INTRODUCTION

- We conducted standard uptake value ratio (SUVR) analyses of florbetaben data to assess the sensitivity and specificity of various SUVR methodologies for discriminating healthy controls (HC) from subjects with probable Alzheimer’s Disease (AD).
- Reference regions optimizing effect size between AD and HC subjects were determined, and SUVR cutpoints were established for native space FreeSurfer-based SUVRs and compared to previously published results using a cerebellar grey reference region and an AAL region/template space SUVR method [Barthel, 2011].

METHODS

- A subset of subjects imaged with florbetaben in a phase II clinical trial was used to assess the influence of quantification method on SUVR accuracy and effect size. SUVR values were computed for two groups: AD with a clinical diagnosis of probable AD and whose scan has been read positive via a majority read visual assessment; and 45 age-matched HC with visually normal scans.

SUVR Quantification Methods

- A composite FreeSurfer SUVR index was computed using the Berkeley ADNI approach [Landau, 2013] combining four cortical regions of interest (ROI): frontal, anterior/posterior cingulate, lateral temporal, and lateral parietal. Nine reference regions including whole cerebellum, brainstem and subcortical white matter were evaluated. Sensitivity and specificity for each SUVR method were computed using cutpoints defined as two standard deviations from the mean HC group SUVR value. Visual assessment was used as the standard of truth to calculate sensitivity and specificity. Cohen’s D effect size between the AD and HC groups was analyzed, as well as the performance of the FreeSurfer method compared to the AAL method (AAs reported by [Barthel, 2011]).

SUVR Reference Regions

- Analysis compared FreeSurfer (FS) to AAL SUVR results.
- Numerous reference regions were evaluated:
  - Brainstem (BS)
  - Cerebellum Grey (CG)
  - Whole Cerebellum (WC)
  - Cerebellum White Matter (WMcerebellum)
  - Whole Brain (WB)
  - Subcortical White Matter (WM)
  - Thalamus (Th)
  - Ecorised Subcortical White Matter (WMeroded)
  - Average of BS, WMeroded, WB (AvgRef)

RESULTS

- Cross-sectional comparison of AD vs HC groups, the numerator was the difference in SUVR values between the two groups and the denominator was the average standard error of each group SUVR.

- Effect Size between AD and HC Group
  - Cross-sectional effect size was larger for SUVR methods including subcortical white matter as a reference region, and highest using a composite reference region including subcortical white matter, brainstem, and whole-cerebellum (Cohen’s D=3.88). Lowest effect size was obtained using the cerebellar grey reference (Cohen’s D=2.66). Results are summarized in Figure 2.

- Cutpoints
  - Optimal SUVR cutpoints were determined using two standard deviations from the mean of the HC group. Accuracy of the SUVR results compared to visual assessment is summarized in Table 1. Accuracy was higher using the composite reference and a cutpoint of 0.845 (sensitivity=0.979, specificity=0.978), compared to the cerebellar grey reference with a cutpoint of 1.346 (sensitivity=0.917, specificity=0.956). The Freesurfer method performed slightly better than the AAL method using the cerebellar grey reference.
  - The optimal composite SUVR cutpoint reported by [Barthel, 2011] using the AAL cerebellar grey matter reference was 1.39. Using the linear regression between Freesurfer and AAL results, the optimal AAL cerebellar grey reference SUVR cutpoint is 0.917.

CONCLUSIONS

- Comparing SUVR cutpoints to visual assessment, an SUVR method using a subcortical white matter reference region appears superior to methods using cerebellar references. These results can be influenced by the visual assessment method used which focuses on comparing the target intensity in the cortical grey matter versus the subcortical white matter.
- As reported previously by Barthel, high sensitivities and specificities are seen for SUVR-based classification using a cerebellar grey reference region, but the results indicate that even higher accuracy is possible using a subcortical white matter reference.
- Correlation analysis of AAL and Freesurfer cerebellar grey reference SUVRs indicate that a AAL cutpoint of 1.39 corresponds to a Freesurfer cutpoint of 1.28.

Table 1: Accuracy of SUVR Methods Compared to Visual

<table>
<thead>
<tr>
<th>SUVR Method</th>
<th>HC mean</th>
<th>HC SD</th>
<th>BIC Cutpoint</th>
<th>Cohen's D</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS WC</td>
<td>0.721</td>
<td>0.679</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>FS CG</td>
<td>1.040</td>
<td>0.729</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>FS BS</td>
<td>1.432</td>
<td>1.089</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>FS Th</td>
<td>0.839</td>
<td>0.729</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>FS WMeroded</td>
<td>0.929</td>
<td>0.679</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>FS WM</td>
<td>0.850</td>
<td>0.729</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>FS AvgRef</td>
<td>0.701</td>
<td>0.679</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 - SUVR Results Using Different Reference Regions

<table>
<thead>
<tr>
<th>SUVR Method</th>
<th>HC mean</th>
<th>HC SD</th>
<th>BIC Cutpoint</th>
<th>Cohen's D</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAL WC</td>
<td>1.360</td>
<td>0.729</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>AAL CG</td>
<td>1.073</td>
<td>0.729</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>AAL BS</td>
<td>1.432</td>
<td>1.089</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>AAL Th</td>
<td>0.839</td>
<td>0.729</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>AAL WM</td>
<td>0.929</td>
<td>0.679</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>AAL AvgRef</td>
<td>0.701</td>
<td>0.679</td>
<td>0.608</td>
<td>0.938</td>
<td>0.978</td>
<td></td>
</tr>
</tbody>
</table>

References

- Landau, 2013
- Bartel, 2011
- Washington, DC, USA
- Milzel, 2011
- Lipton, 2013
- AAN

Alzheimer’s Association International Conference (AAIC) • July 18 – 23, 2015 • Washington, DC, USA