Introduction

The ability to identify individuals in the pre-symptomatic stages of Alzheimer’s disease is desirable for early diagnosis, intervention, counselling, and drug discovery. Pathological changes in the brain precede cognitive symptoms by several years. Disease-specific imaging biomarkers could potentially detect pre-clinical disease. We use multi-region analysis of MR images acquired at a single timepoint to identify early signs of neurodegeneration in cognitively normal elderly individuals with evidence of cortical β-amyloid deposition.

Study populations

Cognitively normal participants from two independent studies:
- ADNI (1.5T MRI and CSF Aβ)
- AIBL (1.5T or 3T MRI and PiB-PET)

<table>
<thead>
<tr>
<th>H(%)</th>
<th>Age (mean ± std dev)</th>
<th>MMSE score (mean ± std dev)</th>
<th>CDR 0.5</th>
<th>N18 conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNI 109(55)</td>
<td>75.8 ± 5.2</td>
<td>29.1 ± 1.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AIBL 119(63)</td>
<td>73.2 ± 7.2</td>
<td>28.8 ± 1.2</td>
<td>91</td>
<td>8</td>
</tr>
</tbody>
</table>

Methods

MRI anatomical segmentation

Automatic whole-brain segmentations into 83 anatomical regions were prepared in native MRI space for both ADNI and AIBL participants using multi-atlas propagation with enhanced registration (MAPER) [1]. Cortical regions were masked with a grey matter label, and lateral ventricles with a CSF label. Regional volumes were normalised by total intracranial volume. Although MAPER produced consistent results across field strengths in ADNI [1], regional volume differences were observed between the 1.5T and 3T AIBL MRI. These sets of images were therefore analysed separately.

Amyloid-based risk status - ADNI

The 109 ADNI participants were assigned to high- and low-risk groups for the development of Alzheimer’s disease based on CSF measures of Aβ42 (high risk ≤ 192 pg/mL) [2]. Following sub-division, 39% were assigned to the high-risk sub-set.

Amyloid-based risk status - AIBL

The 119 AIBL participants were assigned to high- and low-risk groups for the development of Alzheimer’s disease based on neocortical-to-cerebellar ratios of amyloid deposition on PiB-PET imaging (high risk > 1.5) [3]. Each PiB-PET image was affinely co-registered with its corresponding MRI. The extent of cortical β-amyloid deposition was assessed using a PiB-PET SUVR computed between a composite neocortical region and the cerebellar grey matter [4]. The AIBL participants were divided according to scanner model (1.5T, n = 39; 3T, n = 80). Following sub-division, 21% of the 1.5T participants and 34% of the 3T participants were assigned to the high-risk sub-sets.

Results

Comparisons by t-test were performed between the ICV-normalised, age-corrected MR volumes in the high- and low-risk sub-sets of each group (ADNI, 1.5T AIBL, 3T AIBL). Correction for multiple comparisons was performed using the P plot graphical method [5]. Figures show regional t-values, with a cyan outline highlighting regions for which p<0.1, and a navy outline highlighting regions for which p<0.05.

ADNI

5/83 regions were smaller in the high-risk sub-set (p<0.05). The difference in the right anterior orbital gyrus remained significant after correction for multiple comparisons.

AIBL 1.5T

5/83 regions were smaller in the high-risk sub-set (p<0.05). The difference in the left occipitotemporal gyrus remained significant after correction for multiple comparisons.

AIBL 3T

4/83 regions were smaller in the high-risk sub-set (p<0.05). No differences remained significant after correction for multiple comparisons.

Conclusions

Reduced volumes in temporo-parietal and orbito-frontal regions in high risk individuals were observed in both ADNI and AIBL. Differences could be indicative of very early changes associated with the development of Alzheimer’s disease. The consistency of regional differences observed in two independent groups suggests that volumetric MRI can reveal structural brain changes that precede the onset of clinical symptoms.

References


Acknowledgements

Images were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI; adni.loni.ucla.edu) and the Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing (AIBL; www.aibl.csiro.au).