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Voxel-based assessment of gray and white matter volumes in Alzheimer's disease

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Abstract

Using the study-specific templates and optimized voxel-based morphometry (VBM), this study investigated abnormalities in gray and white matter to provide depiction of the concurrent structural changes in 13 patients with Alzheimer's disease (AD) compared with 14 age- and sex-matched normal controls. Consistent with previous studies, patients with AD exhibited significant gray matter volume reductions mainly in the hippocampus, parahippocampal gyrus, insula, superior/middle temporal gyrus, thalamus, cingulate gyrus, and superior/inferior parietal lobule. In addition, white matter volume reductions were found predominately in the temporal lobe, corpus callosum, and inferior longitudinal fasciculus. Furthermore, a number of additional white matter regions such as precentral gyrus, cingulate fasciculus, superior and inferior frontal gyrus, and sub-gyral in parietal lobe were also affected. The pattern of gray and white matter volume reductions helps us understand the underlying pathologic mechanisms in AD and potentially can be used as an imaging marker for the studies of AD in the future.

Keywords

Alzheimer's disease; Gray matter; Magnetic resonance imaging; Voxel-based morphometry; White matter

A number of brain magnetic resonance imaging (MRI) studies have indicated gray matter abnormalities in patients with Alzheimer's disease (AD). Compared to normal controls, patients with AD had significantly lower global gray matter volume, lower whole brain volume and greater ventricles [10,4,14]. At the early stages of the disease, regional gray matter atrophy was mainly restricted to the medial temporal structures including bilateral hippocampus, amygdala and entorhinal cortex, as well as the posterior cingulate gyrus and medial thalamus [13,12,2]. The abnormal brain areas extended to the parietal and frontal lobes with the advancement of the disease [10,19].

Neurodegenerative diseases lead to not only gray matter atrophy but also white matter abnormality. For patients with AD, white matter impairment is related to Wallerian degeneration [15]. Its pathological feature is primarily the loss or disconnection of fiber tracts [20]. The decreases in white matter volume measured by MRI may reflect such changes. For example, significant corpus callosum (CC) volume reduction was detected in the splenium, isthmus, body and genu in AD [3]. In the meanwhile, these reductions demonstrated corresponding gray matter neurodegenerative changes interconnected by CC [17,23,3]. A recent MRI study using cortical surface model measured the volume of gyral white matter and found that many white matter areas, including the parahippocampal, entorhinal, inferior parietal and middle frontal regions, showed the strongest AD-associated reductions [18].

Voxel-based morphometry (VBM) is a fully automated and objective method of examining voxel-based gray or white matter differences across the whole brain in different populations [1,9]. Using VBM, Baxter et al. studied the relationship of cognitive measures, respectively with regional gray and white matter volumes in patients with AD, and also reported gray and white matter differences between patients with AD and normal controls [2]. To date, most brain structural MRI studies using VBM in AD have focused on only gray matter abnormalities [12-14,6] with the exception above [2] and some other reports investigated either only CC changes in AD [3] or white matter abnormalities in patients with mild cognitive impairment (MCI) [21]. In addition, less is known about the relationship of regional volume changes between gray and white matter in AD.

Using optimized VBM, this study further systematically investigated regional volume abnormalities in gray matter and especially white matter in patients with AD. We also provided some discussion on how gray and white matter abnormalities were interrelated.

Thirteen patients with AD and 14 healthy controls, recruited from memory clinic at Xuanwu Hospital of Capital Medical University, were included in this study. Written informed consent was obtained from all participants. This study was approved by the Medical Research Ethics Committee of Xuanwu Hospital. The diagnosis of probable AD was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [16]. Severity of cognitive impairment was assessed with Mini-Mental State Examination (MMSE) [8]. Healthy controls had no cognitive complaints and did not have neurological or psychiatric disorders. Subjects with visible white matter hyperintensities (WMH) (grade 2 or more by a reported rating scale [7]) were excluded. Demographic and clinical characteristics of subjects are given in Table 1. The AD group did not differ from healthy controls in sex ratio, age or education, but had significantly lower MMSE scores [$T(25) = 10.575$, $P < 0.001$].

