ANNALS of Clinical and Translational Neurology
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RESEARCH ARTICLE

Diagnostic accuracy of CSF Ab42 and florbetapir PET for Alzheimer's disease

Niklas Mattsson[1,2,3], Philip S. Insel[2], Susan Landau[4], William Jagust[4], Michael Donohue[5], Leslie M. Shaw[6], John Q. Trojanowski[6], Henrik Zetterberg[1,7], Kaj Blennow[1], Michael Weiner[2,3] & for the Alzheimer's Disease Neuroimaging Initiative[a]

[1]Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
[2]Department of Radiology and Biomedical Imaging, University of California, San Francisco, California
[3]Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, San Francisco, California
[4]Helen Wills Neuroscience Institute and School of Public Health, University of California, Berkeley, California
[5]Division of Biostatistics and Bioinformatics, Department of Family & Preventive Medicine, University of California, San Diego, La Jolla, California
[6]Department of Pathology and Laboratory Medicine, Institute on Aging, Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
[7]UCL Institute of Neurology, Queen Square, London, WC1N 3BG, United Kingdom

Correspondence
Niklas Mattsson, Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, Building 13, San Francisco, CA 94121. Tel: +1 415 494 1139; Fax: +1 (415) 668-2864;
E-mail: niklas.mattsson@neuro.gu.se

Funding Information
Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, Glaxo-SmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace Inc., Merck and Co. Inc., Novartis AG, Pfizer Inc., F. Hoffman-La Roche, Schering-Plough, Synarc Inc., as well as nonprofit partners the Alzheimer's Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (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

Abstract

Background: Reduced cerebrospinal fluid (CSF) β-amyloid42 (Aβ42) and increased florbetapir positron emission tomography (PET) uptake reflects brain Aβ accumulation. These biomarkers are correlated with each other and altered in Alzheimer's disease (AD), but no study has directly compared their diagnostic performance. **Methods**: We examined healthy controls (CN, $N = 169$) versus AD dementia patients ($N = 118$), and stable (sMCI; no dementia, followed up for at least 2 years, $N = 165$) versus progressive MCI (pMCI; conversion to AD dementia, $N = 59$). All subjects had florbetapir PET (global and regional; temporal, frontal, parietal, and cingulate) and CSF Aβ42 measurements at baseline. We compared area under the curve (AUC), sensitivity, and specificity (testing a priori and optimized cutoffs). Clinical diagnosis was the reference standard. **Results**: CSF Aβ42 and (global or regional) PET florbetapir did not differ in AUC (CN vs. AD, CSF 84.4%; global PET 86.9%; difference [95% confidence interval] −6.7 to 1.5). CSF Aβ42 and global PET florbetapir did not differ in sensitivity, but PET had greater specificity than CSF in most comparisons. Sixteen CN progressed to MCI and AD (six Aβ negative, seven Aβ positive, and three PET positive but CSF negative). **Interpretation**: The overall diagnostic accuracies of CSF Aβ42 and PET florbetapir were similar, but PET had greater specificity. This was because some CN and sMCI subjects appear pathological using CSF but not using PET, suggesting that low CSF Aβ42 not always translates to cognitive decline or brain Aβ accumulation. Other factors, including costs and side effects, may also be considered when determining the optimal modality for different applications.

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Imaging at the University of California, Los Angeles. This research was also supported by NIH grants P30 AG010129 and K01 AG030514, the Swedish Research Council, Goteborgs Lakaresallskap, Svenska Lakaresallskapet, Sahlgrenska Universitetssjukhuset, Carl-Bertil Laurells fond, and Klinisk Biokemi i Norden.

Received: 12 May 2014; Accepted: 13 June 2014

***Annals of Clinical and Translational Neurology* 2014; 1(8): 534–543**

doi: 10.1002/acn3.81

[a]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/wpcontent/ uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Introduction

Brain β-amyloid (Aβ) accumulation is a hallmark of Alzheimer's disease (AD), and may be identified in living humans using cerebrospinal fluid (CSF) measurements of the 42 amino acid variant of β-amyloid (Aβ42)[1] and positron emission tomography (PET) imaging using Aβ ligands (e.g., florbetapir).[2] The findings that CSF and PET Aβ positivity are associated with clinical AD dementia,[4,5] future conversion to AD dementia in patients with mild cognitive impairment (MCI),[6,7] and future cognitive impairment in healthy controls,[8,9] have led to the definition of novel AD research criteria, incorporating biomarkers of Aβ pathology into the diagnostic algorithms.[10–12] In vivo identification of brain Aβ has become increasingly important due to the development of novel AD drugscite ref 3 here, which are likely to be effective only in patients with Aβ pathology, and maybe only in early disease stage, when a correct clinical diagnosis of AD is difficult to make.

