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Regional White Matter Decreases in Alzheimer’s Disease Using Optimized Voxel-Based Morphometry

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Background: Most studies that attempt to clarify structural abnormalities related to functional disconnection in patients with Alzheimer’s disease (AD) have focused on exploring pathological changes in cortical gray matter. However, white matter fibers connecting these cerebral areas may also be abnormal.

Purpose: To investigate the regional changes of white matter volume in patients with AD compared to healthy subjects.

Material and Methods: White matter volume changes in whole-brain magnetic resonance images acquired from 19 patients with AD and 20 healthy subjects (control group) were observed using the optimized voxel-based morphometry (VBM) method. In addition, the corpus callosum (CC) of AD patients and the control group was investigated further by outlining manually the boundary of the CC on a midsagittal slice. Each area of the CC was then corrected by dividing each subject’s intracranial area in the midsagittal plane.

Results: Compared with the control group, AD patients showed significantly reduced white matter volumes in the posterior part of the CC and the temporal lobe in the left and right hemispheres. Moreover, the voxel showing peak statistical difference in the posterior of the CC was left sided. The five subdivisions of the CC were also significantly smaller among the AD patients relative to the control group.

Conclusion: Our findings suggest that these abnormalities in white matter regions may contribute to the functional disconnections in AD.

Key words: Alzheimer’s disease; optimized voxel-based morphometry; white matter

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Many electrophysiological and neuroimaging studies have suggested functional disconnections between the anterior and posterior areas of the brain and between the cerebral hemispheres of patients with Alzheimer’s disease (AD) (1). However, the underlying structural bases of the functional disconnections are so far largely unknown. Most studies have attempted to clarify pathological changes in the cortical gray matter of AD patients, such as the medial temporal lobe, insula, and parietal lobe (2, 3). However, such studies for mapping regional gray matter changes may not be enough to understand the structural basis for functional disconnections in AD because white matter fibers connecting these cerebral areas may also be affected.

Several previous studies have indicated AD-related abnormalities in the density and volume of white matter regions, such as the temporal lobe, the frontal lobe, and the splenium of the corpus callosum (CC) (4–6). Most of these studies were performed using region-of-interest (ROI) analysis and standard voxel-based morphometry (VBM) methods. Although ROI analysis based on manual segmentation needs prior knowledge of the selection of anatomical structures (7), it can precisely outline the regions in anatomy and represent the gold standard in the detection of atrophic changes. Standard VBM (8) is an automated, unbiased analysis of differences in tissue concentration throughout the brain on structural magnetic resonance imaging (MRI) scans. In this method, each
tissue (gray or white matter) image is smoothed by convolving with an isotropic Gaussian kernel, and thus each voxel in the smoothed images contains the average tissue (gray or white matter) concentration from around the voxel (where the region around the voxel is defined by the form of the smoothing kernel). This is often referred to as “tissue density,” but should not be confused with cell-packing density measured in cytoarchitectonics (8). Recently, it has been used to examine AD-related changes in white matter density (6). However, those who studied the imperfect registration of MRI scans to a common template may lead to false estimates of atrophy (9). The optimized VBM proposed by GOOD et al. (10) provided a more objective representation for AD-related changes in tissue density, because the method utilized customized stereotaxic templates from the population sample.

An additional modulation step is also often included when using optimized VBM, which multiplies gray (or white) matter voxel values by the Jacobian determinants, i.e., the determinant of the deformation parameters obtained from spatial normalization. This modulation method enables comparisons of voxel-wise gray (or white) matter volume differences between two groups (11). Furthermore, a recent study (12) suggested that, in studies of neurological disorders, optimized VBM analyses of gray matter volume might reveal subtle neuroanatomical changes that are not identified in analyses of gray matter density. Thus, in the present study, we adopted optimized VBM with modulation to detect white matter volume changes among AD patients.

However, some AD-related studies using VBM have suggested that the atrophy of callosal white matter tracts probably reflects an interface shift due to the adjacent enlarged lateral ventricle (9, 13, 14). To clarify VBM investigations of group differences in CC volumes, we analyzed further the CC of AD patients and compared them with healthy subjects on a voxel-by-voxel basis; and 2) to compare optimized VBM with ROI measurements of the CC.

