Neuroimaging

Using florbetapir positron emission tomography to explore cerebrospinal fluid cut points and gray zones in small sample sizes

Philip S. J. Weston, Ross W. Paterson, Marc Modat, Ninon Burgos, Manuel J. Cardoso, Nadia Magdalino, Manja Lehmann, John C. Dickson, Anna Barnes, Jamshed B. Bomanji, Irfan Kayani, David M. Cash, Sebastien Ourselin, Jamie Toombs, Michael P. Lunn, Catherine J. Mummery, Jason D. Warren, Martin N. Rossor, Nick C. Fox, Henrik Zetterberg, Jonathan M. Schott

Abstract

Introduction: We aimed to assess the feasibility of determining Alzheimer's disease cerebrospinal fluid (CSF) cut points in small samples through comparison with amyloid positron emission tomography (PET).

Methods: Twenty-three individuals (19 patients, four controls) had CSF measures of amyloid beta (Aβ1–42) and total tau/Aβ1–42 ratio, and florbetapir PET. We compared CSF measures with visual and quantitative (standardized uptake value ratio [SUVR]) PET measures of amyloid.

Results: Seventeen of 23 were amyloid-positive on visual reads, and 14 of 23 at an SUVR of ≥1.1. There was concordance (positive/negative on both measures) in 20 of 23, of whom 19 of 20 were correctly classified at an Aβ1–42 of 630 ng/L, and 20 of 20 on tau/Aβ1–42 ratio (positive ≥0.88; negative ≤0.34). Three discordant cases had Aβ1–42 levels between 403 and 729 ng/L and tau/Aβ1–42 ratios of 0.54–0.58.

Discussion: Comparing amyloid PET and CSF biomarkers provides a means of assessing CSF cut points in vivo, and can be applied to small sample sizes. CSF tau/Aβ1–42 ratio appears robust at predicting amyloid status, although there are gray zones where there remains diagnostic uncertainty.

Keywords: Cerebrospinal fluid; Amyloid PET; Aβ; Tau; Phosphorylated tau; Cut points; Diagnosis

1. Introduction

Molecular biomarkers are increasingly used to improve diagnostic accuracy in Alzheimer’s disease (AD) [1]. In AD, cerebrospinal fluid (CSF) amyloid beta (Aβ)1–42 and Aβ1–42/Aβ1–40 ratio are reduced, and total tau/Aβ1–42 ratio and phosphorylated tau (p-tau) both elevated [2]. For these continuous measures to be used diagnostically, dichotomized cut points are often used to define individuals as “AD-positive” or “AD-negative.” Determining such cut points in vivo is not straightforward. It is rarely feasible to seek autopsy confirmation of the presence/absence of AD pathology close to the time of CSF sampling, as has been done for amyloid positron emission tomography (PET).
CSF is typically calibrated against clinical conversion to AD dementia, or in patients versus controls. However, a clinical diagnosis of AD is inaccurate in a proportion of cases, and a proportion of apparently healthy elderly individuals have CSF changes consistent with AD. There is considerable between-center variability in CSF assays, and results can be influenced by sample handling. Finally, although dichotomization may be helpful diagnostically, a single cut point is unlikely to be biologically plausible and requires a trade-off between sensitivity and specificity. Perhaps as a result of these factors, CSF biomarker cut points vary widely between centers.

Several studies have used data-driven analyses to determine optimal cut points, with one recent large study reporting tau/AB$_{1–42}$ > 0.52 to be the single best discriminator, but such approaches are dependent on large sample sizes, usually derived from several centers. How best to determine cut points in individual centers, where recruiting large cohorts is impractical, is less clear. One approach is to compare CSF with other AD molecular biomarkers, such as amyloid PET, now licensed but not yet widely used in routine clinical practice. Visual assessment of F18 florbetapir amyloid PET correlates closely with Aβ deposition at autopsy. Fibrillar Aβ load can be quantified, usually as a standardized uptake value ratio (SUVR) of cortical regions of interest to a reference region (e.g., cerebellum). Previous studies have shown CSF and florbetapir amyloid measures to have similar diagnostic sensitivities. CSF Aβ$_{1–42}$ and florbetapir PET SUVRs correlate closely, particularly at the mid-range of values where cut points are likely to lie, and comparisons between the two have been used to assess potential cut points in a large cohort of patients with mild cognitive impairment (MCI).