Ultimately, the choice of whether to use CSF or PET for Aβ quantification in research, drug trials, and clinical investigations will depend on many factors, including the methods' costs, availabilities, side effects, and diagnostic performance. Studies that have included both CSF and PET Aβ measurements have suggested strong correlations between them,[7,13–19] but no study has directly compared their diagnostic performance for the clinical diagnosis of AD. When examining Aβ biomarkers in AD, it is possible to either use the clinical diagnosis or the presence of biomarker positivity (suggesting possible brain Aβ pathology) as reference standard. In this study, we used clinical diagnosis as the reference standard. Our goal was to compare CSF Aβ42 and PET Aβ to identify clinical AD. We hypothesized that CSF and PET would have equal diagnostic performance, both when testing healthy controls versus AD dementia patients, and when testing stable MCI patients versus MCI patients who later progressed to AD dementia.

Methods

Study design

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu). 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

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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 data used in this study were acquired in ADNI-2, which is the continuation of ADNI. For up-to-date information, see http://www.adni-info.org.

Participants

Our study population consisted of subjects from ADNI-2. The sample size and demographic characteristics of the subjects are listed in Table 1. Inclusion/exclusion criteria for ADNI-2 subjects are described in detail at http://www.adni-info.org. Briefly, all subjects included in ADNI-2 were between the ages of 55 and 90 years, had completed at least 6 years of education, were fluent in Spanish or English, and were free of any significant neurologic disease other than AD. Cognitively normal (CN) subjects had Mini Mental State Examination (MMSE) score ≥24 and clinical dementia rating scale (CDR) score 0. MCI subjects (including both so-called "early" and "late" MCI) had MMSE score ≥24, objective memory loss as shown on scores on delayed recall of the Wechsler Memory Scale Logical Memory II (>0.5 standard deviations below the normal mean), CDR 0.5, preserved activities of daily living, and absence of dementia. AD dementia subjects fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD, and had MMSE scores between 20 and 26 and a CDR of 0.5 or 1.0.

The original data set consisted of 185 CN, 435 MCI, and 118 AD subjects. We inspected the clinical follow-up data (using up to 3-year follow-up) to assess conversion between diagnostic groups. Among CN, 14 subjects converted to MCI and 2 to AD. These 16 progressive CN were excluded from all comparisons, to keep the control group as AD free as possible (but we report CSF and PET data on these subjects in the result section, see below). Among MCI, 59 subjects converted to AD and were labeled progressive MCI (pMCI), while 165 subjects did not convert to AD (during at least 2-year follow-up) and were labeled stable MCI (sMCI; these also included five subjects who reverted from MCI to CN). The remaining MCI patients, who did not convert to AD but who had less than 2-year clinical follow-up, were excluded, since their long-term clinical status was uncertain, and to have groups balanced on follow-up time. No AD subjects reverted to MCI or CN during follow-up. Thus, the comparisons in this study were done on the diagnostic groups CN ($N = 169$) versus AD ($N = 118$), sMCI ($N = 165$) versus pMCI ($N = 59$).

Florbetapir PET

ADNI PET image data were acquired at baseline. Data were processed as described previously.[20] In sum, florbetapir image data were acquired 50–70 min post injection. Images were reconstructed immediately following the scan, and repeat scans were acquired if motion artifact was detected. For quantification of florbetapir, 3T 3D MP-RAGE MRI scans were used. MRI images were segmented and parcellated into individual cortical regions with FreeSurfer, and used to extract mean florbetapir uptake (standardized uptake value ratio, SUVr) from gray matter within lateral and medial frontal anterior, posterior cingulate, lateral parietal, and lateral temporal regions relative to uptake in the whole cerebellum (white and gray matter). Both the overall cortical mean SUVr from these regions combined and the regional SUVr were used in this study. Full protocols and data are available online (http://adni.loni.ucs.edu).

CSF biomarker concentrations

CSF was acquired at baseline by lumbar puncture, and stored at −80°C at the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center. Aβ42, T-tau, and P-tau were measured using the multiplex xMAP Luminex platform (Luminex Corp., Austin, TX) with Innogenetics (INNOBIA AlzBio3; Ghent, Belgium; for research-use only reagents) immunoassay kit-based reagent as

Table 1. Demographics.

