OBJECTIVES
The Alzheimer’s Disease Neuroimaging Initiative (ADNI) PET Core has analyzed FDG PET images using ROI, summary index and voxel-based approaches. We compare longitudinal effect sizes for these methodologies along with Freesurfer ROI approaches using the same ADNI datasets for all methods.

METHODS

Population
Quantitative analyses of baseline and 24-MD FDG data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) study were completed for 399 subjects who had at least two FDG and corresponding MRI. All subjects also had Florbetapir scans for classification of Aβ status. Subject demographics are shown in Table 1. The dataset used for comparison clinically diagnosed as:

- 158 Normal (N) (52 Aβ+, 106 Aβ-)
- 208 Mild Cognitive Impairment (MCI) (108 Aβ+, 100 Aβ-)
- 33 Alzheimer’s Disease (AD) (27 Aβ+, 6 Aβ-)

Clinical status determined from Baseline Dx at visit one, adjusted if Dx at visit two showed improved status.

Aβ status (determined via baseline Florbetapir PET, 1.1 threshold Freesurfer Whole Cerebellar reference) was used to stratify the analysis into “likely decliner” (N Aβ+, MCI Aβ+, AD Aβ+) vs “likely stable” (N Aβ-) groups.

Table 1. Subject Demographics.

<table>
<thead>
<tr>
<th>Gender</th>
<th>AD (n=64)</th>
<th>AD (n=27)</th>
<th>MCI (n=100)</th>
<th>MCI (n=108)</th>
<th>N (n=106)</th>
<th>N (n=108)</th>
<th>N (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>71.4 ± 7.7</td>
<td>71.8 ± 7.8</td>
<td>72.6 ± 5.6</td>
<td>72.1 ± 6.7</td>
<td>72.9 ± 7.8</td>
<td>71.5 ± 8.0</td>
<td>69.0 ± 8.9</td>
</tr>
<tr>
<td>Female</td>
<td>71.2 ± 9.1</td>
<td>73.5 ± 8.8</td>
<td>72.8 ± 5.9</td>
<td>72.5 ± 6.8</td>
<td>72.9 ± 8.2</td>
<td>71.5 ± 9.2</td>
<td>69.0 ± 8.9</td>
</tr>
</tbody>
</table>

SUVR Methodologies
Methods 1-3 have been described previously (Fig 1). Methods 4 and 5 used a Freesurfer (FS) MRI segmentation to obtain SUVR indices from co-registered PET data. Both Freesurfer methods evaluated whole brain (WB) and subcortical white matter (WM) reference regions and target regions known to be affected by AD (Figs 1,2). Longitudinal Cohen’s effect size was evaluated for each method, as well as the absolute difference in measures between time points.

1. SPM Method [1]

- SUVR alignment into template space
- Voxels nearest reference region
- Fixed-effects analysis
- Left Angular Gyrus
- Right Angular Gyrus
- Bilateral Posterior Occipital
- Left inferior Temporal Gyrus
- Right inferior Temporal Gyrus

2. Statistical ROI (sROI) Method [2]

- SPM-based template alignment
- Requires a training population to establish ROIs

3. Longitudinal Hypermetabolic Convergence Index (L-HCI) [3]

- Voxel-based SUVR methods
- No cross-sectional effect
- High metabolic regions

4. Freesurfer ROI (FS-WB, FS-WM)

5. LASSO-optimized Freesurfer (LASSO-FS-WB, LASSO-FS-WM)

Figure 1 Hypometabolic Quantifications Methodologies

Figure 2. Optimization of Freesurfer ROI Selection. Method #4 used ROIs with highest individual cross-sectional effect size between AD Aβ+ vs N Aβ- subjects. Selected regions were grouped into six functional ROIs and a target average ROI was formed to create the composite index. Method #5 used a LASSO logistic regression and 5-fold cross validation to select the optimal grouping of Freesurfer ROIs maximizing AD Aβ+ vs N Aβ- cross-sectional effect size. The middle plot identifies the minimum-deviance point with a green circle and dashed line as a function of the regularization parameter Lambda. The trace plot (Right) shows non-zero model coefficients as a function of the regularization parameter parameter Lambda. Each predictor is represented by a single curve. As Lambda increases to the left, LASSO sets various coefficients to zero, making them vanishing from the model.

RESULTS

Longitudinal Effect Size
All analysis methods show increasing absolute longitudinal effect size and effect sizes for the Aβ+ Normals, Aβ+ MCI, and Aβ+ AD decliner groups respectively compared to the Aβ-Normals (Fig 3). While the MetaROI method showed the largest absolute effect size (Fig 4), effect size for the LASSO-FS and L-HCI showed the highest effect sizes. The sROI, FS and MetaROI methods showed a smaller effect size. Comparing among the Freesurfer methods, the LASSO-optimized ROIs were superior and the greatest effect size was seen using the WM reference.

Sample Size Considerations
Sample size estimates per arm were calculated to detect a 25% treatment effect with 80% power and 5% type I error, assuming two-sample, two-sided tests (Table 3). An optimal analysis can reduce required sample size dramatically.

CONCLUSIONS
Though the MetaROI method shows the greatest longitudinal effect size, it actually has the smallest effect size of all methods. Considerable reduction in sample size to adequately power clinical trials may be possible using alternate methods, such as the LASSO-FS-WM or L-HCI techniques.

REFERENCES

Figure 3. Mean SUVR difference for each quantification method.

Figure 4. Mean SUVR difference (numerator of effect size).

Table 2. Longitudinal Effect Size

Table 3. Sample Size Estimates

ACKNOWLEDGMENTS
The authors are extremely thankful for the work of Asha George for her statistical analysis of the data.