We aimed to assess whether comparing CSF and PET biomarkers might provide a means of determining local CSF cut points in relatively small, clinically diverse samples.

2. Methods

We recruited 23 individuals: 19 patients with a range of dementia syndromes and four healthy controls. As part of their clinical evaluation, each had a diagnostic lumbar puncture, with CSF samples obtained using a 22G Quincke needle. Optimum CSF handling and transfer procedures were used. Each sample was analyzed for Aβ$_{1–42}$, total tau, and p-tau using INNOTEST enzyme-linked immunosorbent assays (Fujirebio, Ghent, Belgium). Although not in routine clinical use at our center, we also measured Aβ$_{1–40}$. We preferentially chose individuals with CSF Aβ$_{1–42}$ levels in a potential border zone range of 400–700 pg/mL. Each patient’s cognition was assessed using the Addenbrook’s Cognitive Examination III, scored out of 100.

Each patient had an F18 florbetapir PET scan on a Siemens 3-T PET/MR unit, with a 50-minute dynamic acquisition commencing immediately after intravenous injection of 370 MBq of florbetapir. A volumetric T1-weighted MRI scan was acquired concurrently. Attenuation correction was performed using synthetic computed tomographies (CTs) generated from the MR images. A single static PET image, reconstructed from the last 10 minutes of the PET acquisition, was used for the analysis. PET images were registered to the MRI and segmented using a semiautomated parcellation tool.

The four age-matched healthy controls previously had a florbetapir PET/CT scan as part of another study, with a separate T1-weighted MRI acquisition. These images were processed in the same way as described previously, excluding the generation of synthetic CTs. Clinical studies were approved by the Queen Square Research Ethics Committee.

PET images were analyzed in two ways. First, three trained nuclear medicine physicians blinded to the clinical diagnosis visually rated the images positive/negative according to clinical criteria. Second, an SUVR was calculated by comparing uptake in six predefined cortical regions to the whole cerebellum. A positive/negative SUVR cutoff of 1.10 was used as described.

Statistical analyses were performed in STATA version 12.0 (College Station, TX, USA). Independent of clinical diagnosis, we compared CSF Aβ$_{1–42}$, Aβ$_{1–42}$/Aβ$_{1–40}$, tau/Aβ$_{1–42}$, and p-tau in subjects rated amyloid positive/negative on visual reads, and based on SUVR. Linear regression was used to assess the relationship between CSF and SUVR, covarying for the interval between lumbar puncture and PET.

A secondary analysis compared amnestic and nonamnestic AD clinical syndromes for each of the CSF biomarkers.

3. Results

Patients and controls were well matched for age (63.7 ± 7.6 vs. 62.9 ± 7.0). Nine patients had amnestic and 10 nonamnestic (five posterior cortical atrophy, four progressive aphasia, and one behavioral) clinical syndromes (Table 1). CSF examination was done before scanning, with a median delay of 145 days (range, 32–427). Across all subjects, CSF Aβ$_{1–42}$ ranged from 343 to 1199 ng/L, tau/Aβ$_{1–42}$ 0.11–2.54, and p-tau 14–227 g/L.

Seventeen of 23 participants were rated as amyloid-positive on visual assessment. SUVRs ranged from 0.87 to 1.66. At an SUVR cutoff of 1.10, 14 of 23 were amyloid-positive. Comparing SUVR and clinical reads, 20 were concordant (14 positive, six negative); and three discordant (Fig. 1, Table 2). The discordant group all had positive amyloid reads, negative SUVRs (0.88, 1.05, and 1.03), and tau/Aβ ratios between 0.54 and 0.58.

