Journal of Alzheimer's Disease 51 (2016) 793–800
DOI 10.3233/JAD-150829
IOS Press

What are the Most Frequently Impaired Markers of Neurodegeneration in ADNI Subjects?

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Accepted 27 December 2015

Abstract. The aim of this study was to examine the relationship between cerebrospinal fluid (CSF) levels of biomarkers for Alzheimer's disease (AD) ($A\beta_{1–42}$, t-tau, and p-tau) and ^{18}Fluorodeoxyglucose positron emission tomography (FDG-PET) hypometabolism in subjects from the Alzheimer's Disease Neuroimaging Initiative, and specifically to determine which index of neurodegeneration was most frequently affected. The secondary objective was to determine the most frequently hypometabolic region in patients with a CSF AD signature (abnormal $A\beta_{1–42}$ and abnormal p-tau). We included the 372 subjects (85 normal subjects, 212 patients with mild cognitive impairment, and 75 patients with AD) with a CSF biomarker dosage ($A\beta_{1–42}$, t-tau, and p-tau) and brain FDG-PET. The relationship between FDG-PET metabolism (in five regions of interest (ROI) known to be damaged in AD) and CSF t-tau and p-tau levels was studied as a function of CSF $A\beta_{1–42}$ status. FDG-PET hypometabolism and CSF t-tau and p-tau levels were correlated only in patients with an abnormal CSF $A\beta_{1–42}$ level (t-tau: $R^2 = 0.044$, $p = 0.001$; p-tau: $R^2 = 0.02$, $p = 0.03$). In the latter patients, CSF p-tau was the most frequently ($p = 0.0001$) abnormal neurodegeneration marker (p-tau: 92.8%; FDG-PET: 56.5%; CSF t-tau: 59.1%). Within the five ROI of FDG PET, the angular gyrus metabolism ($R^2 = 0.149$; $p = 0.0001$) was selected as the most tightly associated with CSF AD signature. The relation between CSF markers of neurodegeneration (p-tau and t-tau) and brain hypometabolism (in FDG-PET) is conditioned by presence of amyloid abnormality. This finding supports the current physiopathological model of AD. P-tau is the most frequently impaired biomarker. Using FDG PET angular gyrus hypometabolism is the most sensitive to CSF-biomarker-defined AD.

Keywords: Alzheimer's disease, cerebrospinal fluid biomarkers, FDG-PET metabolism, neurodegeneration markers, tau

INTRODUCTION

^{18}Fluorodeoxyglucose positron emission tomography (FDG-PET) and cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) have a key role in the recently formulated diagnostic criteria for AD [1]. Low CSF amyloid-β $(A\beta)_{1–42}$ indicates the

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (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. 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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presence of Aβ pathology [2], whereas low FDG uptake in PET and elevated CSF total tau (t-tau) and hyperphosphorylated tau (p-tau) indicate the presence of neurofibrillary tangle (NFT) pathology, and testify to this presence of neurodegeneration [2–4]. In most confirmed cases of AD, the Aβ plaque pathology precedes the NFT pathology [5–7]. However, this prevailing view has been challenged by the data from a few cases [8, 9].

In order to apply the recently formulated AD criteria in clinical practice, the relationship between the various neurodegeneration markers has to be determined. This has been performed in a few studies with small sample sizes (fewer than 40 patients). The three studies with the largest sample sizes found (i) a positive correlation between metabolism in the temporal and parietal lobes and hippocampus on one hand, and CSF levels of t-tau and p-tau on the other ($n = 28$ AD patients) [10]; (ii) a negative correlation between precuneus and posterior cingulate metabolism and CSF $A\beta_{1–42}$ levels ($n = 33$ AD patients) [11]; and (iii) a negative correlation between right temporal, prefrontal, and anterior cingulate metabolism and CSF $A\beta_{1–42}$ levels ($n = 32$ AD patients) [12]. These initial results did not establish the respective values of CSF and FDG-PET markers for the diagnosis of AD. Furthermore, these results indicated that analyses of FDG-PET data must focus on the regions that are most sensitive to change in early-stage AD. Accordingly, studies based on clinical criteria for AD [13] have variously found that FDG-PET hypometabolism affects the posterior cingulate and the superior and inferior parietal regions [14–17], the temporoparietal lobes [18, 19], the parietal lobe [20], and the cingulate cortex [21]. The few studies based on neuropathological criteria indicated that the hypometabolism concerns the temporoparietal cortex but did not provide greater detail [22–25]. With a view to applying the recently established AD criteria in clinical practice, it would be useful to know whether metabolism in all the affected regions (i.e., temporoparietal and posterior cingulate regions) has to be taken into account or whether one of these regions is particularly sensitive to AD.