	CN	AD	sMCI	pMCI
N	169	118	165	59
Sex, M:F (%F)	85:84 (50%)	70:48 (41%)	90:75 (46%)	33:26 (44%)
Age, years	74.5 (6.6)	75.4 (7.7)	71.8 (7.6)	72.8 (7.0)
Education, years	16.5 (2.5)	15.8 (2.6)	16.2 (2.6)	16.2 (2.7)
APOE, ε4 (%+)	123:45 (27%)	35:83 (70%)	107:57 (35%)	12:47 (80%)
Follow-up, years	1.7 (0.6)	1.2 (0.7)	2.2 (0.3)	1.7 (0.6)

Data on age, education, and follow-up presented as mean (standard deviation). CN, cognitively normal controls, sMCI, stable mild cognitive impairment; pMCI, progressive mild cognitive impairment; AD, Alzheimer's disease.

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described and validated previously.[21,22] The biomarker data sets used in this study ("UPENNBIOMK5.csv" and "UPENNBIOMK6.csv") and additional analysis details and quality control procedures are available at http://adni.loni.usc.edu/. All CSF Aβ42 concentration data were anchored to the same baseline assay data set to enable use of the cutoff value for abnormal/normal Aβ42 status that were established and validated for that assay.[21] Full methodological details of this procedure are described at http://adni.loni.usc.edu. For each subject we used data from the first CSF analysis that could be merged with PET imaging data. We merged CSF and PET data by collapsing the measurements that were closest in time, restricted to lumbar punctures and PET measurements performed within 100 days of each other (mean difference 5 days, IQR: 1–10 days difference, max difference 97 days).

Statistical analyses

We performed several comparisons of the diagnostic performance of CSF and PET for CN versus AD, and for sMCI versus pMCI. The primary analysis was a comparison of diagnostic accuracy (area under the curve, AUC), which was done for CSF versus global or regional (temporal, frontal, parietal, and cingulate) PET.

Secondarily, we compared sensitivities and specificities for CSF and global PET. These were first compared at a priori cutoffs, using previously established cutoffs for AD (CSF Aβ42 192 ng/L and global PET florbetapir SUVr 1.11, normalized to whole cerebellum). Since these cutoffs were generated from different samples (only partly based on pathological diagnosis),[20,22–24] they may not be comparable. We therefore also compared sensitivities and specificities at cutoffs that were optimized for this study. Optimized cutoffs were defined using logistic regression models, where diagnosis was the response variable and a binary classifier (biomarker < cutoff) was the predicting variable (models adjusted for age and sex). The cutoff that resulted in the logistic regression model with highest AUC (mean of 10 cross-validation samples) was defined as the optimized cutoff.

For all measurements of diagnostic performance (AUC, sensitivity, and specificity) we used bootstrap ($N = 1000$ iterations) to estimate 95% confidence intervals (CI) for the difference of CSF and PET (mean difference $\pm$ 1.96 $\times$ SD). All analyses were adjusted for age and sex. All statistics were done in R (v.3.0.2, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study demographics are shown in Table 1. CSF and PET measurements are shown in Figure 1. As it is evident, CSF Aβ42 was lower, and florbetapir retention higher in both the AD and pMCI groups as compared with the CN and sMCI groups.

Overall diagnostic accuracies for CSF and PET were evaluated by AUC. The AUCs of CSF and PET (using either global or regional PET) were not significantly different, either for CN vs. AD or sMCI vs. pMCI (Table 2 and Fig. 2).

When tested at a priori cutoffs (CSF < 192 ng/L, PET > 1.11), the sensitivities of CSF and PET were not significantly different, either for CN versus AD (CSF 92.4%; PET 89.0%; difference CSF-PET [95% CI] −0.46% to 7.6%) or for sMCI versus pMCI (CSF 91.5%, PET 91.5%; difference CSF-PET [95% CI] −4.6% to 4.6%). The specificity was higher for PET in CN versus AD (CSF 56.8%, PET 70.4%; difference CSF-PET [95% CI] −21% to −6.6%), but did not differ significantly in sMCI versus pMCI (CSF 50.3%, PET 55.8%; difference CSF-PET [95% CI] −12% to 0.7%).

Optimized cutoffs were defined by logistic regression models, by maximizing AUC, as explained above. The highest accuracies were seen for cutoffs that were slightly different from the a priori cutoffs (Fig. 3). The optimized cutoffs were as follows: CSF Aβ42 < 157 ng/L in CN versus AD (AUC 85.3%), CSF Aβ42 < 174 ng/L in sMCI versus pMCI (AUC 76.5%), and PET florbetapir > 1.24 in both CN versus AD (AUC 86.8%) and in sMCI versus pMCI (AUC 80.9%). At these cutoffs, the sensitivities were not significantly different in CN versus AD (CSF 84.7%, PET 83.1%, difference CSF-PET [95% CI] −4.5% to 8.0%) or in sMCI vs. pMCI (CSF 88.1%, PET 81.4%: difference CSF-PET [95% CI] −3.4% to 16%). However, PET had greater specificity in both CN versus AD (CSF 75.7%, PET 81.7%; difference CSF-PET [95% CI] −11.2% to −0.91%) and in sMCI versus pMCI (CSF 60.6%, PET 74.5%; difference CSF-PET [95% CI] −20% to −7.8%). For prospective evaluation, we tested the optimized CSF Aβ42 cutoff from CN versus AD (<157 ng/L) in the sMCI vs. pMCI subjects. Compared to the 174 ng/L CSF cutoff, this had lower sensitivity (71.2%, not significantly different from PET, difference CSF-PET [95% CI] −23% to 1.8%) and higher specificity (70.9%, difference CSF-PET −9.8% to 4.6%).

