Evaluation of the screening power of Cognitive Abilities Screening Instrument for probable Alzheimer’s disease using voxel-based morphometry

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Abstract

Objective: The aim of this study was to compare two screening methods, total score of the Cognitive Abilities Screening Instrument (CASI\textsubscript{T}) and the combined score for the short-term memory and orientation domains (CASI\textsubscript{R}) for screening and grading probable Alzheimer’s disease (AD), based on their correlations with voxel-based morphometry (VBM). Materials and methods: Forty-five subjects with probable AD and normal controls underwent magnetic resonance imaging and CASI testing. Their corresponding T1-weighted magnetic resonance images were analyzed using VBM. Results: VBM results showed that in moderate-to-severe AD subgroups, significant whole-brain gray matter loss was detected using both CASI\textsubscript{T} and CASI\textsubscript{R}. Significantly more voxels were detected using the CASI\textsubscript{T} compared with the CASI\textsubscript{R} system in mild AD subjects (\(P<.05\)). Conclusions: Based on their correlations with VBM results, there is no significant difference for CASI\textsubscript{R} and CASI\textsubscript{T} for grading moderate-to-severe AD subgroups, and CASI\textsubscript{R} scoring system may be more accurate and effective than the CASI\textsubscript{T} for screening mild AD.

Keywords: Alzheimer's disease; Cognitive Abilities Screening Instrument; Voxel-based morphometry

1. Introduction

Alzheimer’s disease (AD) is a condition in which progressive neurofibrillary changes lead to neuronal death and dementia [1,2]. The distinct pathological features for AD include neuritic plaques and neurofibrillary tangles in the brain, which are related to the overproduction and deposition of amyloid \(\beta\) peptide, and the hyperphosphorylation of microtubule-associated Tau protein inside the neurons [3,4]. Early signs of AD, easily to be mistaken with normal aging, include gradual onset of declination in cognition, memory impairment and difficulties to obtain new information and remember it after a few minutes, with progressive cognitive...
loss and sparing of motor and sensory functions in later stages [5]. Correct diagnosis is critical for the implementation of treatment to halt AD progression. Given this, it is important that there are accurate and reliable methods available for screening and diagnosis of AD. The Cognitive Abilities Screening Instrument (CASI) has frequently been used as a dementia screening tool, and its clinical usefulness has been well recognized [6–10]. A Chinese version of the CASI (CASI C-2.0) has been carefully developed and is well verified [11–15]. The CASI C-2.0 consists of 20 items, which can be divided into nine domains, including attention, concentration, short- (STM) and long-term memory, orientation, language abilities, visual construction, abstraction and judgment and category fluency. The current scoring system for the CASI C-2.0 involves summing the scores from each of the nine domains to obtain a total score (CASI T), which ranges from 0 to 100, with a higher score indicating better cognitive ability. The instrument can typically be administered within 15 to 20 minutes in the clinic. The CASI incorporates the Mini-Mental State Examination (MMSE) and the Hasegawa Dementia Scale [16–18], both of which are cognitive tests widely used for screening dementia and evaluating the severity of overall cognitive dysfunction. Indeed, the MMSE score can be directly extracted from the CASI. The CASI has been found to be equally as effective as the MMSE for dementia screening, more useful for determining the severity of dementia, covering more cognitive domains, providing a more detailed assessment and broader scoring ranges [13] and being less susceptible to floor and ceiling effects.

To assess the likelihood that a patient has dementia or other cognitive impairments, the clinician looks for suspiciously low scores in any one or multiple CASI domains, or compares the CASI T to a predetermined cutoff score based on data obtained from documented demented and nondemented patients. Tsai et al. [11] have demonstrated that assessment of the combined STM and orientation domain scores (CASI R) is more effective than CASI T for dementia screening.

On the other hand, magnetic resonance imaging (MRI) provides structural information about the atrophy of the medical temporal lobe, including the amygdala, entorhinal cortex and hippocampal complex, which appears at the early stage of AD. Voxel-based morphometry (VBM) is a neuro-imaging analysis method that facilitates the assessment of focal differences in brain anatomy. It is an automatic whole-brain analysis that evaluates the signal intensity voxel by voxel after anatomic standardization, based on T1-weighted acquisitions with voxel size of approximately 1 mm³. This technique has been utilized to determine subtle changes in brain structure in healthy and diseased individuals [19–21]. Indeed, VBM has also been extensively used to assess gray matter loss in patients with AD as compared with healthy elderly subjects [22–24]. It also shows promise in tracking the severity of dementia [25].

