Characterization and optimized measurement of longitudinal PiB changes by accurate sampling and quantification for clinical trials

Lisa Mosconi1,2,3, PhD, Dawn Matthews1,2, MS, Randolph Andrews1,2, MS, Enchi Liu4, PhD, Mark Schmidt5, MD, and ADNI
1Abiant, Inc., Grayslake, IL, 2 ADM Diagnostics LLC, Chicago, IL, 3 New York University School of Medicine, NY, 4 Janssen Alzheimer Immunotherapy, South San Francisco, CA, 5Janssen Research and Development, Beerse, Belgium

Background

Disease burden from Alzheimer’s disease (AD) is expected to rise rapidly in the next decades and the need for new treatments is urgent. Amyloid-beta (Ab) plaques are a hallmark of AD pathology and Ab accumulation is an early event in AD. Many amyloid-removal agents are currently being developed and tested and imaging endpoints, especially by use of Positron Emission Tomography (PET) with Ab radiotracers, now appear in many therapeutic trials. The use of Ab-PET endpoints to evaluate AD therapeutics requires an understanding of amyloid progression rates within the target population, and the impact of sampling methods. As such, a fair and data processing and analysis is raised and particular attention must be given to technical sources of variability or noise that could obscure a treatment signal. For more rigor must be applied to image analysis, sampling and quantitation.

Objectives

The goal of this study was to characterize and maximize detection of longitudinal changes in 11C-PiB, the most widely used Ab-PET tracer so far, in a multi-center setting using accurate sampling techniques and by comparing several optimized reference regions and clinical groups.

Methods

We analyzed 20 NL, 45 MCI, and 18 AD subjects with 2 or more PiB scans from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database.

Table 1. Demographic and clinical characteristics at baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yrs)</th>
<th>Gender (M/F)</th>
<th>Education (years)</th>
<th>MMSE</th>
<th>ADNI (yrs)</th>
<th>ApoE4 (M/C/A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL</td>
<td>17 (45)</td>
<td>10/13</td>
<td>17 (9/8)</td>
<td>28.5</td>
<td>7 (5/2)</td>
<td>0/11</td>
</tr>
<tr>
<td>MCI</td>
<td>66 (29)</td>
<td>7/22</td>
<td>14 (6/8)</td>
<td>28.5</td>
<td>5 (3/2)</td>
<td>0/11</td>
</tr>
<tr>
<td>AD</td>
<td>70 (30)</td>
<td>7/23</td>
<td>16 (6/10)</td>
<td>28</td>
<td>5 (3/2)</td>
<td>0/11</td>
</tr>
</tbody>
</table>

Subjects were stratified into:
- Baseline clinical groups (NL vs MCI vs AD)
- Outcome groups: based on clinical diagnosis at the last available PiB scan (dichotomous or non-dichotomous). Subjects could retain a stable diagnosis (NL-NL, MCI-MCI, or AD-AD) or decline to MCI or AD (NL-MCI, NL-AD, MCI-AD)
- PiB groups: subjects dichotomized as PiB positive or negative, using a global cortical to whole cerebellum ratio cut-point of 1.5 (PiB+<1.5, PiB+≥1.5, PiB−)

All PET scans were processed to uniform resolution as implemented by ADNI.

Automated ROI Method. Using Statistical Parametric Mapping (SPM), each PiB scan was registered with the standard template (MNI152) and stereotaxic warped to AC-PC. The Pirouette software (IntraRx, Inc.) was used to coregister each PiB scan on an individual basis.

A set of template regions-of-interest (ROIs) was used as the anatomical basis to generate optimized, PiB-defined masks (anterior and posterior cingulate, precuneus, frontal, parietal, and temporal cortices), which were used to sample each scan. A systematic approach (a region from edges to minimize sipkoller and atrophy effects) was developed to create 5 optimized reference regions: whole cerebellum, cerebellum gray matter, corona radiata, pons and chiasm (Fig. 1). Additionally, we included the cerebellum from the automated anatomical labeling (AAL) atlas. A global cortical PiB retention summary was formed by averaging the target ROIs, normalized to each reference region to obtain global PiB (Glo).<ref>Pons et al. (2008) Neuroimage 41: 1024-1033</ref>

Discussion and Conclusions

PiB-PET is valuable in classifying clinical and outcome groups at cross-section. Besides providing diagnostic discrimination of NL vs MCI vs AD, PiB measures distinguish stable MCI from AD to decline to AD.