The primary objective of the present study was to examine the relationship between CSF biomarker levels and FDG-PET hypometabolism according to the data gathered by the Alzheimer's Disease Neuroimaging Initiative (ADNI) and specifically, to determine which index of neurodegeneration (FDG-PET hypometabolism or t-tau/p-tau) was most frequently affected. The secondary objective was to determine the most frequently hypometabolic region in patients with a CSF AD signature (abnormal $A\beta_{1–42}$ and p-tau levels).

METHODS

The study population

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5- year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (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, as well as 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 co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, 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 http://www.adni-info.org.

We included all subjects from the ADNI databank with available data on CSF biomarker levels and brain FDG-PET (Table 1). Application of these criteria led to the inclusion of a total of 372 subjects: 85 (22.85%) normal subjects (Clinical Dementia Rating [CDR] score of 0), 212 (56.99%) patients with MCI (CDR score = 0.5), and 75 (20.16%) patients with mild-to-moderate AD dementia, according to McKhann's criteria [13].

Table 1
Demographic information for all participants

	Population	
n	372	
Age	72.6	±7.38
Gender, female†	163	(43.8%)
Education (years)	16.38	±2.64
Delay PET/CSF (months)	0.34	±0.74
Clinical Diagnosis†		
Normal	85	(22.85%)
Mild cognitive impairment	212	(56.99%)
Alzheimer's disease	75	(20.16%)
MMSE		
Normal	29.1	±1.6
Mild cognitive impairment	27.8	±1.8
Alzheimer's disease	23.1	±2

PET, positron emission tomography; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; †expressed as number and percentage.

CSF AD biomarkers

The CSF levels of $A\beta_{1–42}$, t-tau, and p-tau were measured using the multiplex xMAP Luminex Innogenetics system (http://adni.loni.usc.edu/methods/biomarker-analysis/). The CSF cutoffs from the autopsy-validated baseline assay used in this study were: $A\beta_{1–42}$<192 pg/mL, t-tau>93 pg/mL, and p-tau>23 pg/mL [26].

FDG-PET

In the ADNI study, FDG imaging data were acquired 30 to 60 min post-injection; the images were averaged, spatially aligned, interpolated to a standard voxel size, smoothed to a common resolution of 8 mm full width at half maximum, and spatially normalized against the standard [15O]H_2O PET template using SPM5. The mean FDG uptake for each subject was determined with a set of predefined, previously validated regions of interest (ROI) based on a review of the literature. Each subject's summary FDG index was the mean of the five ROI: The right and left inferior temporal region, right and left angular gyrus regions, and a bilateral posterior cingulate cortex, relative to the mean of a pons and cerebellar vermis reference region [27]. The FDG cutoff for the same, predefined ROI had been determined in a previous study (albeit in the absence of autopsy validation); a threshold value of 1.21 best differentiated between ADNI AD patients and normal subjects [28].

Statistical analyses

As AD CSF profile is defined by the association of $A\beta_{1–42}$ and t/p-tau abnormalities, the statistical analysis involved both $A\beta_{1–42}$, t/p-tau, and p-tau/$A\beta_{1–42}$ ratio [29]. The relationship between mean FDG-PET metabolism and CSF biomarker levels was first assessed in stepwise regression analyses. The strong correlation between t-tau and p-tau ($r = 0.683$, $p = 0.0001$) prompted us to analyze the relationship between FDG-PET metabolism and CSF tau using two stepwise regression analyses: First for t-tau and then for p-tau. The FDG-PET metabolism value was the dependent variable; $A\beta_{1–42}$ and t-tau were fed into the first stepwise regression analysis, and $A\beta_{1–42}$ and p-tau fed into the second. To further analyze the complex relationship between PET metabolism and the two CSF biomarkers, values of the first selected factor ($A\beta_{1–42}$) were dichotomized (normal versus abnormal) [30]. Next, the correlations between the two indexes of neurodegeneration, mean FDG-PET metabolism and t-tau and p-tau levels were examined as a function of $A\beta_{1–42}$ status (normal versus abnormal).

In a second series of analyses, we compared the frequency of abnormal mean FDG-PET metabolism and CSF t-tau and p-tau levels in subjects with abnormal $A\beta_{1–42}$ levels (using a McNemar test). The mean values of FDG-PET metabolism, t-tau and p-tau were dichotomized according to previously validated cutoffs [26, 28].