The purpose of this study was to investigate the substantial correlations between CASI and VBM, and based on this result, we compare CASI T and CASI R for screening and grading AD in Taiwanese patients.

2. Materials and methods

2.1. Subjects and CASI scoring system

We studied 22 patients with probable AD (10 men and 12 women; mean age, 69.25 years; SD, 10.13 years; range, 53 to 84 years) and 23 education-matched and age-matched healthy controls without any concomitant disease. Inclusion criteria for the patients were a diagnosis of probable AD, age ≥50 years and no other concomitant diseases. The diagnosis of probable AD was established according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria. Exclusion criteria included any clinical history of brain trauma, seizures or other psychological symptoms. All subjects were Taiwanese. The overall severity of cognitive impairment was determined using the CASI C-2.0. The study was approved by a local ethics board, and written informed consent was obtained from all patients.

Subjects were divided into three subgroups with respect to dementia severity level (normal, mild or moderate to severe) using the two scoring systems, CASI T and CASI R. It has previously been demonstrated that CASI T is significantly associated with an individual’s level of education [15]. Hence, the subjects were further stratified with respect to education level (no education, 1–5 years of schooling and 6 or more years of schooling) with differing cutoff scores. The cutoff scores for the education levels were as follows: (1) no formal education: 50, 43; (2) 1–5 years of education: 68, 55; and (3) 6 or more years of education: 80, 65. In each case, the first score was used to differentiate between normal and demented subjects, whereas the second score further categorized the subjects as having mild or moderate-to-severe AD. For CASI R, which is independent of educational level, the cutoff score dividing normal subjects and those with AD was 22.5 [11]. Subjects with AD were further classified with respect to dementia severity (mild or moderate to severe) by a cutoff score of 10 [12].

2.2. Magnetic resonance imaging

Each subject underwent MRI using a clinical GE Signa 1.5-T MRI system. Routine scans were first performed to rule out other possible causes of dementia such as epilepsy and severe head injury. High-resolution T1-weighted magnetic resonance images were then obtained using three-dimensional fast-spoiled gradient-recalled acquisition. The acquisition parameters were as follows: 12.2 ms/4.2 ms/400 ms (TR/TE/TI); flip angle, 15°; slice thickness, 1.4 mm; field-of-view, 240 mm; matrix size, 256×256; and 124 coronal slices. The sequence was chosen in order to provide high anatomical resolution with good gray/white matter contrast for subsequent segmentation in VBM analysis.
2.3. Image and statistical analysis

Images were transferred to a Linux computer and converted to the analysis format for statistical parametric mapping (SPM5) [26]. Standard VBM was performed according to the theory and algorithm by Mechelli et al. [21] and is briefly introduced here. Initially, images were spatially normalized to the standard T1-MRI template provided in SPM5, the space defined in the atlas of Talairach. This spatial normalization protocol included a linear 12-parameter affine transformation to match images with the template, as well as a small degree of nonlinear transformation [27]. Following spatial normalization, the resultant images were then segmented into gray matter, white matter and cerebrospinal fluid, based on the Bayesian probability of each tissue class obtained from the prior MRI for each voxel [28]. After segmentation, the resultant gray matter images from all AD patients and healthy controls were smoothed using an isotropic Gaussian kernel of 8-mm full-width-at-half-maximum to reduce individual variations in gyral anatomy and increase the signal-to-noise ratio. We additionally modulate images by the Jacobian determinants derived from the spatial normalization to obtain gray matter with absolute volume values, rather than concentration [21,29]. This was achieved by scaling voxel values by the Jacobian determinants derived from the spatial normalization.

Data are presented as number or mean± S.D. Comparisons were made using Wilcoxon rank sums test. A two-sample t test was used to compare gray matter volume between the normal and AD subjects. After the image preprocessing, data from the two groups of subjects were compared based on the general linear model and random Gaussian field theory [30,31]. Data were analyzed using SAS 9.0 statistical software (SAS Institute Inc., Cary, NC, USA).

Table 1

<table>
<thead>
<tr>
<th>CASI_T</th>
<th>Normal</th>
<th>Mild AD</th>
<th>Moderate-to-severe AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>11:12</td>
<td>8:6</td>
<td>2:6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.9±8.4</td>
<td>69.7±10.6</td>
<td>73.2±5.2</td>
</tr>
<tr>
<td>Score</td>
<td>87.3±4.8</td>
<td>72.0±6.7</td>
<td>42.8±2.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CASI_R</th>
<th>Normal</th>
<th>Mild AD</th>
<th>Moderate-to-severe AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>11:12</td>
<td>5:5</td>
<td>5:7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.9±8.4</td>
<td>68.8±11.1</td>
<td>74.0±4.7</td>
</tr>
<tr>
<td>Score</td>
<td>26.3±2.0</td>
<td>16.1±4.1</td>
<td>4.0±2.8</td>
</tr>
</tbody>
</table>

Data are presented as number or mean±S.D.