The SUVR correlated with CSF Aβ$_{1–42}$ ($R^2 = 0.26$, $P = .013$), CSF Aβ$_{1–42}$/Aβ$_{1–40}$ ($R^2 = 0.32$, $P = .033$), CSF tau/Aβ$_{1–42}$ ($R^2 = 0.47$, $P < .001$), and CSF p-tau ($R^2 = 0.34$, $P = .005$), with no evidence for an influence of duration between CSF sampling and scanning.

At a CSF tau/Aβ$_{1–42}$ ratio cut point of 0.52, the sensitivity and specificity for a positive amyloid scan based on
Table 1
Clinical details for each of the 19 patients

| Patient ID | Age at LP | Clinical presentation | IWG-2 criteria | Coexisting pathology | ACE-III score |
|------------|-----------|-----------------------|----------------|----------------------|--------------|
| 1          | 67.9      | PCA Atypical          | No             | 31                   |              |
| 2          | 59.5      | PCA Atypical          | No             | 67                   |              |
| 3          | 67.6      | PPA (logopenic)       | Atypical       | 30                   |              |
| 4          | 63.0      | Amnestic              | —              | No                   | 86           |
| 5          | 60.0      | PPA (logopenic)       | Atypical       | No                   | 40           |
| 6          | 61.2      | AD (t) Typical        | No             | 62                   |              |
| 7          | 69.0      | PCA                   | Atypical       | Mild SVD             | 58           |
| 8          | 80.0      | Amnestic              | Typical        | No                   | 86           |
| 9          | 70.9      | Frontal Atypical      | No             | 54                   |              |
| 10         | 57.9      | PPA (logopenic)       | —              | No                   | 93           |
| 11         | 67.0      | PCA                   | Atypical       | No                   | 61           |
| 12         | 64.9      | Amnestic              | Typical        | No                   | 86           |
| 13         | 57.9      | Amnestic              | Typical        | No                   | 24           |
| 14         | 59.3      | Amnestic              | Typical        | No                   | 45           |
| 15         | 79.7      | PCA                   | Atypical       | Positive VGKC        | 69           |
| 16         | 56.5      | Amnestic              | Typical        | No                   | 49           |
| 17         | 57.1      | Amnestic              | Typical        | No                   | 31           |
| 18         | 51.7      | Amnestic              | Typical        | No                   | 64           |
| 19         | 58.9      | PPA—nonfluent         | Atypical       | No                   | 70           |

Abbreviations: ACE-III, Addenbrooke’s Cognitive Examination III; PCA, posterior cortical atrophy; PPA, primary progressive aphasia; AD, Alzheimer’s disease; SVD, small vessel disease; VGKC, voltage-gated potassium channel complex antibodies.

NOTE. For the two patients who were florbetapir negative (on visual read), and so do not satisfy criteria for AD, the IWG-2 column is marked with a “—”.

Although the concordant cases produced relatively clear cut points, the three discordant cases showed considerable overlap between the positive/negative ranges for $\text{A}_\beta_{1-42}$ (403–729 ng/L) and p-tau (26–49 ng/L). The tau/$\text{A}_\beta_{1-42}$ ratios for all three cases were remarkably similar, and in a “gray zone” between 0.54 and 0.58, very close to the previously proposed optimal cut off (0.52) [9]. Although a tau/$\text{A}_\beta_{1-42}$ ratio of 0.52 had very good sensitivity/specifcity for determining amyloid status, these results suggest that rather than a strict dichotomy, introducing a gray zone (e.g., 0.5–0.6) might be more appropriate. However, the significantly narrower gray zone for tau/$\text{A}_\beta_{1-42}$ than for the other CSF measures assessed is consistent with previous findings that this is likely to be the most robust marker for underlying AD pathology [9,22]. $\text{A}_\beta_{1-42}/\text{A}_\beta_{1-40}$ has until now been used less commonly in clinical practice than the other markers but does appear to potentially provide more precise separation of AD-positive and AD-negative cases compared with $\text{A}_\beta_{1-42}$ alone [23]. However, the overlap in $\text{A}_\beta_{1-42}/\text{A}_\beta_{1-40}$ values between the PET concordant and PET discordant groups would suggest, consistent with findings from other studies [9], that $\text{A}_\beta_{1-42}/\text{A}_\beta_{1-40}$ may not be as reliable a marker as tau/$\text{A}_\beta_{1-42}$.