Material and Methods

Subjects
19 AD patients (9 females and 10 males; age (mean ± SD) 72.6 ± 6.9 years) and 20 healthy subjects (10 females and 10 males; age (mean ± SD) 70.7 ± 6.4 years) were invited to participate in this study. The education levels of the AD patients were 11.3 ± 4.0 years, and those of the control group were 10.9 ± 4.5 years. No significant difference in age (P = 0.38), gender (P > 0.95), and education (P = 0.76) was found between the two groups. All patients with AD were subjected to neurologic, neuropsychologic, and psychiatric examinations. The examination results fulfilled the National Institute of Neurological and Communicative Disorders and Stroke-ADRDA work-group criteria (15). All subjects’ cognitive status had been evaluated using the Mini-Mental State Exam (MMSE) (16). The MMSE scores of the AD patients were 18.9 ± 3.9, while those of healthy controls were 29.5 ± 0.9. There was a significant difference in MMSE (P < 0.0001) between the two groups. Subjects were excluded if they presented symptoms of other neuropsychiatric disorders that could confound the diagnosis of dementia of the Alzheimer type. All subjects were right handed, and all gave informed consent before being scanned. The research protocol was approved by the Institute of Automation of the Chinese Academy of Sciences.

Image acquisition
Scans were acquired on a 1.5T GE Signa Twin Speed scanner (General Electric, Milwaukee, Wisc., USA). A standard head coil was used for radiofrequency (RF) transmission and reception of the nuclear magnetic resonance (NMR) signal. Head motion was minimized with restraining foam pads offered by the manufacturer. High-resolution 3D T1-weighted images (TR/TE 11.3/4.2 ms, inversion time 400 ms, flip angle 15°, field of view [FOV] 24 × 24 cm, matrix 256 × 224, in-plane voxel sizes of 0.94 × 1.07 mm², slice thickness 1.8 mm, number of excitations [NEX] 2) were acquired by a spoiled gradient-recalled (SPGR) sequence with axial volume excitation.

Image processing
Data analysis was performed using mainly statistical parametric mapping software (17), in conjunction with MATLAB version 7 (Mathworks, Inc., Natick, Mass., USA). Manual CC measurement was performed using the manual segmentation function of the MRICro Software (18).

Optimized voxel-based morphometry. All images were analyzed using optimized voxel-based morphometry (10). The entire procedure consisted of five steps. Each one is described in detail below.
1) Customized template formation: First, each native image was registered into the statistical parametric mapping (SPM) T1 template using a 12-parameter affine transformation (19). Second, each normalized image was segmented into gray and white matter and cerebral spinal fluid (CSF) compartments (8). Third, these normalized images as well as gray and white matter and CSF segments were smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM). Finally, all the smoothed images were averaged in turn to create a customized T1 template, gray and white matter, and CSF templates.

2) Scan-to-template matching: Each native scan was further registered to the customized T1 template by affine transformations. Subsequently, nonlinear iterations using $5 \times 5 \times 5$ basis functions were performed for global nonlinear shape differences (20). The transformed volumes were then resampled to a voxel size of $1 \times 1 \times 1$ mm by trilinear interpolation.

3) Tissue segmentation: We classified the normalized images into gray matter, white matter, cerebrospinal fluid, and background (8) using customized gray as well as white matter and CSF templates as prior probability maps.

4) Modulation for volume preservation: Since nonlinear normalization might cause the local volumes of certain regions of the brain to expand or contract, it is important to correct them for the effects of volume changes during the identification process of the regional differences in white matter between groups. Here, we multiplied each white matter voxel value by the Jacobian determinants derived from the above spatial normalization process, and thereby preserved the amount of white matter in each voxel (8). Thus, the analysis of the modulated data focused on volume differences. In this study, modulation was performed on all image data sets.

5) Smoothing process: The individual white matter mask was smoothed using a 12-mm FWHM isotropic Gaussian kernel to make the data suitable for parametric statistical analysis.

**ROI analysis of the corpus callosum.** We selected the middle slice of the sagittal planes for each native scan as the midsagittal plane, and the boundaries of the CC in the midsagittal plane were manually outlined by one rater who was blind to the diagnosis. Pixels of high signal intensity were assigned to the CC, and the CC was then divided into five subregions, namely, CC1 = rostrum and genu, CC2 = rostral body, CC3 = midbody, CC4 = isthmus, CC5 = splenium, as suggested by Weis et al. (21) (as shown in Fig. 1A). The area of each subsection was calculated. To address interindividual differences in head size, each area was corrected by dividing each subject’s intracranial area in the midsagittal plane.

Inter- and intrarater reliability measurements were also performed. Total and regional callosal areas from 10 random traces were obtained by two raters. The intraclass correlation coefficient for interrater reliability for the total area was 0.92. For the regional areas, each was at least 0.90. For each section of the CC and the total area, intrarater reliability was high (all intraclass correlation coefficients $>0.92$).