Table 2

<table>
<thead>
<tr>
<th>Region</th>
<th>Coordinates x, y, z</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbic lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L hippocampus</td>
<td>−18, −30, −8</td>
<td>2.91</td>
</tr>
<tr>
<td>R hippocampus</td>
<td>34, −16, −16</td>
<td>3.37</td>
</tr>
<tr>
<td>R anterior cingulate cortex</td>
<td>10, 40, 18</td>
<td>3.28</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L superior frontal gyrus</td>
<td>−6, 38, 52</td>
<td>4.77</td>
</tr>
<tr>
<td>R superior frontal gyrus</td>
<td>8, 30, 56</td>
<td>4.43</td>
</tr>
<tr>
<td>L middle frontal gyrus</td>
<td>−28, 6, 58</td>
<td>4.31</td>
</tr>
<tr>
<td>R middle frontal gyrus</td>
<td>26, 10, 54</td>
<td>3.34</td>
</tr>
<tr>
<td>L inferior frontal gyrus</td>
<td>−50, 10, 26</td>
<td>3.69</td>
</tr>
<tr>
<td>R inferior frontal gyrus</td>
<td>32, 10, −18</td>
<td>4.30</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L precuneus</td>
<td>−12, −80, 42</td>
<td>4.08</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L superior temporal gyrus</td>
<td>−60, −16, 8</td>
<td>4.27</td>
</tr>
<tr>
<td>R superior temporal gyrus</td>
<td>58, −56, 18</td>
<td>4.60</td>
</tr>
<tr>
<td>L middle temporal gyrus</td>
<td>−44, −80, 24</td>
<td>3.95</td>
</tr>
<tr>
<td>R middle temporal gyrus</td>
<td>60, −36, 2</td>
<td>4.50</td>
</tr>
<tr>
<td>R inferior temporal gyrus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Insula</td>
<td>−34, 0, 6</td>
<td>3.19</td>
</tr>
<tr>
<td>R Insula</td>
<td>36, −12, 16</td>
<td>3.81</td>
</tr>
</tbody>
</table>

L, left; R, right.
NC, USA), and the level of statistical significance was set at .05.

3. Results

Fig. 1 shows representative T1-weighted brain images from a normal subject, a subject with mild AD and a subject with moderate-to-severe AD. Decreases in gray matter volume are clearly evident with increasing severity of the disease. Table 1 summarizes the demographic information and CASI scores for subjects with respect to the CASIT and CASIR scoring systems.

Tables 2 and 3 summarize the regions of reduced gray matter volume in subjects in the mild AD as determined using the CASIT and CASIR scoring cutoffs, respectively. The results are shown as the spatial x, y and z coordinates of the voxels in the reference space, and the Z scores indicate the significance of difference between normal and diseased subjects. When the CASIT scoring system was used to screen for mild AD, significant brain atrophy was apparent in the bilateral hippocampus, frontal gyrus, temporal gyrus, insula, right anterior cingulate cortex and left precuneus (Table 2).

When the CASIR scoring cutoff was used to define mild AD, however, significant brain atrophy was apparent in the bilateral hippocampus, amygdala, posterior cingulated cortex, temporal gyrus and insula (Table 2). Atrophy in amygdala and posterior cingulated cortex was only observed using CASIR and not in CASIT, while only CASIT detects atrophy in frontal gyrus, right anterior cingulated cortex and left precuneus.

In the moderate-to-severe AD subgroups, significant whole-brain gray matter loss was apparent (particularly in amygdala, hippocampus, precentral gyrus, temporal lobe and frontal lobe) regardless of scoring system (Fig. 3). The total number of voxels detected in the mild and moderate-to-severe AD groups is summarized in Table 4, stratified with respect to two CASI scoring systems.

Significantly more voxels were detected using the CASIT scoring system compared with the CASIR system in mild AD subjects. Representative parametric map findings illustrating significant clustering of voxels in brains of individual subjects with mild or moderate-to-severe AD as defined using both scoring systems are presented in Figs. 4 and 5, respectively.