4. Discussion

As more centers use CSF examination in the investigation of cognitive impairment, local validation of cut points becomes increasingly necessary. Our results show that combining amyloid biomarkers may be a useful means of establishing such cut points. As shown in previous studies [12,19], there was good correlation between CSF and PET measures of $\text{A}_\beta$, noting that we selected individuals in the mid-range of values where linear associations are more likely [11]. When comparing the two methods for determining amyloid positivity, there were some discordant cases—it is not clear whether these reflect misreading by experts, errors in the methodology to calculate the SUVRs, that the SUVR cut point is incorrect [20], or true biological uncertainty. It is notable that in two of the three cases with positive clinical reads but negative SUVR, the latter was close to the cut off of 1.10 (1.03 and 1.05, respectively) and that more consistent relationships between PET amyloid load and CSF were observed using the visual reads.

Considering only individuals with concordant positive/ negative PET clinical reads and SUVRs, there was almost complete separation (19 of 20 correctly classified) at a CSF $\text{A}_\beta_{1-42}$ of 630 ng/L and there was perfect separation on tau/$\text{A}_\beta_{1-42}$ ratio (positive: ≥0.88, negative: ≤0.34), $\text{A}_\beta_{1-42}/\text{A}_\beta_{1-40}$ ratio (positive: ≤0.13, negative: ≥0.14 ng/L), and p-tau (positive: ≥49, negative: ≤40 ng/L). A CSF $\text{A}_\beta_{1-42}$ cutoff of ~630 ng/L is very similar to those proposed by other recent studies [13,21] and our results are consistent with a previously determined optimal tau/$\text{A}_\beta_{1-42}$ cut point [9], supporting the use of this methodology to produce valid cut points in small samples.

Although the concordant cases produced relatively clear cut points, the three discordant cases showed considerable overlap between the positive/negative ranges for $\text{A}_\beta_{1-42}$ (403–729 ng/L) and p-tau (26–49 ng/L). The tau/$\text{A}_\beta_{1-42}$ ratios for all three cases were remarkably similar, and in a “gray zone” between 0.54 and 0.58, very close to the previously proposed optimal cut off (0.52) [9]. Although a tau/$\text{A}_\beta_{1-42}$ ratio of 0.52 had very good sensitivity/specifcity for determining amyloid status, these results suggest that rather than a strict dichotomy, introducing a gray zone (e.g., 0.5–0.6) might be more appropriate. However, the significantly narrower gray zone for tau/$\text{A}_\beta_{1-42}$ than for the other CSF measures assessed is consistent with previous findings that this is likely to be the most robust marker for underlying AD pathology [9,22]. $\text{A}_\beta_{1-42}/\text{A}_\beta_{1-40}$ has until now been used less commonly in clinical practice than the other markers but does appear to potentially provide more precise separation of AD-positive and AD-negative cases compared with $\text{A}_\beta_{1-42}$ alone [23]. However, the overlap in $\text{A}_\beta_{1-42}/\text{A}_\beta_{1-40}$ values between the PET concordant and PET discordant groups would suggest, consistent with findings from other studies [9], that $\text{A}_\beta_{1-42}/\text{A}_\beta_{1-40}$ may not be as reliable a marker as tau/$\text{A}_\beta_{1-42}$.