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![Fig. 1. A. Manual tracing of the CC on a midsagittal slice. A rectangle was constructed around the CC and divided into five parts of the same size (from the anterior to the posterior of the CC: CC1–CC5). B. Comparison of regional relative callosal area in patients with AD and healthy controls (HC).](image)
Table 1. White matter volume reduction in AD patients as compared to the control group

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Number of voxels*</th>
<th>Coordinates†, mm</th>
<th>Minimum t‡</th>
<th>White matter volumes§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>5096</td>
<td>-15 -27 28</td>
<td>-6.45</td>
<td>Isthmus and splenium of the CC</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>2437</td>
<td>-37 -19 -12</td>
<td>-4.83</td>
<td>Left temporal lobe</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>203</td>
<td>37 -8 -34</td>
<td>-4.15</td>
<td>Right temporal lobe</td>
</tr>
</tbody>
</table>

* Total number of contiguous voxels in each cluster that presented t values ≤−4.0 (corresponding to P<0.05, corrected for multiple comparisons using random field theory (30)) and a cluster size ≥200 voxels. † MNI (Montreal Neurological Institute) coordinates at the local minima of white matter volume reduction within each cluster in AD patients compared with the control group. The x value indicates the distance from the left (negative values) to the right (positive values) side of the brain, passing through the anterior commissure (0). The y value indicates the distance in millimeters from the posterior (negative values) to the anterior (positive values). The z value indicates the distance from the inferior (negative values) to the superior (positive values). ‡ T values at the local minima with each cluster. § Regional white matters encompassed in each cluster of between-group volumetric differences.

Statistical analyses

The smoothed data were analyzed using MATLAB 7 and statistical parametric mapping (SPM99), which employed the framework of the General Linear Model. Regionally specific differences in white matter were assessed statistically using a two-tailed test, namely, testing for increases or decreases in white matter. The voxel-by-voxel two-sample t test was used to detect regional white matter volume differences between the AD and control groups. The statistical map was thresholded at P<0.05 at the cluster level (and P<0.001 at the voxel level), with whole-brain corrections for multiple comparisons (22). Only significant results (P<0.05, corrected for multiple comparisons using random field theory (22)) and a cluster size equal to or greater than 200 voxels were reported. The statistical parameter map was overlapped onto the customized template from all spatially normalized images. Finally, a two-tailed two-sample t test was also performed to compare differences in the regional callosal areas between the AD patient group and the control group.

Results

Between-group white matter volume decrease using optimized VBM

In AD patients, significant decreases in white matter volume were found in the posterior regions of the CC (isthmus and splenium) and the temporal lobe in the left and right hemispheres. Moreover, the voxel showing peak statistical difference in the posterior of the CC was left sided. The results are shown in Table 1 and Fig. 2. No significant decreases of white matter volume were found in other areas of the cerebrum.

Between-group CC area differences using ROI analysis

The five subdivisions of the CC were found to occupy significantly smaller areas in patients with AD relative to healthy controls using ROI measurements (CC1: $P=0.025$; CC2: $P=0.0456$; CC3: $P=0.0065$; CC4: $P=0.0026$; and CC5: $P=0.0164$).

The comparisons of the regional relative callosal area are shown in Fig. 1B. The P value was obtained by a two-sample two-tailed t test.

Fig. 2. Regional white matter volume decreases in AD patients compared to healthy controls by optimized VBM. Only significant results ($t\leq -4.0$, corresponding to $P<0.05$, corrected for multiple comparisons using random field theory) and a cluster size ≥200 voxels are reported. The first row shows the affected CC with three views, and the threshold map is superimposed on a coronal (y=−27), sagittal (x=−15), and axial (z=−28) section through the customized template. The second row shows the left temporal lobe with significant changes on a coronal (y=−19), sagittal (x=−37), and axial (z=−12) section. Similarly, the third row demonstrates the affected right temporal lobe on a coronal (y=−6), sagittal (x=37), and axial (z=−34) section. X, y, and z indicate the MNI (Montreal Neurological Institute) coordinates.
Discussion

Many studies have suggested functional disconnections between brain regions among AD patients (1), but the structural basis of functional disconnections is not fully understood. Previous AD-related studies for gray matter may not be enough to understand this structural basis because the white matter fibers connecting these cerebral areas may also be affected. Although optimized VBM, as an automated, unbiased analysis of the differences in tissue concentration throughout the whole brain, has been successfully used in research regarding gray matter loss among AD patients (14), until now it has been infrequently used as it has in the present study. Our study of the decreases in regional white matter volume may provide an insight into the structural basis for functional disconnections among AD patients.