MRI was performed on a 3.0T Siemens Trio Tim scanner. For each subject, a whole brain T1-weighted, sagittally oriented 3D anatomical imaging data was acquired using a magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence (TR = 1900 ms, TE = 2.2 ms, TI = 900 ms, flip angle = 9°, field of view = 224 mm×256 mm, matrix size = 448×512 and voxel size = 0.5 mm×0.5 mm×1 mm).

Data analysis was performed according to the optimized VBM protocol [9] using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>). The study-specific templates, including T1 template, gray and white matter and cerebral spinal fluid (CSF) prior probability maps, were created from all participants avoiding possible inaccuracy in the spatial normalization and segmentation using SPM default templates. The customized templates were created following what described in a number of studies. For completeness, the step-by-step procedure is briefly noted here: (1) the native T1 image for each subject was segmented into gray, white matter and CSF using the default SPM brain tissue prior probability maps; (2) the segmented gray matter was spatially

normalized to the SPM gray matter prior map by using affine registration and nonlinear warping, normalization parameters estimated were then applied to the raw T1 image; (3) the normalized T1 image was segmented into gray, white matter and CSF; and (4) The T1, gray and white matter and CSF maps obtained from step 3 were respectively averaged over all subjects and smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel to create the study-specific templates.

Data spatial preprocessing was similar to the template creation step, but using the study-specific templates. The normalization parameters were determined only to match the individual gray matter image to the customized gray matter prior map so that the normalized T1 images were segmented into three compartments in the complementary space. In addition, the normalized gray and white matter partitions were each multiplied by the Jacobian determinants from the normalization to preserve the total amount of tissue in the native images [9], then smoothed with an 8 mm FWHM Gaussian kernel.

Global tissue volumetric differences between groups were performed using two samples *T*-test ($P < 0.05$). Regional differences in respective gray and white matter between groups were examined using general linear model to account for the effects of age, sex and the total intracranial volume (TIV).

The normalized global volume of gray matter (relative to TIV) was significantly smaller for AD subjects than controls (0.3212 ± 0.0287 vs. 0.3403 ± 0.0186 , $T = 2.07$, $P = 0.025$), and that of white matter was also significantly smaller (0.2156 ± 0.0090 vs. 0.2287 ± 0.0156 , $T = 2.64$, $P = 0.007$).

Table 2 shows the detailed locations of gray matter volume reductions significant at $P < 0.05$, corrected for multiple comparisons using the False Discovery Rate (FDR) across the whole brain. Compared with normal controls, patients with AD exhibited significant gray matter volume reductions mainly in the hippocampus, parahippocampal gyrus, insula, superior/middle temporal gyrus, thalamus, caudate head, cingulate gyrus, superior/inferior parietal lobule, middle occipital gyrus, and superior/inferior frontal gyrus (Fig. 1).

Table 3 shows the detailed locations of white matter volume reductions significant at $P < 0.05$, FDR corrected across the whole brain. Compared with normal controls, patients with AD exhibited white matter volume reductions predominantly in the temporal lobe (parahippocampal gyrus, superior temporal gyrus, and sub-gyral in temporal lobe), corpus callosum, and inferior longitudinal fasciculus. In addition, there were diffuse reductions in precentral gyrus, cingulate fasciculus, superior/inferior frontal gyrus, and sub-gyral in parietal lobe (Fig. 2).

There were a number of voxel-based MRI studies about gray matter changes in AD [12-14, 6]. The findings of the global volumetric measures and regional gray matter volume reductions in AD from this current investigation are consistent with, or complementary to, the previous studies. Our study added to the existing few VBM reports on white matter volume across the whole brain [21,3] and the one on both gray and white matter in AD [2]. An important finding in this study is the AD-related widespread distribution of white matter volume defects.