The gold standard for setting cut points to dichotomize any surrogate biomarker of a continuous biological variable would be to calibrate the cut points against direct measurements of the pathologic entity in question; in this case, brain amyloid and tau. However, the only available method of directly measuring these proteins in the brain is to perform an autopsy. Collecting CSF in a cohort of end-of-life patients to then validate postmortem is not straightforward, and it is unlikely to be feasible to collect sufficient numbers of samples in a relevant time frame in any individual center. In the absence of postmortem pathologic confirmation of diagnosis, we, like a number of other centers, have previously tried to determine individuals with AD or non-AD pathology based on clinical diagnosis, and defined cut points accordingly [9]. However, the clinical diagnosis of AD is known to be unreliable [5],
particularly in clinically atypical syndromes, which can be caused by a number of different distinct underlying pathologies [24,25]. An alternative approach has been to measure CSF degenerative markers in individuals with MCI and then follow-up individuals to find the cut points separating those who do and do not convert to dementia [9]. However, this approach requires large numbers of patients followed over several years making it not feasible for single centers; furthermore, it addresses a related but slightly different clinical questions, i.e., the determination of amyloid-positive individuals versus controls or individuals with non-AD MCI rather than between individuals with AD and non-AD dementias. The unreliability of clinical diagnosis, combined with the variation in assays used, is likely to contribute to the very significant differences between centers with regard to the cut points they use, as exemplified in a recent multicenter study where individual centers’ cut points for CSF Aβ1–42 varied by over 400 ng/L, from 192 ng/L to 638 ng/L [8]. These differences may also be compounded by the fact that there is no perfect statistical method for determining cut points, which in the absence of a gold-standard with which to compare is inevitably a trade-off between sensitivity and specificity [26]. Unlike CSF measurements, amyloid PET has been validated against postmortem data [3,4]. Comparing local CSF cut points against a validated in-vivo measure of AD pathology, particularly in clinically atypical syndromes, which can be caused by a number of different distinct underlying pathologies [24,25]. An alternative approach has been to measure CSF degenerative markers in individuals with MCI and then follow-up individuals to find the cut points separating those who do and do not convert to dementia [9]. However, this approach requires large numbers of patients followed over several years making it not feasible for single centers; furthermore, it addresses a related but slightly different clinical questions, i.e., the determination of amyloid-positive individuals versus controls or individuals with non-AD MCI rather than between individuals with AD and non-AD dementias. The unreliability of clinical diagnosis, combined with the variation in assays used, is likely to contribute to the very significant differences between centers with regard to the cut points they use, as exemplified in a recent multicenter study where individual centers’ cut points for CSF Aβ1–42 varied by over 400 ng/L, from 192 ng/L to 638 ng/L [8]. These differences may also be compounded by the fact that there is no perfect statistical method for determining cut points, which in the absence of a gold-standard with which to compare is inevitably a trade-off between sensitivity and specificity [26]. Unlike CSF measurements, amyloid PET has been validated against postmortem data [3,4]. Comparing local CSF cut points against a validated in-vivo measure of AD pathology,
such as amyloid PET, is, therefore, likely to provide more robust cut points than using clinical diagnoses alone, without the necessity for postmortem examination. The findings of the study have contributed to a change in CSF cut points at our center.

All amyloid-positive individuals in our study had dementia, thus fulfilling IWG-2 criteria for AD [27]. The criteria also allow for patients to be divided according to their clinical presentation into either typical (amnestic) or atypical (nonamnestic) subgroups. Our study includes a relatively even mixture of typical and atypical cognitive syndromes (Table 1); and in those with biomarker evidence for AD, a mixture of those with IWG-2 typical and atypical AD. When comparing the amnestic and nonamnestic AD cases, there was no evidence of any difference in CSF Aβ or total tau (Fig. 2). There was a suggestion of higher p-tau in typical AD compared with atypical AD, although this only reached trend significance. Although given the small numbers in each of the subgroups, any comparisons should be interpreted with caution; this finding is, however, consistent with previous work performed in larger samples [28]. When assessing all participants together, the p-tau cut point we determined (described previously) is somewhat lower than typically used, perhaps reflecting that a significant proportion of our patients had atypical, nonamnestic presentations.