As explained above, we excluded 16 CN subjects (five females, two *APOE* ε4+, mean age 76.3 [SD 7.5] years, mean education 15.6 [SD 3.2] years) who progressed to MCI ($N = 14$) or AD ($N = 2$) from all comparisons of diagnostic performance. Notably, these progressive CN subjects included both Aβ positive and Aβ negative subjects (six CSF and PET Aβ negative, seven CSF and PET Aβ positive, and three CSF negative but PET Aβ positive, Fig. 4).

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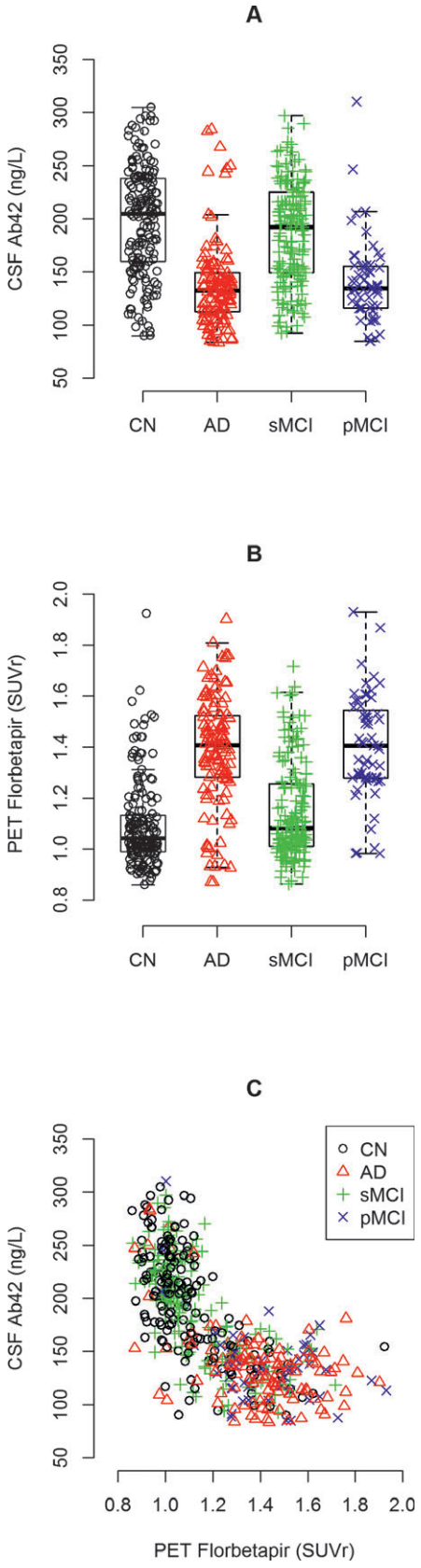

Figure 1. CSF Aβ42 and PET florbetapir. CSF Aβ42 (A) and global PET florbetapir SUVr (B) in different diagnostic groups, and matched CSF and PET data (C) in all diagnostic groups. All data were adjusted (residualized) for age and sex. In statistical comparisons (linear regressions with Aβ42 or SUVr as response and group [CN vs. AD, and sMCI vs. pMCI] as predictor, adjusted for age and sex), AD did always differ significantly from CN, and sMCI did always differ significantly from pMCI (all $P < 0.0001$). CSF, cerebrospinal fluid; PET, positron emission tomography; SUVr, standardized uptake value ratio; sMCI, stable mild cognitive impairment; pMCI, progressive mild cognitive impairment.

Table 2. Diagnostic accuracy of CSF Aβ42 and PET florbetapir (18F).

