%; EMCI, 104 of 256 [40.6%]; and LMCI, 92 of 145 [63.4%]). The SUVR classifications were [18F] florbetapir positive for 221 participants (55.1%; EMCI, 123 [48.0%]; and LMCI, 98 [67.6%]) (Table 1), yielding substantial to very high intermethod agreement (κ = 0.74 for all patients: EMCI, κ = 0.66; LMCI, κ = 0.85). Dis-cordance between visual and SUVR analysis occurred in 53 participants (13.2%; EMCI, 43 [16.8%]; and LMCI, 10 [6.9%]). [18F] Florbetapir SUVR values of 23 of those 53 cases were within...
the ±5% CI of, and thus close to, the SUVR cutoff (1.11 [5% CI, 1.06-1.17]).[^18F] Florbetapir scans of exemplary discordant cases are demonstrated in Figure 1; the findings of a detailed visual inspection of all 53 discordant cases are given in eAppendix 2 in the Supplement. Demographic data, baseline cognition, and biomarkers did not differ significantly between participants with discordant and concordant visual and SUVR analysis (eAppendix 2 in the Supplement).

Compared with visual readings, SUVR tended to categorize more participants as [^{18F}F] florbetapir positive and fewer cases as [^{18F}F] florbetapir negative. Compared with visual readings, SUVR thus resulted in greater sensitivity (79% vs 85%) and less specificity (96% vs 90%), with CSF Aβ used here as the reference standard (eTable 1 in the Supplement).

Across all 256 participants with CSF Aβ, agreement between PET and CSF was substantial for visual [^{18F}F] florbetapir positive (κ = 0.65, 95% CI: 0.58-0.72) and negative (κ = 0.70, 95% CI: 0.63-0.76). Concordance was also high for SUVR positive (κ = 0.67, 95% CI: 0.60-0.74) and negative (κ = 0.72, 95% CI: 0.65-0.79). Positive and negative predictive values for visual readings of florbetapir positivity were 96% and 89%, respectively, and for SUVR positivity were 95% and 85%, respectively. Concordance was also high for SUVR positive (κ = 0.67, 95% CI: 0.60-0.74) and negative (κ = 0.72, 95% CI: 0.65-0.79). Concordance was also high for visual and SUVR readings, with Cohen’s κ for agreement on florbetapir positivity of 0.65 (95% CI: 0.58-0.72) and for concordance of 0.70 (95% CI: 0.63-0.76).
When visual and SUVR analysis agreed, CSF Aβ was also highly concordant (κ = 0.82) (Figure 2; orange diamonds in sector I, blue diamonds in sector III; however, when visual and SUVR ratings disagreed (Figure 2; sectors II and IV), agreement with CSF was very poor (visual readings: κ = 0.05; SUVR, κ = 0.08). When [18F] florbetapir scans were assessed as positive visually, agreement between PET and CSF was very high (Figure 2; orange diamonds in sectors I and II), and the same was true when [18F] florbetapir scans were assessed as positive by SUVR (sectors I and IV). When the scans were assessed as negative, concordance between PET and CSF was lower (Figure 2; blue diamonds in sectors III and IV [visual readings]) and sectors II and III [SUVR analysis]).
Table 2. Cox Proportional Hazards Regression Models to Assess the Conversion HR for a [18F]
Florbetapir-Positive vs a [18F] Florbetapir-Negative Baseline Scan

<table>
<thead>
<tr>
<th>[18F] Florbetapir Scan Assessment (Dichotomous Predictor Variable)</th>
<th>Covariates</th>
<th>−2 Log Likelihood</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual analysis</td>
<td>Age, sex, educational level</td>
<td>603.38</td>
<td>11.38 (5.10-25.39)</td>
</tr>
<tr>
<td></td>
<td>Age, sex, educational level, ADAS-cog baseline</td>
<td>549.14</td>
<td>5.67 (2.49-12.93)</td>
</tr>
<tr>
<td></td>
<td>Age, sex, educational level, APOEε4 status</td>
<td>634.31</td>
<td>8.71 (3.77-20.11)</td>
</tr>
<tr>
<td></td>
<td>Age, sex, educational level, FDG status</td>
<td>578.09</td>
<td>8.02 (3.56-18.06)</td>
</tr>
<tr>
<td>SUVR measurements</td>
<td>Age, sex, educational level</td>
<td>623.05</td>
<td>6.91 (3.24-14.67)</td>
</tr>
<tr>
<td></td>
<td>Age, sex, educational level, ADAS-cog baseline</td>
<td>559.11</td>
<td>3.63 (1.68-7.86)</td>
</tr>
<tr>
<td></td>
<td>Age, sex, educational level, APOEε4 status</td>
<td>614.75</td>
<td>4.88 (2.20-10.82)</td>
</tr>
<tr>
<td></td>
<td>Age, sex, educational level, FDG status</td>
<td>593.43</td>
<td>4.87 (2.28-10.40)</td>
</tr>
</tbody>
</table>

Abbreviations: ADAS-cog, Alzheimer’s Disease Assessment Scale-Cognitive Subscale; APOE, apolipoprotein; FDG, fludeoxyglucose F 18; [18F] florbetapir, florbetapir F 18; HR, hazard ratio; SUVR, standardized uptake values ratio.

