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

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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 (Aβ) plaques are a hallmark of AD pathology and Aβ 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 Aβ radioligands, now appear in many therapeutic trials. The use of Aβ-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, the bar for 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. Far 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 ^{11}C-PiB, the most widely used Aβ-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[1].

Table 1: Demographic and clinical characteristics at baseline

	N	Age (yrs)	Gender (M/F)	Education (yrs)	MMSE	ApoE ε4+/ε4-
Baseline groups						
NL	20	77(6)	13/7	16(3)	29(1)	6/14
MCI	45	75(8)	29/16	16(3)	27(2)	26/19
AD	18	75(7)	11/7	15(3)	23(3)	13/5
Outcome groups						
NL-NL	17	76(6)	13/4	16(3)	29(1)	5/12
NL-MCI	2	82	0/2	12,18	28,29	1/1
NL-AD	1	79, 84	0/1	12	30	0/1
MCI-MCI	29	75(8)	21/8	16(3)	28(2)	14/15
MCI-AD	15	76(7)	7/8	16(3)	26(2)	11/4
MCI-NL	1	64	1/0	13	28	1/0
AD-AD	18	75(7)	11/7	15(3)	23(3)	13/5
Clinical by PiB groups						
NL PiB-	11	74(5)	7/4	16(3)	29(1)	1/10
PiB+	9	79(6)	6/3	16(3)	29(2)	5/4
MCI PiB-	21	76(8)	15/6	16(2)	28(2)	8/13
PiB+	24	74(8)	14/10	16(3)	27(2)	18/6
AD PiB-	3	79(6)	2/1	13(2)	24(2)	1/2
PiB+	15	74(7)	9/6	15(3)	22(3)	12/3

Values are mean (SD). *Different from controls, P<0.05

Subjects were stratified into:

- Baseline clinical groups (NL vs MCI vs AD)
- Outcome groups: based on clinical diagnosis at the last available PiB scan (decliners vs non-decliners). Subjects could retain a stable diagnosis (NL-NL, MCI-MCI) or decline to MCI or AD (NL-MCI, NL-AD, MCI-AD)
- PiB groups: subjects were dichotomized as PiB positive or negative, using a global cortical to whole cerebellum ratio cut point of 1.5 (PiB+: SUVR≥1.5; PiB-<1.5 SUVR)[2]

All PET scans were processed to uniform resolution as implemented by ADNI[3]. The late uptake PIB images used in this study were the 'maximally pre-processed files' 50-70 min. available for download as of August 2011.

Automated ROI Method. Using Statistical Parametric Mapping (SPM8), each subject's baseline MRI was coregistered to the corresponding baseline FDG and all available PiB scans using Normalized Mutual Information (NMI), and spatially normalized to MNI space by high-dimensional warping (DARTEL) with the standard template included in the VBM8 toolbox[4]. The subject-specific transforms were applied to each coregistered PiB scan on an individual basis.

A set of template regions-of-interest (ROI)[5-7] 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 (i.e., erosion from edges to minimize spillover and atrophy effects) was developed to create 5 optimized reference regions: whole cerebellum, cerebellar gray matter, crus gray matter, pons and centrum ovale (Fig. 1). Additionally, we included the cerebellum from the automated anatomic labeling (AAL) atlas[8]. A global cortical PIB retention summary was formed by averaging the target ROIs, normalized to each reference region to obtain global PiB SUV ratios (SUVR) .

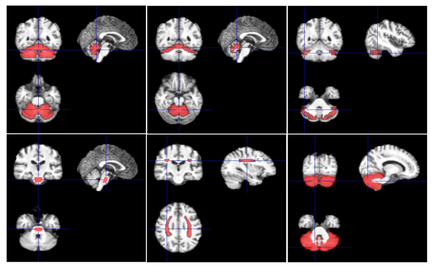


Fig. 1. Reference regions. Top to bottom, left to right: Whole cerebellum (WholeCer), Cerebellar gray matter (CerGM), Crus gray matter (CrusGM), Pons, Centrum ovale (CO), AAL Cerebellum (CerAAL)[8]

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. The explanatory variables 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 generates 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 clear diagnostic effect on PiB uptake such as: AD>MCI>NL, 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 overall stable (Fig. 2). In NL subjects, PiB retention increased by β=.037-.046 SUVR for every unit increase in time (i.e., every 12 months) with CerGM and Wcer (P≤.04). In MCI, PiB retention increased by β=.018-.049 SUVR every 12 months with all reference regions except for Pons (P≤.01).

Outcome groups. At baseline and at 36 months, PiB uptake was significantly higher in MCI-AD and AD-AD than in NL-NL and MCI-MCI (P<0.005, Fig. 2). There were no interaction effects between groups, although there was a linear trend towards higher rates of PiB accumulation in MCI-AD vs MCI-MCI using Pons, CerAAL, and WCer (Fig. 2, arrows). PiB retention increased by β=.023-.086 SUVR per year using these regions (P≤.05), whereas MCI-MCI remained stable (Fig. 2). Of other decliners, one NL-MCI and the MCI-NL showed mild PiB increases, whereas the other NL-MCI and the NL-AD subjects had stable, low PiB levels. Two out of 3 AD PiB- subjects showed mild PiB increases over time, and the third subject had stable, low PiB measures. Excluding AD PiB- from analysis left results substantially unchanged (Fig. 3).