Measurement	AUC (%)	$AUC_{CSF} - AUC_{PET}$ (95% CI)
CN (n = 169) versus AD (n = 118)		
CSF Aβ42	84.4	NA
Global PET	86.9	−6.7 to 1.5
Temporal PET	86.9	−6.4 to 1.9
Frontal PET	87.3	−7.1 to 1.4
Parietal PET	86.4	−6.0 to 2.1
Cingulate PET	86.0	−5.0 to 2.5
sMCI (n = 165) versus pMCI (n = 59)		
CSF Aβ42	78.3	NA
Global PET	81.8	−8.3 to 1.6
Temporal PET	81.8	−7.7 to 2.7
Frontal PET	82.3	−8.8 to 1.0
Parietal PET	80.8	−7.5 to 2.4
Cingulate PET	81.8	−8.3 to 1.8

AUC were calculated using logistic regression models. Differences between AUC for CSF and PET were calculated using bootstrap. PET measurements were SUVr. For global PET, measurements were averaged from temporal, frontal, parietal, and cingulate regions, and divided by the measurement in whole cerebellum. For regional PET, measurement in respective region was divided with the measurement in whole cerebellum. All analyses were adjusted for age and sex. AUC, area under the curve; CSF, cerebrospinal fluid; PET, positron emission tomography; SUVr, standardized uptake value ratio.

Discussion

Although several studies have shown strong correlations between CSF Aβ42 and PET Aβ imaging,[7,13–19] this study is the first to directly compare their diagnostic performance for clinical AD. We compared the biomarkers both at optimized cutoff levels and (to avoid overfitting problems), at a priori defined cutoffs, established in independent study populations. We found that (1) the overall diagnostic accuracy, measured by AUC, was similar between CSF Aβ42 and (global or regional) PET florbetapir both for CN versus AD and sMCI versus pMCI, (2) the diagnostic sensitivity of the methods was similar, both when using a priori defined cutoffs and when optimizing cutoffs for this study sample, (3) the diagnostic specificity of the methods was often slightly higher for PET specificity (when using a priori cutoffs and optimized cutoffs),

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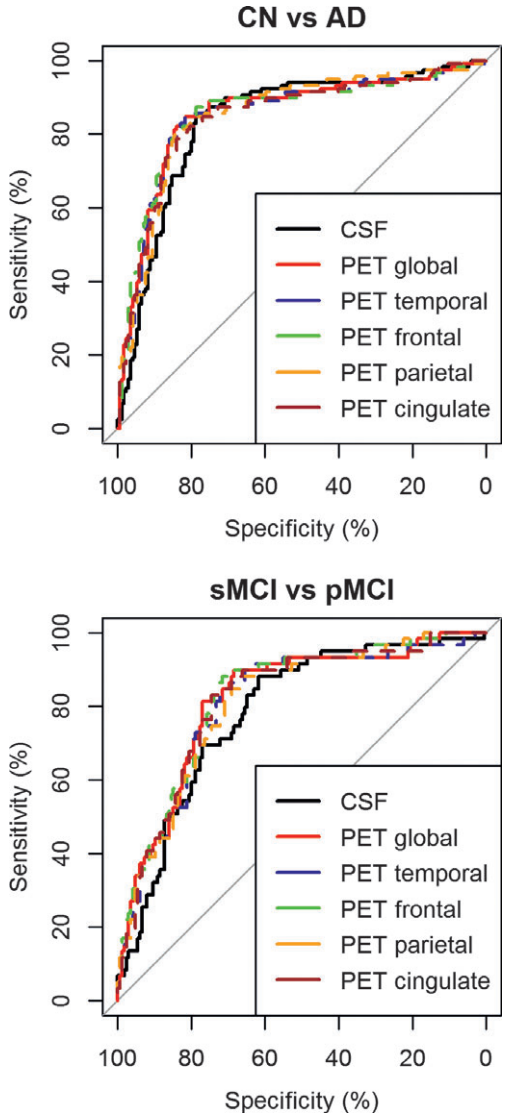

Figure 2. ROC plots. ROC plots for CSF Aβ42 and (global and regional) PET florbetapir SUVr, for CN versus AD (A) and sMCI versus pMCI (B). AUC data are available in Table 2. CSF, cerebrospinal fluid; SUVr, standardized uptake value ratio; sMCI, stable mild cognitive impairment; pMCI, progressive mild cognitive impairment; AD, Alzheimer's disease.

(4) the progressive CN group consists of both Aβ positive and Aβ negative subjects, where CSF and PET modalities were most often in agreement.

The finding that the overall accuracy was similar between CSF and PET is in line with previous studies showing strong correlations between the two biomarker modalities.[7,13–19] This indicates that CSF and PET Aβ biomarkers are overall equally associated with clinical AD, both at the dementia stage and at the MCI stage. The similar accuracy of CSF and regional PET is in agreement with previous data showing similar associations between CSF Aβ42 and PET Aβ in different brain regions.[7,19] Likewise, the finding that the methods' sensitivities were similar confirms the widely held but not previously tested belief that CSF Aβ42 and PET Aβ have similar capability to identify AD patients, both at dementia stage and at the early clinical stage, in MCI patients who later convert to AD.