This study has a number of limitations. The sample size is small, although in keeping with our aim to assess methods for determining cut points in samples appropriate for single centers. There were in some cases significant delays between the CSF and PET scan, although there was no evidence that this influenced the relationship between the two measures; and pragmatically, the fact that delays of some months between CSF and PET do not have a significant influence means that applying this approach in other clinical centers is more feasible. All the patients were scanned on the same PET/MR unit, whereas the controls were scanned on a PET/CT. However, all the controls were very clearly and consistently amyloid negative based on visual read, SUVR, and Aβ1–42, suggesting that this is unlikely to have influenced results; and a previous large study has demonstrated excellent concordance between SUVR measurements made in different centers and pipelines [11]. Finally, although amyloid PET correlates well with postmortem pathologic findings, without autopsy confirmation, the true amyloid burden for the individuals in this study is unknown.

5. Conclusions

Comparing amyloid PET and CSF biomarkers provides a means of assessing CSF cut points in vivo, and can be applied to small sample sizes. Although in unequivocal cases, a CSF Aβ1–42 cut point of ~630 ng/L and tau/Aβ1–42 ratio of ~0.52 provide good group separation, these data provide evidence that incorporating biomarker gray zones (e.g., 0.5–0.6 for tau/Aβ1–42 ratio) may be more biologically plausible.
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Research in Context

1. Systematic review: The authors used PubMed to review the literature pertaining to cerebrospinal fluid (CSF) cut points and, in particular, (1) what methods have been used to determine cut points and (2) what the optimum cut points are thought to be.

2. Interpretation: Our results demonstrate the value of comparing CSF and positron emission tomography biomarkers in relatively small cohorts to assess local CSF cut points. In keeping with previous studies, the tau:amyloid beta42 ratio was found to be the most robust CSF measure. Although cut points have utility in clinical practice, these data show that in some cases there may be discordance, suggesting the need for biomarker gray zones to reflect diagnostic uncertainty.

3. Future directions: Replication of our approach to determine CSF cut points in other centers will provide further validation. Other future studies should aim to further assess and quantify CSF biomarker gray zones to improve understanding of how best to incorporate these in to clinical practice.