Within the temporal lobe and its medial regions, our results showed gray matter volume reductions in the hippocampus, parahippocampal gyrus, and superior temporal gyrus as well as the white matter volume decreases in the parahippocampal gyrus, superior temporal gyrus and sub-gyral in temporal lobe. An investigation by Stoub et al. showed decreases in both white matter volume in the parahippocampal gyrus and gray matter volume in the hippocampus contributed to memory decline in individuals with MCI [21]. Our recent study also found diffusively reduced white matter volumes in patients with MCI prominently in the bilateral

temporal gyrus [24]. In contrast to these two previous studies, it seemed that there were greater and more extensive white matter abnormalities in the temporal lobe in AD than in MCI patients, indicative that the progressive brain tissue changes are associated with the development of disease. Consistently, the study by Baxter et al. also found gray and white matter reductions in the temporal lobe in AD [2]. Moreover, they reported that the Alzheimer's Disease Assessment Scale-Cognitive subtest (ADAS-Cog) was more specific to gray matter integrity whereas the MMSE reflected a more global reduction in both gray and white matter [2].

It is worth noting that white matter volume decreases coincided with adjacent gray matter volume reductions in both left and right temporal lobes. This finding is similar to fractional anisotropy (FA) decrease using DTI [25], which suggests that interconnection among medial temporal structures as well as related cortical regions is disrupted or impaired. In light of the detected entorhinal volume changes, loss of parahippocampal white matter volume and hippocampal atrophy observed in MCI patients, Stoub et al. offered three possible causes [21]: entorhinal atrophy being part of the cause of this decrease in white matter volume; changes in afferent connections to the entorhinal cortex that would result in the disruption of multi-modal sensory input to the hippocampus; and partial demyelination in remaining fibers. Though we are not able to exclusively identify the cause, the detected abnormalities in white and gray matter in this current study are concurring.

The CC volume reduction in AD was significant in the genu, rostrum, rostral and anterior of body as well as in the isthmus and splenium (with higher but still significant type-I error). In general, our CC atrophy finding agreed well with the results of several MRI studies [17,23,3] but was more bilateral. Reporting left lateralization, Chaim et al. indicated that lateral atrophic change of the CC in the early stages of AD should be further investigated in longitudinal MRI studies [3].

CC is a crucial fiber tract interconnecting corresponding cortical regions in left and right hemispheres. As discussed in previous studies [17,3], the anterior callosal abnormalities were related to gray matter atrophy in the frontal lobe, the isthmus and splenium related to that in the temporal and parietal lobes. Pantel et al. also reported that regional CC atrophy was correlated with regional cerebral volume reduction in these related lobes [17]. Consistent with these explanations above, we observed white matter abnormalities in various CC parts and simultaneous gray matter atrophy in the corresponding frontal, temporal and parietal lobes. Thus, our findings seem to support the view on the relationship between gray matter atrophy in various parts of the brain and especially the CC white matter abnormalities.

This study also found significant white matter volume decrease in inferior longitudinal fasciculus. Using DTI data, Stricker et al. observed that patients with AD had reduced FA in the late-myelinating pathways including inferior longitudinal fasciculus and superior longitudinal fasciculus. Our findings and the one by Stricker et al. are in agreement with the retrogenesis model of white matter degeneration in AD [22]. The retrogenesis model suggests that the late-myelinating fiber tracts are more vulnerable to degeneration than the early-myelinating tracts in AD. Interestingly, in our previous study about brain development, we also found notable positive increases in white matter volume in inferior and superior longitudinal fasciculus [11].

We also noted that sparse and widespread white matter regions in precentral gyrus, cingulate fasciculus, superior/inferior frontal gyrus and sub-gyral in parietal lobe were affected. White matter volume reductions in some of these regions, such as precentral gyrus and superior frontal gyrus, are in line with a recent MRI study [18].