The diagnostic specificities of the methods differed for most comparisons, with greater specificity for PET. This was caused by some CN and sMCI subjects who appear pathological using CSF Aβ42 but not using PET, which is consistent with previous observations.[13,15] This indicates that low CSF Aβ42 does not always translate to accumulation of fibrillar amyloid in the brain (or to subsequent cognitive decline). Another possibility, which has been suggested previously, is that low CSF Aβ42 in the absence of a positive PET scan may reflect the presence of diffuse Aβ deposits that bind amyloid ligands poorly.[15,25] Since diffuse Aβ deposits may not have a central role in the neuropathological changes of AD,[26] it is logical that a biomarker which partly reflects diffuse deposits (possibly CSF Aβ42) has lower specificity but equal sensitivity compared to a biomarker that mainly reflects fibrillar deposits (PET Aβ). Other causes of isolated low CSF Aβ42 are also possible, including increased peptide degradation, altered transport over the blood–brain barrier, and differences in the species of Aβ measured by PET versus ELISA or other immunoassays, although it is not known if this is important for the development of AD. Diseases that are associated with low CSF Aβ42 in the absence of Aβ plaque pathology include cerebrovascular disease, and neuroinflammatory and neuroinfectious conditions such as bacterial meningitis, HIV-associated dementia, and multiple sclerosis.[27,28] In these conditions, C-terminally truncated CSF Aβ peptides (e.g., Aβ38 and Aβ40) are also reduced, which is not the case in AD, and a ratio between CSF Aβ42 to Aβ40 may help to resolve this issue. Finally, it is also possible that preanalytical or analytical factors affecting the Aβ42 measurement may result in false low measurements. Ongoing development of novel measurement procedures may be useful to overcome this.[29,30] In sum, the existence of subjects who are CSF Aβ42 positive but PET Aβ negative warrants further study, especially long-term longitudinal studies with repeated biomarker assessments, to learn whether the lowering of CSF Aβ42 precedes PET positivity, or whether other factors underlie this discrepancy in amyloid biomarker outcome. Further comparative studies are also needed to determine the possible clinical implications of the greater specificity of PET Aβ seen here.

The ultimate diagnostic sensitivity and specificity depend on the choice of cutoff. The optimized CSF cutoffs (157 ng/L for CN vs. AD and 174 ng/L for sMCI vs.

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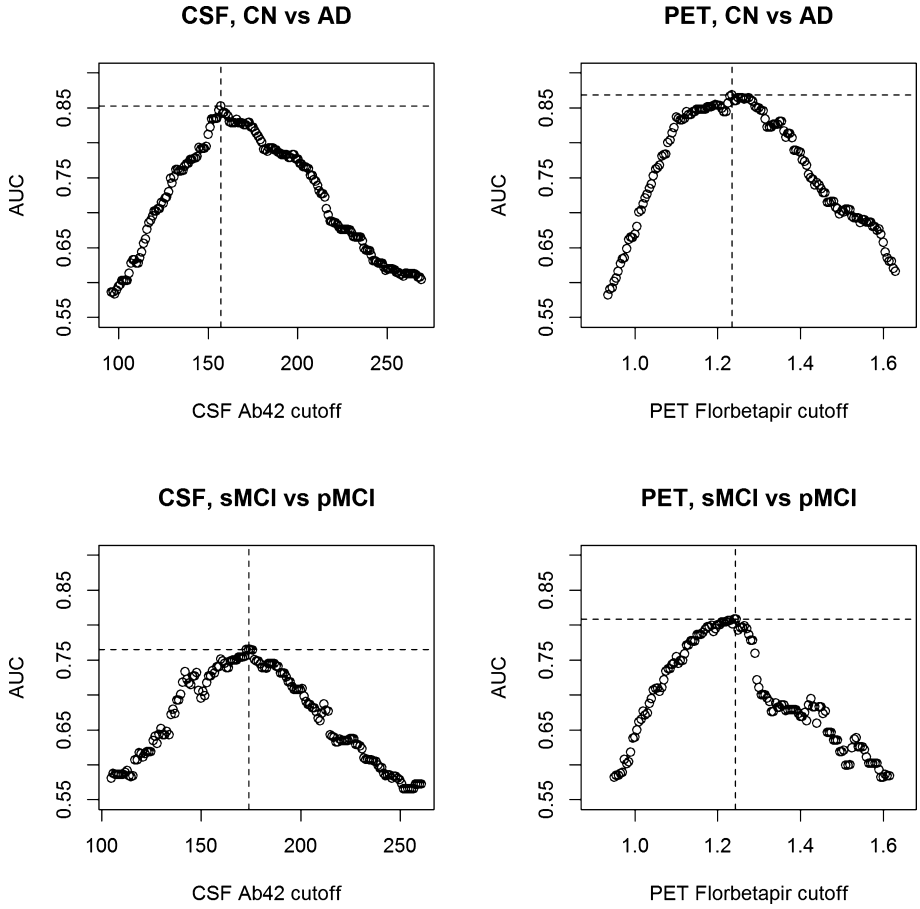