4. Discussion

In this study, we showed the correlation of the CASIT and CASIR with VBM. In the mild dementia CASIT AD
subgroup, VBM revealed significant brain atrophy of the limbic system, frontal gyrus, temporal gyrus and insula. While in the corresponding CASIR subgroup, brain atrophy was apparent in the limbic system, temporal gyrus and insula. Regardless of the scoring system used, however, the overall regions of atrophy were symmetric. Indeed, atrophy of these regions is related to the onset of symptoms of cognitive impairment in AD. Previous AD VBM studies have also demonstrated that atrophy in gray matter in early AD patients begins in amygdala, hippocampus, parietal and posterior cingulate cortices of limbic system and temporal lobe, as compared with the control group [24,30–35], which are more consistent with the VBM results defined using the CASIR as compared with those of the CASIT. Our finding that gray matter loss occurs predominantly in medial temporal lobe and nearby region is also consistent with that reported by Lehericy et al. [2]. The use of the CASIT scoring system may mistakenly categorize patients with moderate AD, where regions of atrophy are more scattered, as having mild AD, and CASIR may allow better differentiation of AD patients in earlier stages of the disease.

In the moderate-to-severe dementia AD subgroups, marked whole-brain gray matter loss was apparent for both scoring systems. Compared with the mild AD subgroup, atrophy was more severe and evident in other regions. In the later stages of AD, the majority of neurons are affected; hence, the widespread brain atrophy is not surprising. As the patients in the moderate-to-severe AD subgroups were older than those in the control group, it is possible that some of the atrophy detected may have been age related. These findings further validate the usefulness of the CASI (both CASIT and CASIR) for assessing the severity of dementia.

Our VBM analysis revealed that subjects in the CASIR mild AD subgroup had slight brain atrophy in several regions. While frontal lobe atrophy was more advanced in the CASIT mild AD subgroup than the corresponding CASIR group, atrophy in the amygdala and posterior cingulate cortex were apparent in the CASIR subgroup only. It is not conclusively known whether frontal lobe atrophy is a characteristic of mild AD. Indeed, previous studies have generally reported that frontal lobe atrophy is not evident in mild AD [24,35,36]. However, postmortem analysis has revealed neuronal and synaptic loss and tau pathology in the frontal lobe region of brains from patients with AD [37,38]. Shiino and colleagues [35] have reported posterior cingulate cortex atrophy in AD patients. Other studies have reported amygdala and hippocampal atrophy [24,33–35]. Guo et al. also showed patients with AD exhibited significant gray matter loss in hippocampus, insula, thalamus, cingulated gyrus, superior/inferior parietal lobule, parahippocampal gyrus and superior/middle temporal gyrus, regardless of the severity of the disease. They suggested white matter regions also provided important information for diagnosing AD [39]. More MRI and pathological studies with more subjects are needed to assert the atrophy regions in AD patients with different stages.

As already noted, the CASI comprises nine cognitive domains, each of which can be calculated and interpreted.

Table 4
Summary of voxel numbers for the mild and moderate-to-severe dementia AD subgroups as determined using the CASIT and CASIR scoring systems

<table>
<thead>
<tr>
<th>AD subgroup</th>
<th>CASIT</th>
<th>CASIR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>7031</td>
<td>4830</td>
<td>.0054</td>
</tr>
<tr>
<td>Moderate-to-severe</td>
<td>38,464</td>
<td>48,347</td>
<td>.2801</td>
</tr>
</tbody>
</table>

Data are presented as median (range).
* Indicates a statistically significant difference in voxel numbers between CASIT and CASIR (P<.05).
independently of other domains. Thus, the scores of each domain should be interpreted carefully. In a previous study, the investigators assigned different weights to the nine domains in an effort to increase the screening power as well as to determine the effects on efficacy of the CASI C-2.0 [11]. It has been reported that the STM and orientation domains are relatively more important for detecting dementia than other domains in the CASI [11]. This finding is
consistent with those from other common cognitive screening tests, such as the MMSE and the Hasegawa Dementia Scale, both of which contains the STM and orientation domains and is effective in screening AD patients [11]. However, when detecting other types of dementia, the MMSE and the Hasegawa Dementia Scale are less effective for assessing cognitive impairment as compared with the CASI, in which the scores from the other domains can be examined to determine the possible cause [11]. Therefore, interpreting the scores in each domain appropriately can potentially deliver more meaningful information.

5. Conclusions

In summary, this is the first study to correlate the VBM results with those of the CASI for probable AD. Our findings indicate that the combined score of the STM and orientation domains (CASI3) may be more accurate and effective than the CASI1 for screening mild AD, while there is no significant difference for grading moderate-to-severe AD subgroups between them. However, scores from each CASI domain should be interpreted carefully as they also provide meaningful information.

References