References

[1] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011;7:263–9.
[2] Blennow K, Hampel H. CSF markers for incipient Alzheimer’s disease. Lancet Neurol 2003:2:605–13.
[3] Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 2011:305:275–83.
[4] Sabri O, Sabbagh MN, Seibyl J, Barthel H, Akatsu H, Ouchi Y, et al. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer disease: Phase 3 study. Alzheimers Dement 2015:11:964–74.
[5] Gearing M, Mirra SS, Hedreen JC, Sami SM, Hansen LA, Heyman A. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part X. Neuropathology confirmation of the clinical diagnosis of Alzheimer’s disease. Neurology 1995;45:461–6.
[6] Schott JM, Bartlett JW, Fox NC, Barnes J. Alzheimer’s Disease Neuroimaging Initiative Investigators. Increased brain atrophy rates in cognitively normal older adults with low cerebrospinal fluid Abeta 42. Ann Neurol 2010;68:825–34.
[7] Mattsson N, Andreasson U, Persson S, Carrillo MC, Collins S, Chalbot S, et al. CSF biomarker variability in the Alzheimer’s Association quality control program. Alzheimers Dement 2013;9:251–61.
[8] Yos SJ, Verhey F, Frolich L, Kornhuber J, Wiltfang J, Maier W, et al. Prevalence and prognosis of Alzheimer’s disease at the mild cognitive impairment stage. Brain 2015;138:1327–38.
[9] Duits FH, Tennissen CE, Bouwman FH, Visser PJ, Mattsson N, Zetterberg H, et al. The cerebrospinal fluid “Alzheimer profile”: Easily said, but what does it mean? Alzheimers Dement 2014;10:713–723.
[10] Mattsson N, Insel PS, Donohue M, Landau S, Jagust WJ, Shaw LM, et al. Independent information from cerebrospinal fluid amyloid-beta and florbetapir imaging in Alzheimer’s disease. Brain 2015;138:772–83.
[11] Toledo JB, Bjerke M, Da X, Landau SM, Foster NL, Jagust W, et al. Nonlinear association between cerebrospinal fluid and Florbetapir F-18 beta-amyloid measures across the spectrum of Alzheimer disease. JAMA Neurol 2015;72:571–81.
[12] Landau SM, Lu M, Joshi AD, Pontecorvo M, Mintun MA, Trojanowski JQ, et al. Comparing positron emission tomography imaging and cerebrospinal fluid measurements of beta-amyloid. Ann Neurol 2013;74:826–36.
[13] Palmqvist S, Zetterberg H, Blennow K, Vestberg S, Andreasson U, Brooks DJ, et al. Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid beta-amyloid 42: A cross-validation study against amyloid positron emission tomography. JAMA Neurol 2014;71:1282–9.
[14] Vanderstichele H, Bibl M, Engelborghs S, Le Bastard N, Lewczuk P, Molinuevo JL, et al. Standardization of preanalytical aspects of cerebrospinal fluid biomarker testing for Alzheimer’s disease diagnosis: A consensus paper from the Alzheimer’s Biomarkers Standardization Initiative. Alzheimers Dement 2012;8:65–73.
[15] Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR. Validation of the Addenbrooke’s Cognitive Examination III in frontotemporal dementia and Alzheimer’s disease. Dement Geriatr Cogn Disord 2013;36:242–50.
[16] Burgos N, Cardoso MJ, Thielemans K, Modat M, Dickson J, Schott JM, et al. Multi-contrast attenuation map synthesis for PET/ MR scanners: Assessment on FDG and Florbetapir PET tracers. Eur J Nucl Med Mol Imaging 2015;42:1447–58.
[17] Cardoso MJ, Wolz R, Modat M, Fox NC, Rueckert D, Ourselin S. Geodesic information flows. Med Image Comput Comput Assist Interv 2012;15:262–70.
[18] Joshi AD, Pontecorvo MJ, Clark CM, Carpenter AP, Jennings DL, Sadowsky CH, et al. Performance characteristics of amyloid PET with florbetapir F 18 in patients with Alzheimer’s disease and cognitively normal subjects. J Nucl Med 2012;53:378–84.
[19] Hake A, Trzepacz PT, Wang S, Yu P, Case M, Hochstetler H, et al. Florbetapir positron emission tomography and cerebrospinal fluid biomarkers. Alzheimers Dement 2015:11:986–93.
[20] Villeneuve S, Rabinovici GD, Cohn-Sheehy BI, Madison C, Ayakta N, Ghosh PM, et al. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: Statistical and pathological evaluation. Brain 2015;138:2020–33.

[21] Zwan M, van Harten A, Ossenkoppele R, Bouwman F, Teunissen C, Adriaanse S, et al. Concordance between cerebrospinal fluid biomarkers and [11C]PIB PET in a memory clinic cohort. J Alzheimers Dis 2014;41:801–7.

[22] Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. Arch Neurol 2007;64:343–9.

[23] Slaets S, Le Bastard N, Martin JJ, Sleegers K, Van Broeckhoven C, De Deyn PP, et al. Cerebrospinal fluid Abeta1–40 improves differential dementia diagnosis in patients with intermediate P-tau181P levels. J Alzheimers Dis 2013;36:759–67.

[24] Rohrer JD, Schott JM. Primary progressive aphasia: Defining genetic and pathological subtypes. Curr Alzheimer Res 2011;8:266–72.

[25] Crutch SI, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. Lancet Neurol 2012;11:170–8.

[26] Bartlett JW, Frost C, Mattsson N, Skillback T, Blennow K, Zetterberg H, et al. Determining cut-points for Alzheimer’s disease biomarkers: Statistical issues, methods and challenges. Biomark Med 2012;6:391–400.

[27] Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer’s disease: The IWG-2 criteria. Lancet Neurol 2014;13:614–29.

[28] Paterson RW, Toombs J, Slattery CF, Nicholas JM, Andreasson U, Magdalinou NK, et al. Dissecting IWG-2 typical and atypical AD: insights from cerebrospinal fluid analysis. J Neurol 2015. In Press.