Figure 3. Optimized cutoffs. Plots of accuracy over a range of possible cutoffs for CSF Aβ42 and PET florbetapir, used to define optimized cutoffs. The AUCs (*y*-axes) are from logistic regression models with diagnostic group as response and a binary classifier (biomarker <> cutoff, *x*-axes) as predictor, adjusted for age and sex. AUC, area under the curve; CSF, cerebrospinal fluid; PET, positron emission tomography.

pMCI) were lower than the a priori cutoff (192 ng/L), and the optimized PET cutoff (1.24 SUVr for both CN vs. AD and sMCI vs. pMCI) were higher than the a priori cutoff (1.11), indicating that that the optimized cutoffs represented more severe Aβ pathology. Important confounders for study differences in cutoffs include age differences and delays between lumbar puncture and autopsy. The CSF Aβ42 192 ng/L cutoff was originally defined to maximize the accuracy in a cohort including 56 autopsy-confirmed AD cases and 52 age-matched living healthy controls.[22] The AD subjects in that study were on average 71 (SD 10) and the healthy controls were on average 70 (SD 10) years old at lumbar puncture, and the AD patients died at an average age of 77 (SD 10) years (L. M. Shaw, pers. commun. 2014). The time gap between lumbar puncture and death may have confounded the relationship between CSF Aβ42 and autopsy findings in AD (some subjects with brain Aβ plaques on autopsy may have lacked brain Aβ and corresponding low CSF Aβ42 at time of lumbar puncture). The PET florbetapir 1.11 cutoff was defined differently, using the confidence limit for the upper 5% of the distribution in 21 controls younger than 55 years.[23] This cutoff (originally 1.10, but later modified to 1.11[20]) also divided patients with "low likelihood AD" and "high likelihood AD" based on histopathology in an independent study of 35 subjects.[24] Since the subjects in this study were older than the subjects in the derivation studies, and since the prevalence of Aβ pathology increases rapidly with age,[31] the non-AD subjects in this study likely had higher prevalence of Aβ pathology than the controls in the derivation studies. This may have lowered the cutoff for CSF Aβ42 and increased the cutoff for PET Aβ to identify clinical AD. The main effect of changing from the a priori to the (more pathological) optimized cutoffs was improvement of diagnostic specificity, which was likely caused by greater prevalence of Aβ pathology among the controls in the present sample than in the derivation samples.

When comparing the diagnostic performance of CSF and PET we excluded 16 CN subjects who progressed

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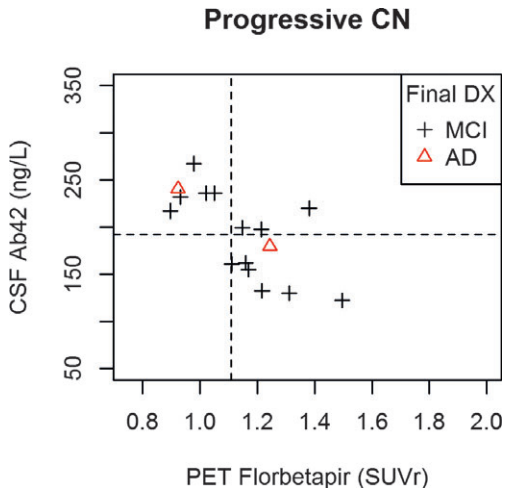

Figure 4. CSF Aβ42 and PET florbetapir in progressive controls. Matched CSF and PET data in the 16 CN who progressed to MCI or AD during follow-up. All data were adjusted (residualized) for age and sex. Dashed lines indicate the a priori cutoffs for CSF and PET Aβ measurements. CSF, cerebrospinal fluid; PET, positron emission tomography; MCI, mild cognitive impairment; AD, Alzheimer's disease.