Discussion

We found substantial agreement between visual Aβ PET, quantitative Aβ PET, and CSF Aβ-42 analysis in patients with MCI. In approximately 10% of all cases, agreement between visual and quantitative [18F] florbetapir analysis was poor, as was agreement between both readers and between PET and CSF data. Furthermore, both visual and quantitative Aβ PET assessment performed similarly in predicting longitudinal cognitive function and MCI to AD conversion.

Concordance between visual and quantitative image analysis was lower than that reported in a study that included patients with AD. Similarly, acquisition of data in a single center, as opposed to this multicenter study, appears to result in a higher concordance between qualitative and SUVR measures (κ values up to 0.96). In addition to its multicenter approach, our study differs from previous MCI investigations that compared visual and quantitative PET analysis by (1) the use of [18F] florbetapir images instead of Pittsburgh compound-B PET scans, flutemetamol F 18 PET scans, or flutemetamol F 18 PET scans; (2) the inclusion of individuals with EMCI; (3) the application of a less conservative SUVR threshold; and (4) the examination of a much larger and likely more heterogeneous MCI sample. All of those aspects may have contributed to the somewhat lower concordance between visual readings and SUVRs in the present study.

In contrast, our interrater reliability (κ = 0.92) was somewhat higher than that in another visual MCI PET study (κ = 0.46-0.86). However, this very high interreader reliability was generated from a subsample of cases that already agreed between visual (reader 1) and SUVR analysis; therefore, it is likely to be biased toward higher concordance. When including all 125 cases rated by both readers (as described in the Methods section), interrater reliability was somewhat lower but still substantial (κ = 0.76). Because the subsample of 125 cases read by rater 2 specifically included the 53 participants with discordant qualitative (reader 1) and quantitative data, corresponding interrater agreement was biased toward lower concordance.

To have an objective, independent criterion, we considered CSF as a reference standard and found that visual readings resulted in lower sensitivity and higher specificity compared with SUVR analysis. The use of CSF as an external reference allowed us to compare visual and SUVR analysis with a third measure. Addition of this measure does not suggest that CSF Aβ should be considered as the reference standard or that our approach refers to general recommendations, especially since CSF and PET Aβ represent different aspects of cerebral Aβ pathology. In fact, it has been proposed that CSF Aβ reduction indicates earlier stages of abnormality and increased Aβ PET retention reflects later stages of cerebral Aβ and AD pathology.

In terms of its high specificity but slightly lower sensitivity, visual analysis may be useful for selection of individuals with MCI for participation in intervention trials aiming to avoid the treatment of true-negatives. Compared with SUVRs, visual readings may be less useful for clinical trials aiming to capture as many Aβ-positive cases as possible, especially those at very early Aβ stages (eg, EMCI). Continuous SUVR measures
may be superior to quantify treatment effects on Aβ, especially if therapeutic impact is moderate. Indeed, current and planned preclinical trials are designed to select and provide treatment for cognitively unimpaired individuals or patients with early cognitive impairment and Aβ biomarker evidence to show that therapy lessens Aβ burden and provides clinical benefit.31,32 Thus, an approach combining visual and quantitative PET analysis may be best for selection of trial participants.33 This idea is supported by the fact that visual and quantitative PET analysis was associated with very high overall intermethod concordance. The combined application of visual and quantitative PET analysis may thus be a valid approach to identify true Aβ-positive and true Aβ-negative cases. In a separate autopsy-validated study,34 there was 100% agreement between visual and quantitative Aβ PET data for cases with concordance between visual [18F] florbetapir and neuropathologic Aβ load classification, which supports this idea.

Classification of Aβ positivity or negativity was inconsistent for approximately 10% of all cases. Most (approximately 81%) of these cases were in the EMCI category. As has also been reported for elderly control participants,33 focal and asymmetric [18F] florbetapir retention explained some of the discrepancy between qualitative and quantitative analysis since it basically leads to visual Aβ positivity but quantitative Aβ negativity. Cerebrospinal fluid Aβ was positive in 85% of the visual [18F] florbetapir–positive cases and quantitative [18F] florbetapir–negative cases with focal Aβ burden, suggesting that focal cortical [18F] florbetapir retention may account for some of the discordance between CSF and SUVR results.3,4,36,35 Qualitative analysis was also superior in detecting [18F] florbetapir retention in nonpaleocortical brain structures, which contributed to its lower false-positive rate. Indeed, visual readings require significant efforts to maintain interrater reliability. Our data, however, show that interreader agreement can be substantial, even if visual analysis includes a fraction of challenging scans.