Lastly, we examined whether any of the FDG-PET ROI were especially sensitive to CSF-biomarker-defined-AD. To reduce multicollinearity, we analyzed the mean of left and right values of angular and temporal regions (thus yielding 3 FDG-PET regions: The angular gyrus, the temporal region, and the posterior cingulate). The values of these three FDG-PET regions were analyzed according to the presence of (i) abnormal $A\beta_{1–42}$ levels and (ii) abnormal $A\beta_{1–42}$ and p-tau levels. The three ROI were submitted to two stepwise logistic analyses: The independent variable was $A\beta_{1–42}$ status (normal versus abnormal) in the first analysis and $A\beta_{1–42}$ and p-tau status (normal versus abnormal for each) in the second.

All statistical tests were performed with SPSS. The threshold for statistical significance was set to $p \leq 0.05$.

RESULTS

Relationships between FDG-PET metabolism and CSF biomarkers

The first stepwise regression analysis showed that mean FDG-PET metabolism was associated

with both $A\beta_{1-42}$ ($R^2 = 0.16$, $p = 0.0001$) and t-tau ($R^2 = 0.036$, $p = 0.001$) levels. The second stepwise regression analysis selected both $A\beta_{1-42}$ ($R^2 = 0.16$, $p = 0.0001$) and p-tau ($R^2 = 0.009$, $p = 0.04$).

To further analyze the contributions of $A\beta_{1-42}$ and tau levels to the regression analysis, the first selected factor ($A\beta_{1-42}$) was dichotomized (normal: $n = 135$; abnormal: $n = 237$) [30]. The relationship between mean FDG-PET metabolism and CSF tau levels (Fig. 1) was statistically significant in subjects with abnormal $A\beta_{1-42}$ levels (t-tau: $R^2 = 0.044$, $p = 0.001$; p-tau: $R^2 = 0.02$, $p = 0.03$) but not in subjects with normal $A\beta_{1-42}$ levels ($R^2 < 0.005$, both).

These results indicate that (i) the two indexes of neurodegeneration (FDG-PET and CSF tau) were related only when amyloid pathology was present, and (ii) further analyses of the association between both FDG-PET data and CSF tau levels had to take account of $A\beta_{1-42}$ status.

Frequency of abnormal FDG-PET metabolism and CSF biomarker status

Mean FDG-PET metabolism was abnormal in 166 (44.6%) subjects; t-tau was abnormal in 154 (41.4%) subjects and p-tau was abnormal in 280 (75.3%) subjects (Table 2). In the 237 subjects with abnormal $A\beta_{1-42}$ levels (Table 2), CSF p-tau ($n = 220$, 92.8%) was more frequently abnormal than either t-tau ($N = 140$, 59.1%) or FDG-PET metabolism (134, 56.5%) (McNemar test; $p = 0.0001$, both). The frequency of CSF t-tau and FDG-PET metabolism did not differ significantly (McNemar test; $p = 0.6$). Accordingly all the 80 subjects with only one abnormal tau value had abnormal p-tau and normal t-tau values.

These results indicate that CSF p-tau is the most frequently abnormal neurodegenerative marker in patients with abnormal $A\beta_{1-42}$, followed (to the same extent) by t-tau and mean FDG-PET hypometabolism.

ROI associated with CSF-biomarker-defined-AD

Abnormal $A\beta_{1-42}$ was associated with hypometabolism in the angular gyrus (odds ratio (OR) 95% confidence interval (CI)]: 276 [57–1345]; $p = 0.0001$), as was the combination of abnormal $A\beta_{1-42}$ and abnormal p-tau (OR [95%CI]: 187 [41.8–838]; $p = 0.0001$) (Table 3). These results indicate that hypometabolism of the angular gyrus was the most tightly associated with CSF AD signature.

DISCUSSION

Our present results revealed firstly that the relationship between two major neurodegenerative markers (brain FDG-PET signature and CSF tau status) was only significant if amyloid abnormality was present. Second, we found that CSF p-tau is the more likely to be abnormal than CSF t-tau levels and FDG-PET status. Lastly, angular gyrus hypometabolism was most sensitive to AD (as defined by CSF biomarker levels).

This study is the first to report that the relationship between CSF tau and FDG-PET metabolism is conditioned by CSF $A\beta_{1-42}$ status. Our finding fits with Jack's physiopathological model of AD [7]. In AD, the NFT pathology is preceded by amyloid deposits [31, 5, 32, 6, 7]. In the most frequent form of AD [33], NFT are first observed in the mediotemporal cortex and then spread to the cingulate cortex and, ultimately, the temporoparietal region [34, 35]. Low brain FDG-PET metabolism and elevated CSF tau levels are observed in parallel with the NFT pathology [3, 36]. Jack's model predicts that the two markers of AD neurodegeneration (i.e., PET hypometabolism and CSF tau levels) will be correlated only if $A\beta$ pathology is present, which corresponds exactly to our present findings. This result emphasizes the importance of CSF $A\beta$ status and contributes to the ongoing debate as to the combination of CSF biomarkers that should be included in the CSF AD signature [37].