clinically to MCI or AD during follow-up, in order to keep the CN group as AD free as possible. However, in an exploratory analysis, we found no clear preference for Aβ positivity in these subjects (Fig. 4; note that three subjects were CSF-PET discordant, and were PET positive, which argues against the notion that CSF positivity precedes PET positivity). Thus, controls that develop cognitive impairment within a few years may be Aβ negative at baseline, independent of biomarker modality. This finding does not necessarily contradict previous findings that Aβ positivity is associated with future cognitive impairment in healthy controls, since the proportion of Aβ positive people who decline cognitively may still be larger than the proportion of Aβ negative people who decline cognitively.[8,9,32,33] However, it does support the notion that Aβ positivity is not a necessary requirement for development of amnestic cognitive impairment.[34] At this point, it is not certain to what degree this impairment is related to AD, since the CN who progressed to MCI may have other underlying neurodegenerative diseases. Two CN subjects progressed to AD dementia, one of them was Aβ positive at baseline and the other was Aβ negative.

The main limitation of this study was the lack of autopsy confirmation of Aβ pathology. We only tested the associations between the biomarkers and clinical AD diagnosis, and it is possible that some of the AD subjects were clinically misdiagnosed with AD, and that some of the controls had nonsymptomatic AD pathology. Another limitation of this study was the short clinical follow-up time. Although we established that the overall diagnostic accuracies of CSF and PET Aβ were similar, especially regarding sensitivity for clinical AD, it remains difficult to interpret Aβ positivity among the CN and sMCI subjects. Although these subjects are "falsely positive" with regard to the currently available clinical information, several studies have shown that Aβ-positive healthy controls have increased risk of future cognitive impairment and development of AD, compared to Aβ negative subjects.[8,9,32,33] Thus, we believe it is likely that Aβ positivity among CN and sMCI in this study is an early biomarker sign of AD, and some – but not necessarily all – of these subjects may go on to develop clinical signs of AD if followed up for several more years.[35,36] It would be interesting to perform longitudinal studies comparing the performance of CSF and PET to predict development of MCI or AD in people who are cognitively healthy at baseline. This would test the novel proposed research criteria for preclinical AD,[10–12,37] which are not taken into account with this study design. This study only included CSF Aβ42, and it is likely that the diagnostic performance of CSF biomarkers increases by including also CSF tau measures (the diagnostic performance of imaging measures is likely also increased by combining PET imaging with other imaging modalities, such as structural MRI). Future studies could also test the importance of *APOE ε4* genotype on these comparisons.

To conclude, the overall diagnostic performance of CSF Aβ42 and PET Aβ to identify clinical AD is similar, but PET has greater specificity in several settings. Other factors than diagnostic performance, including costs, side effects, training and willingness among clinicians to perform lumbar punctures, availability of cyclotrons and PET scanners, and willingness of payers to reimburse different procedures, should also be considered when determining the optimal modality for research, drug trials, and clinical diagnostics.

Acknowledgments

Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace Inc., Merck and Co. Inc., Novartis AG, Pfizer Inc., F. Hoffman-La Roche, Schering-Plough, Synarc Inc., as well as nonprofit partners the Alzheimer's

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Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (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 California, Los Angeles. This research was also supported by NIH grants P30 AG010129 and K01 AG030514, the Swedish Research Council, Goteborgs Lakaresallskap, Svenska Lakaresallskapet, Sahlgrenska Universitetssjukhuset, Carl-Bertil Laurells fond, and Klinisk Biokemi i Norden. N. M. 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. No sponsor had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of Interest

N. M., P. I., S. L., and H. Z. report no conflicts of interest. W. J. serves as a consultant to Synarc, Inc. and Genentech. L. M. S. previously was consultant for Innogenetics and collaborates on quality assessment activities as part of the Alzheimer's Disease Neuroimaging Initiative; and serves as a consultant to Janssen AI R & D on biomarker studies. J. Q. T. 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; and is the William Maul Measey-Truman G. Schnabel, Jr., M.D. Professor of Geriatric Medicine and Gerontology. K. B. has served at Advisory Boards for Pfizer, Roche, Kyowa Kirin Pharma and Innogenetics. M. W. has been on scientific advisory boards for Pfizer and BOLT International; has been a consultant for Pfizer Inc., Janssen, KLJ Associates, Easton Associates, Harvard University, inThought, INC Research, Inc., University of California, Los Angeles, Alzheimer's Drug Discovery Foundation and Sanofi-Aventis Groupe; has received funding for travel from Pfizer, AD PD meeting, Paul Sabatier University, Novartis, Tohoku University, MCI Group, France, Travel eDreams, Inc., Neuroscience School of Advanced Studies (NSAS), Danone Trading, BV, CTAD ANT Congres; serves as an associate editor of Alzheimer's & Dementia; has received honoraria from Pfizer, Tohoku University, and Danone Trading, BV; has research support from Merck, Avid, DOD and VA; and has stock options in Synarc and Elan.

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