Our overall conversion rate was 15% within 1.6 years. With the exception of one study reporting a similar conversion frequency (16% in 1.5 years), most MCI studies8,10,13,36 comprising a mean observation period of approximately 2 years reported higher conversion rates (44%-59%). Higher conversion rates may be explained by the inclusion of MCI cohorts from specialized memory clinics10,13,36 that are characterized by higher cortical Aβ retention,10,13,36 lower baseline Mini-Mental State Examination scores,9,36 and more APOE ε4 carriers.8,10,36 Furthermore, the proportion of converters among our quantitative [18F] florbetapir–positive cases (53 of 221 [24.0%]) was substantially lower than the proportions of 50% to 82% reported in other Aβ PET MCI studies.2,8,9,12,13,17,36–38 which is explained by the inclusion of participants with EMCI and by our less conservative SUVR cutoff assessing comparably more individuals with MCI as Aβ positive. However, the proportion of converters among our quantitative [18F] florbetapir–positive cases (54 of 196 [27.6%]) is in line with the proportions of 29% to 35% found in a previous MCI PET study2,38 assessing [18F] florbetapir scans visually. Our finding that approximately 90% of the converters were Aβ positive for both visual and SUVR analysis is in agreement with the commonly reported frequencies of Aβ positivity among converters2,8,12,14,17,36,37 and supports the increased AD conversion risk in case of a [18F] florbetapir–positive scan.

Amyloid-positive baseline PET predicted approximately 4-fold to 9-fold higher conversion risk even after adjustment for positive APOE ε4 carrier status, an abnormal concurrent FDG PET scan, and 1-score worsening of a lower baseline ADAS-cog score. An Aβ-positive PET scan thus adds considerable predictive value even in the presence of genetic and cognitive status, as well as in the absence of additional biomarkers. Moreover, our data emphasize that the frequency of Aβ positivity and conversion rates increase with severity of cognitive symptoms.33 Depending on the method used for Aβ load assessment, we found that 40.6% to 59.5% and 63.4% to 72.2% of EMCI and LMCI cases, respectively, were Aβ positive and that 5.5% and 32.4% of participants with EMCI and LMCI, respectively, converted to AD within 1.5 years. In general, all results were comparable between the qualitative and quantitative analyses.

Conclusions

Our findings suggest that visual readings and SUVRs are equivalent in their assignment of negative or positive Aβ status in MCI. Even including genetic, cognitive, and FDG status, qualitative and quantitative PET analysis adds significant value for clinical course prognostication. Our data thus support the applicability of a simpler case inclusion algorithm that may facilitate case selection in trials evaluating MCI due to AD.

ARTICLE INFORMATION

Accepted for Publication: June 3, 2015.
Published Online: August 17, 2015.

Author Contributions: Dr S. Schreiber had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: S. Schreiber, Landau, Jagust. Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: S. Schreiber, Jagust. Critical revision of the manuscript for important intellectual content: Landau, Fero, F. Schreiber, Jagust.

Obtained funding: Jagust.
Administrative, technical, or material support: Landau, Fero, F. Schreiber.
Study supervision: Jagust.

Conflict of Interest Disclosures: Dr Landau has served as a consultant to Biogen, Genentech, and Synarc, and Dr Jagust has served as a consultant to Banner Alzheimer Institute/Genentech, Novartis, and Synarc/Bioclinica. No other disclosures were reported.

Funding/Support: Data collection and sharing for this project was funded by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (National Institutes of Health grant U01 AG024904) and Department of Defense ADNI (award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging and the National Institute of Biomedical Imaging and Bioengineering and through generous contributions from the following organizations: Alzheimer’s Association, Alzheimer’s Drug Discovery Foundation, Aracorn Biotech, Bioclinica Inc, Biogen Idec Inc, Bristol-Myers Squibb Company, Eisai Inc, Elan Pharmaceuticals Inc, Eli Lilly and Company, Euroimmun, F. Hoffmann-La Roche Ltd and its affiliated company Genentech Inc, Fujirebio, GE Healthcare, IXICO Ltd, Janssen Alzheimer Immunotherapy Research & Development LLC, Johnson & Johnson Pharmaceutical Research & Development LLC, Medpace Inc, Merck & Co Inc, Meso Scale Diagnostics LLC, NeuroRx Research, Neurotrack.
Technologies, Novartis Pharmaceuticals Corporation, Pfizer Inc, Piramal Imaging, Servier, Synarc Inc, and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This research was also supported by the German Research Foundation grant SCHR 1418/3-1.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: A complete listing of the Alzheimer’s Disease Neuroimaging Initiative investigators can be found in Appendix 1 in the Supplement.

Additional Information: Data used in preparation of this article were obtained from the ADNI database (http://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 analysis or writing of this report.

REFERENCES