Hypometabolism of the angular gyrus proved to be the most sensitive to AD, as defined by a combination of abnormal $A\beta_{1-42}$ and abnormal p-tau. This is a novel finding because most analyses consider only the metabolic values of the temporal, parietal and posterior cingulate regions (or a mean index of these regions). The few studies to have included a neuropathological diagnosis of AD found that hypometabolism occurred in the temporoparietal regions [22–25]. The angular gyrus's prominent role in AD was unexpected, in view of the literature data on early hypometabolism in the posterior cingulate [14–17, 21]. This discrepancy may be due to differences in the disease criteria (i.e. clinical versus biological criteria) and the study design (i.e., longitudinal versus cross-sectional).

The main limit of the present study concerned the diagnostic accuracy of CSF biomarkers, which cannot substitute for a neuropathological diagnosis. In the ADNI sample of autopsy-validated cases, the diagnostic sensitivity and specificity were respectively 96 and 76% for $A\beta_{1-42}$, 69% and 92% for

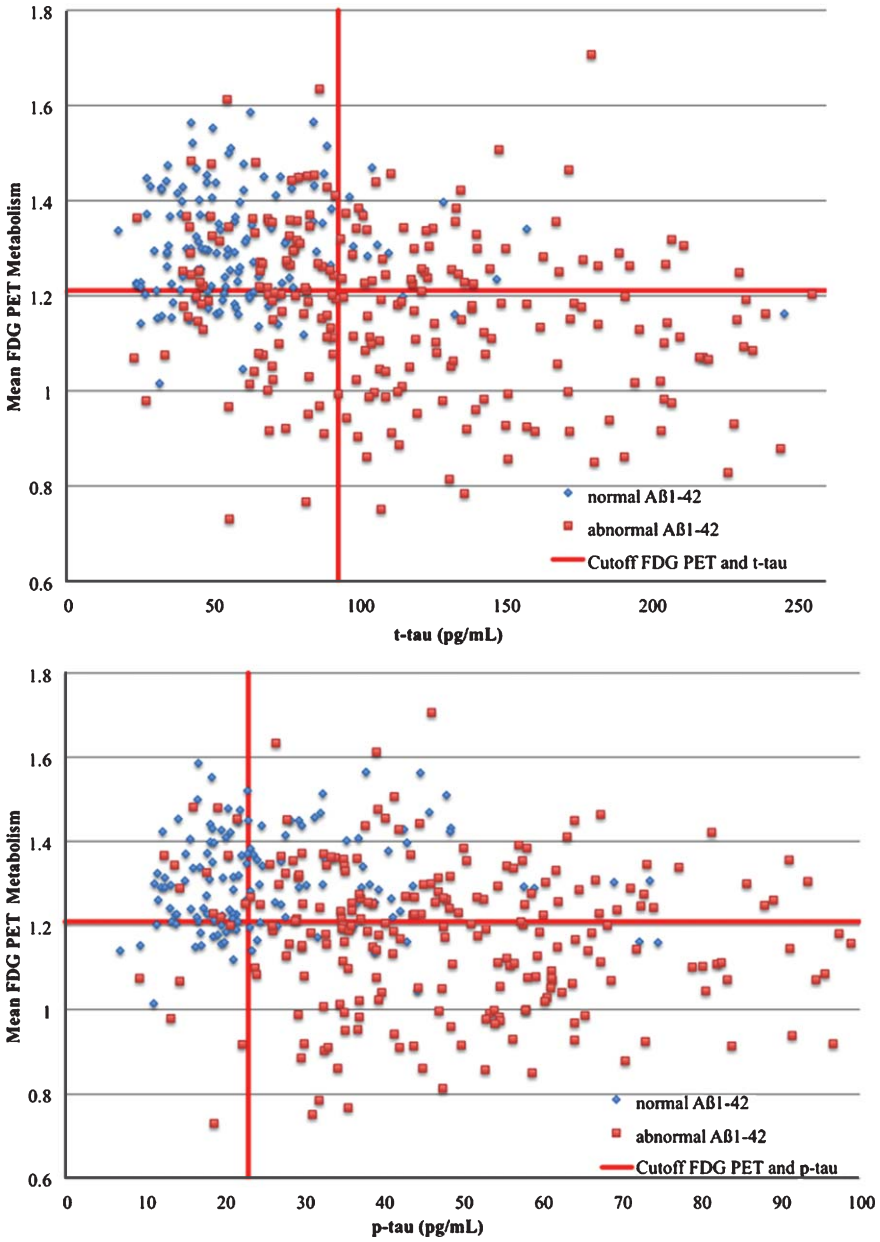

Fig. 1. Correlation between mean FDG PET metabolism and CSF t-tau (top) and p-tau (bottom) according to CSF $A\beta_{1–42}$ status. PET, positron emission tomography; $A\beta_{1–42}$, cerebrospinal fluid $A\beta_{1–42}$; t-tau, cerebrospinal fluid total tau; p-tau, cerebrospinal fluid hyperphosphorylated tau.

t-tau, 67% and 73% for p-tau, 85% and 84% for the t-tau/$A\beta_{1–42}$ ratio, and 91% and 71% for the p-tau/$A\beta_{1–42}$ ratio [26]. In other studies of autopsy-validated cases, CSF biomarkers had a sensitivity of between 65% and 96% and a specificity of between 60% and 100% [38, 26, 39, 40]. Despite this limitation, the use of CSF biomarkers enables the performance of studies in a large clinical sample and is not subject to the sources bias observed in studies with neuropathological verification (such as patient inclusion at all stages of the disease and referral bias).

Furthermore the high frequency of CSF $A\beta_{1–42}$ (237 of 372) and of CSF p-tau (280 of 372) abnormalities, also in ADNI population AD is more frequent

Table 2
Mean FDG PET Metabolism and CSF t/p-tau status in patients with abnormal CSF$A\beta_{1-42}$ ($n = 237$)

$n = 237$		CSF t-tau (pg/mL)		
		Normal	Abnormal	Total
$_{mean}$PET	Normal	52 (21.9%)	51(21.5%)	103(43.5%)