PiB groups. Significant interaction effects were observed for the NL group using WholeCer, CerAAL and Pons (P≤0.03). NL PiB+ showed PiB increases over time (P≤0.006) whereas NL PiB- showed no significant PiB changes (Fig. 3). PiB increased by β=.053 SUVR per year with Pons, β=.09 with WCer and β=.033 with CerAAL (P≤.03, Fig. 4). No significant interaction effects were observed within the MCI group, as PiB accumulation progressed at similar rates between PiB+ and PiB- subgroups (Fig. 3 and 4). After 36 months, NL PiB+ subjects reached PiB levels comparable to those in MCI PiB+ and AD PiB+ using Wcer and CerAAL (Fig. 3).

Fig. 2. Outcome groups. Estimated PiB values at baseline and 36-months and Beta estimates (SEM). Beta values indicate PiB SUVR changes per each 12 months. *Group differences, P<.05

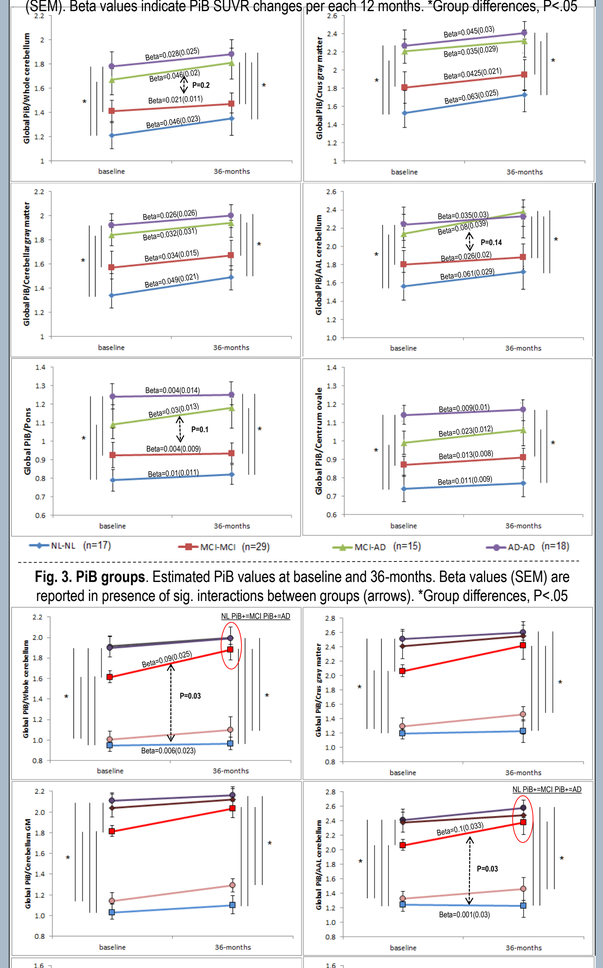
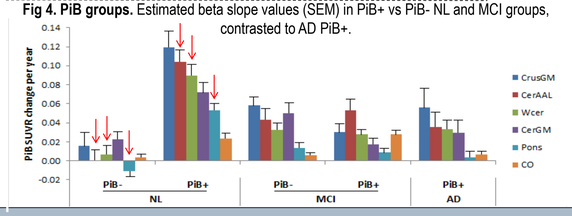
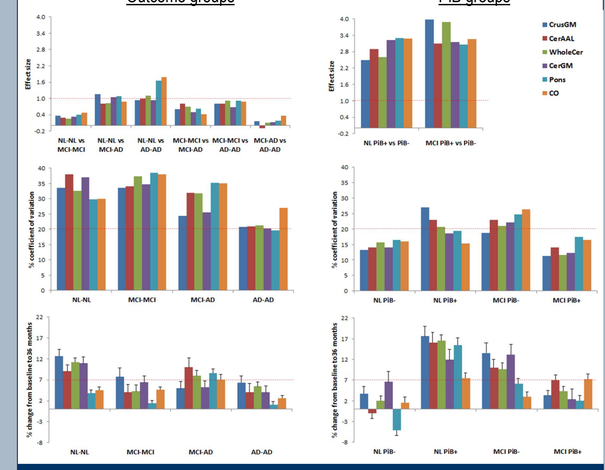


Fig. 3. PiB groups. Estimated PiB values at baseline and 36-months. Beta values (SEM) are reported in presence of sig. interactions between groups (arrows). *Group differences, P<.05

Fig 4. PiB groups. Estimated beta slope values (SEM) in PiB+ vs PiB- NL and MCI groups, contrasted to AD PiB+.



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



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 MCI decliners to AD.

However, PiB accumulation rate was overall comparable across clinical groups, suggesting that PiB accumulation may not be a sensitive correlate of clinical outcome, consistent with previous reports[2]. 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.

Significantly higher rates of PiB accumulation were observed in NL PiB+ vs PiB-. These findings suggest that amyloid increases are more prominent at the presymptomatic stages of AD, and that PiB-PET may be useful to monitor the effect of prevention trials, in addition to therapeutic interventions.

Optimized reference regions were instrumental in improving signal to noise ratio and to maximize detection of cross-sectional and longitudinal effects. Overall, there was consistency across different reference regions. Examination of effect size, %CV, and rate of change over time may help guide selection of the most appropriate reference region, depending on study hypotheses.

These results provide a benchmark for measuring therapeutic impact upon amyloid progression rate, support robustness of findings across multiple reference regions, and demonstrate the benefit of applying quality control and optimization.

References

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Acknowledgements and Contact

Data used in this study were obtained from the ADNI database (www.loni.ucla.edu\ADNI). As such, ADNI investigators contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report (www.loni.ucla.edu\ADNI\Collaboration\ADNI_Manuscript_Citations.pdf). The automated ROI sampling technique was developed at New York University School of Medicine. This study was supported by Janssen Alzheimer Immunotherapy Research & Development, LLC, and Wyeth Research, which was acquired by Pfizer Inc. in October 2009.

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