However, PiB accumulation rate was overall compatible across comparable groups, suggesting that PiB accumulation may not be a sensitive correlate of clinical outcome, consistent with previous reports<ref>Pons et al. (2008) Neuroimage 41: 1024-1033</ref>. Significant heterogeneity in PiB retention and accumulation was observed within clinical groups, suggesting that factors other than clinical parameters influence amyloid progression. Baseline PiB retention was a significant predictor of PiB accumulation over time.<ref>Pons et al. (2008) Neuroimage 41: 1024-1033</ref>

Statistical analysis. Of the 83 subjects, 49 had 2 PiB scans and the remaining subjects had 3 or more scans, with a minimum interval of 12 months between scans. A mixed model for repeated measures (MMRM) was used to examine longitudinal PiB retention across groups for all reference regions. The primary endpoint was the change from baseline to the last follow-up (36 months) in global PiB accumulation. The covariates were clinical group, time, and the interaction between group and time, after adjusting for subject-specific effects, while using all available data and accounting for missing time points. The model was estimated (i.e., predicted PiB values at each time point for all subjects, which were compared across groups using general linear model-univariate analysis. Results were assessed at P<0.05.

Results

Baseline clinical groups. At baseline and at 36 months, there was a critical diagnostic effect on PiB uptake such as: AD>NC>HL with all reference regions (P<0.005). Although there were no significant interaction effects, significant positive associations between PiB accumulation and time were observed for NL and MCI, whereas the AD group remained stable (Fig. 2). In NL subjects, PiB retention increased by j=0.07-0.04 SUV for every unit increase in time (e.g., every 12 months with CerGal and Wcer (P<0.04). In MCI, PiB increase for j=0.08- 0.04 SUV every 12 months with all reference regions except for Pons (P=0.1).

Outcome groups. At baseline and at 36 months, PiB uptake was significantly higher in MCI-AD and AD-AD than in NL-NL, NL-MCI, and MCI-MCI (P<0.005, Fig. 3). There were no interaction effects between groups, although there was a trend towards lower rates of PiB accumulation in MCI-AD vs MCI-MCI using Pons, CerGal, and Wcer (P<0.05), which may suggest that MCI and AD groups have different PiB accumulation trajectories (Fig. 3).<ref>Pons et al. (2008) Neuroimage 41: 1024-1033</ref>

PiB groups: Subjects dichotomized as PiB positive or negative, using a global cortical to whole cerebellum ratio cut-point of 1.5 (PiB+<1.5, PiB+≥1.5, PiB−)

All PET scans were processed to uniform resolution as implemented by ADNI.

Automated ROI Method. Using Statistical Parametric Mapping (SPM), each PiB scan was registered with the standard template (MNI152) and stereotaxic warped to AC-PC. The Pirouette software (IntraRx, Inc.) was used to coregister each PiB scan on an individual basis.

A set of template regions-of-interest (ROIs) was used as the anatomical basis to generate optimized, PiB-defined masks (anterior and posterior cingulate, precuneus, frontal, parietal, and temporal cortices), which were used to sample each scan. A systematic approach (a region from edges to minimize sipkoller and atrophy effects) was developed to create 5 optimized reference regions: whole cerebellum, cerebellum gray matter, corona radiata, pons and chiasm (Fig. 1). Additionally, we included the cerebellum from the automated anatomical labeling (AAL) atlas. A global cortical PiB retention summary was formed by averaging the target ROIs, normalized to each reference region to obtain global PiB (Glo).<ref>Pons et al. (2008) Neuroimage 41: 1024-1033</ref>

Fig. 1. Outcome groups. Estimated PiB values at baseline and 36 months and Beta effects (SUV). Beta values indicate PiB SUV changes per each 12 months. "Group differences, P<0.05"

Fig. 2. PiB groups. Estimated PiB values at baseline and 36 months. Beta values indicate PiB SUV changes per each 12 months. "Group differences, P<0.05"

Fig. 3. PiB groups. Estimated PiB values at baseline and 36 months. Beta values indicate PiB SUV changes per each 12 months. "Group differences, P<0.05"

Comparing reference regions: effect size, %C, % change within groups

Outcome groups

NL vs PiB+ vs NL vs PiB− vs NL vs PiB+ vs NL vs PiB−

Comparing reference regions: effect size, %C, % change within groups

References


Acknowledgements and Contact

Data used in this study were obtained from the ADNI database (www.adni-info.org). As such, ADNI investigators contribute to the paper but do not accept authorship. The ADNI protocol was approved by an institutional review board at each participating site. The ADNI website (www.adni-info.org) contains links to all information released in this paper including study protocols, recruitmentfliers, participant consent forms, and other documents. The ADNI study was co-founded by the National Institute on Aging and the National Institute of Biomedical Imaging and Bioengineering. Its contents are solely the responsibility of the investigators and do not necessarily represent the official views of the National Institutes of Health. 2000. Liaw SX, et al. (2006) Neuroimage 30: 102-110

Dr. Lisa Mosconi, PhD, is the Scientific Director of the ADNI for Imaging,LLC, Grayslake, IL. and ADNI.jpg