	Abnormal	45(18.9%)	89 (37.5%)	134(56.5%)
	Total	97(40.9%)	140(59.1%)	237(100%)
		CSF p-tau (pg/mL)		
$_{mean}$PET	Normal	11(4.6%)	92(38.8%)	103(43.5%)
	Abnormal	6(2.5%)	128(54.0%)	134(56.5%)
	Total	17(7.2%)	220(92.8%)	237(100%)

PET, positron emission tomography; CSF, cerebrospinal fluid; t-tau, total tau; p-tau: hyperphosphorylated tau.

Table 3
FDG PET Metabolism (expressed as mean ± standard deviation) according to CSF biomarkers status

	CSF $A\beta_{1-42}$ (pg/mL)	
	Normal	Abnormal
$_{mean}$ANGULAR gyrus	1.317 ± 0.127	1.168 ± 0.188
$_{mean}$TEMPORAL region	1.251 ± 0.110	1.138 ± 0.170
POSTERIOR CINGULATE	1.392 ± 0.157	1.253 ± 0.190
	CSF $A\beta_{1-42}$ and p-tau (pg/mL)	
	Normal	Abnormal
$_{mean}$ANGULAR gyrus	1.307 ± 0.144	1.164 ± 0.184
$_{mean}$TEMPORAL region	1.246 ± 0.125	1.133 ± 0.167
POSTERIOR CINGULATE	1.378 ± 0.167	1.252 ± 0.188

PET, positron emission tomography; CSF, cerebrospinal fluid; p-tau, hyperphosphorylated tau.

than in the general population [41], this would constitute a limit if we calculated the diagnostic accuracy of the hypometabolism of the angular gyrus in AD; nevertheless the strength of the relation between the hypometabolism of the angular gyrus and the CSF biomarkers remains valid.

Our present results have practical implications for the choice of CSF biomarkers that comprise the AD signature [37] and resolution of disparate results concerning abnormal CSF biomarker levels and regional hypometabolism. The results indicate that when a method similar to that that of ADNI is used, (i) p-tau is the most sensitive marker of neurodegeneration and (ii) the angular gyrus is the most sensitive ROI when considering regional FDG-PET values. Consequently, in clinical practice, abnormal CSF $A\beta_{1-42}$ and p-tau is highly suggestive of AD even in the absence of other abnormalities (CSF t-tau or FDG-PET); besides analysis of FDG-PET should focus on the metabolism of the angular gyrus and a hypometabolism in this area should be regarded as suggestive of AD even when the metabolism of the others regions is normal.

ACKNOWLEDGMENTS

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 DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon 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.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/15-0829r1).

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