In this study, we found that the posterior regions (isthmus and splenium) of the CC showed significantly decreased volume among AD patients using optimized VBM. The CC is the major white matter tract that crosses the interhemispheric fissure in the human brain. The fiber tracts projecting through the posterior regions originate in layer III neurons of the posterior temporal lobe, superior parietal lobe, and occipital association regions (23). Our finding on the abnormalities of the posterior regions of the CC could provide the structural basis for the functional disconnections of homologous regions. Previous functional studies using positron emission tomography (PET) and electroencephalograph (EEG) have suggested interhemispheric disconnections in AD (1, 24). For example, Horwitz et al. (25) and Azari et al. (26) have consistently found weaker functional neocortical interactions among mild to moderate AD patients, especially between frontal association and both parietal association and paralimbic areas, using PET. Alexander et al. (27) have also shown that patients with AD have significantly reduced temporoparietal metabolism compared to healthy subjects, based on PET. Moreover, Wada et al. (24) showed that lower interhemispheric coherence was observed between the hemispheres of 10 mild to moderate AD patients compared to controls, using EEG. Our results can thus be further supported by previous diffusion tensor imaging (DTI) studies. Meanwhile, Rose et al. (28) have found a significant reduction in the structural integrity of white matter tracts in the splenium of AD patients. In addition, we found that the foci of CC atrophy in AD patients had their peak of statistical significance on the left side of the CC. This is consistent with recent AD-related studies (13). Such lateralization of CC variations might relate to patterns of progression of cortical atrophy in AD, because several VBM studies (14, 29), sulcal-warping studies (30, 31), and SPECT and PET studies (2, 32) have supported a laterality trend of the atrophic process, and greater left than right hemispheric involvement in AD.

Another finding of this study was that temporal white matter in the left and right hemispheres showed AD-related volume decreases. Temporal white matter contains fibers that interconnect the temporal cortex and amygdala with other brain structures, and there are greater numbers of nerve fibers along the horizontal and longitudinal (bore) directions than those in the vertical direction (e.g., inferior occipitofrontal fasciculus, uncinate fasciculus, and fiber bundle crossing anterior commissure) (33). Our finding was consistent with previous DTI studies (4, 28), showing abnormalities in the white matter of the temporal lobe in the early course of AD patients. The decreases in volume of the bilateral temporal lobe white matter fibers may be related to the abnormal functional connectivity of the temporal regions. One recent fMRI study (34) demonstrated that AD patients showed decreased functional connections between the right hippocampus and the medial prefrontal cortex, right inferior-temporal cortex, bilateral cuneus, right superior and middle temporal gyrus, and posterior cingulate cortex (PCC). The temporal lobe white matter abnormality shown in this study may contribute to the underlying structural substrate of the functional disconnectivity found among AD patients.

Some limitations of the study need to be considered. Firstly, from a methodological perspective, certain previous studies have suggested that VBM should be used with caution (9, 14). One of the reasons is that anatomical standardization may not fully account for the atrophy of callosal white matter tracts due to the adjacent enlarged lateral ventricle. In this study, although the optimized VBM that utilized customized stereotaxic templates from AD patients and the normal control group was adopted to decrease the normalization error, all reported areas were periventricular, and no other significant changes were found. Thus, VBM investigations on CC volume reduction need to be further validated. In the present study, we employed manual measurements on the CC based on ROI analysis. The ROI results showed that the five subdivisions of the CC were significantly smaller in patients with AD relative to the control group. VBM findings on the temporal white matter also confirm previous studies in AD. Secondly, this study has explored regional white matter volume...
decreases in AD. However, it is not clear whether the gray matter regions associated with these abnormal white matter fibers are indeed abnormal. In the future, it will be interesting to investigate the correlation between white matter abnormalities and the interrelated gray matter regions. It will further contribute to our understanding of the underlying structural substrates of functional disconnections among AD patients.

In conclusion, compared with the control group, AD patients showed significantly reduced white matter volume in the posterior regions of the CC and the temporal lobe in the left and right hemispheres by optimized VBM. The foci of the CC atrophy in AD patients had their peak of statistical significance on the left side of the CC. Meanwhile, diffuse CC reductions (all five portions) were found by ROI measurements. Our findings suggest that these abnormal white matter regions may contribute to the functional disconnections among AD patients.

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