Comparison of SUVR Methods and Reference Regions in Amyloid PET

INTRODUCTION

We compare results of standard uptake value ratio (SUVR) analyses of Alzheimer’s Disease Neuroimaging Initiative (ADNI) florbetapir PET scans using a native space compared to SPM template methods and a variety of possible SUVR reference regions.

The objective is to find a method with highest longitudinal effect size to allow a sufficiently powered clinical trial efficacy measure using the smallest number of subjects.

METHODS

Study Population

Quantitative analysis of longitudinal florbetapir data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) study were completed for 476 subjects clinically diagnosed as:

- 179 Normal
- 160 Early Mild Cognitive Impairment (EMCI)
- 93 Late Mild Cognitive Impairment (LMI)
- 44 Alzheimer’s Disease (AD)

The focus of the analysis for this work are SUVRs for AD vs Normal subjects. Characteristics of these two groups are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>AD</th>
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<tbody>
<tr>
<td>Mean Age</td>
<td>73.7</td>
<td>77.8</td>
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<tr>
<td>Mean Age Std*</td>
<td>7.4</td>
<td>7.4</td>
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* standard deviation corrected to a similar cortical reference region

Input data were ADNI “level 4 data”: uniformly smoothed, co-registered, averaged dynamic PET data that have been reoriented into a standard voxel grid.

SUVR Reference Regions

Numerous reference regions were evaluated:

- Brainstem (BS)
- Cerebellar Grey (CG)
- Cerebellar White Matter (WMcreb)
- Subcortical White Matter (WM)
- Eroded Subcortical White Matter (WMeroded)
- WM + WMcreb (WMall)
- Pons
- Whole Brain (WB)
- Whole Cerebellum (WC)
- Average of BS, WMeroded, WC (AvgRef)

Comparison Metric – Effect Size

Cohen’s d effect size is the metric used for comparison of methods:

For the cross-sectional comparison of AD vs Normal groups, the numerator was the difference of mean SUVRs between the two groups and the denominator was the average standard error of each group SUVR. For the longitudinal analysis of AD SUVR change, the numerator was the mean SUVR difference between time points, and the denominator was the SUVR std error.

RESULTS

- Effect size in the cross-sectional analysis showed similar results for most methods, with these general trends:
  - Higher effect size using WM references
  - Higher effect size using SPM methods
  - Lower effect size with cerebellar grey (CG)

Longitudinal effect size showed large differences between methods, with these general trends:

- Much higher effect with WM references
- Fusiform method superior across all reference regions
- Whole brain, subcortical, and cerebellar regions alone gave poor results when used as a longitudinal reference region.

DISCUSSION / CONCLUSIONS

- Results indicate that while effect size in a cross-sectional analysis does not vary greatly across different SUVR methods and reference regions, there is a very large difference seen in the longitudinal analysis. This is an important consideration in the selection of methods for use as an efficacy endpoint in clinical trials.
- A reference region including white matter consistently performs better in both the cross-sectional and longitudinal analyses. Possible reasons for this compared to pons, brainstem, or cerebellar references include increased noise of the latter reference regions due to their position at the outer extremes of the axial PET scanner field of view, methodological difficulties in correct segmentation of these regions compared to white matter, or possibly increased biological variability in these regions compared to white matter.
- In both the cross-sectional and longitudinal analyses, and across all reference regions, the native-space Freesurfer method produced the greater effect size. 
We hypothesize this is most likely due to possible increased accuracy of regional segmentation for individual scans using the Freesurfer method, and to the use of smaller regions less likely to be biased by partial volume effects of uptake seen in white matter and other non-grey matter regions.
- Though the Freesurfer method requires co-registered T1-MRI and extensive computation, it appears that the method can offer improved sensitivity and reduced sample size in longitudinal clinical trial efficacy endpoints.

REFERENCES


ACKNOWLEDGMENTS

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Figure 1: SUVR Methods and ROI Definitions

Figure 2: Cross-Sectional Effect Size

Figure 3: Longitudinal Effect Size