Combining complementary information from more than one dataset can potentially increase the sensitivity and specificity to distinguish the patients with AD from normal controls. One

of the approaches is the use of the multi-modal partial least square (PLS) method we recently introduced [5]. In this study, we investigated both gray and white matter, complementarily providing information about brain tissue loss from these two tissue types. Using multi-modal PLS or other multi-modal integration techniques to combine information from the two complementary brain tissue datasets, it is possible to construct a more sensitive and reliable imaging marker for the studies of AD in the future.

Using the study-specific templates and optimized VBM, this study investigated abnormalities in gray matter and, more importantly, white matter to provide a comprehensive depiction of the structural changes in patients with AD relative to healthy controls. The pattern of gray and white matter reductions helps us in better understanding the underlying pathologic mechanisms in AD.

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Fig. 1. Significance maps of gray matter volume decreases in AD superimposed on the customized average template from all subjects (left of the plane is the left of brain, axial slices). The color bar represents the T score.

Fig. 2. Significance maps of white matter volume decreases in AD superimposed on the customized average template from all subjects (sagittal slices). The color bar represents the T score.

Table 1

Demographic and clinical characteristics of subjects.

	Alzheimer's disease	Healthy controls
No. of subjects	13	14
Sex (F/M)	7/6	8/6
Age (years $\pm$ SD) (range years)	72.1 $\pm$ 6.5 (58–81)	70.4 $\pm$ 3.5 (61–82)
MMSE scores (range)	18.5 $\pm$ 3.5 (12–23)	28.5 $\pm$ 0.6* (27–29)

* MMSE scores were statistically significant at $P < 0.001$

Table 2

Locations of gray matter volume reductions in patients with AD compared to normal controls.

Brain regions	P	T*	Peak coordinates	Cluster size (mm ³)
L middle temporal gyrus	0.010	4.19	-52 -67 10	15,263
R middle temporal gyrus	0.007	5.33	52 -68 11	9,303
R superior temporal gyrus	0.007	5.18	58 -41 9	3,649
L superior frontal gyrus	0.017	3.45	-8 23 61	1,622
R superior frontal gyrus	0.008	4.95	19 15 62	1,450
R inferior frontal gyrus	0.021	3.28	52 36 -10	688
L inferior parietal lobule	0.023	3.20	-36 -48 57	404
R inferior parietal lobule	0.008	4.71	36 -51 56	338
L hippocampus	0.011	4.06	-30 -14 -14	5,622
L parahippocampal gyrus	0.007	6.82	-14 -34 -6	3,045
R parahippocampal gyrus	0.032	2.92	24 -54 5	1,899
L insula	0.007	6.77	-39 4 6	9,826
R caudate head	0.007	6.68	6 1 5	3,907
L thalamus	0.007	6.21	-15 -31 0	5,015
L cingulate gyrus	0.019	3.35	-13 8 42	260
R posterior cingulate	0.026	3.08	17 -60 8	347

T*: $P < 0.05$, corrected using False Discovery Rate (FDR); L: left; R: right; coordinates in Talairach space.

Table 3
Locations of white matter volume reductions in patients with AD compared to normal controls.

Brain regions	P	T*	Peak coordinates	Cluster size (mm ³)
L parahippocampal gyrus	0.015	5.73	-35 -11 -17	16,204
L temporal lobe, sub-gyral	0.015	5.66	-36 -12 -15	
L inferior longitudinal fasciculus	0.015	4.33	-42 -33 -6	
R superior temporal gyrus	0.015	6.11	39 -54 14	18,136
R parietal lobe, sub-gyral	0.015	5.02	32 -44 22	
R inferior longitudinal fasciculus	0.015	4.40	42 -38 0	
R corpus callosum	0.015	4.85	7 21 16	4,335
R anterior cingulate	0.015	4.76	12 22 18	
L corpus callosum	0.015	4.83	-3 25 1	4,468
L precentral gyrus	0.015	5.50	-51 -3 27	1,349
R precentral gyrus	0.015	6.14	48 -3 31	694
L superior frontal gyrus	0.015	4.90	-11 27 50	514
R superior frontal gyrus	0.018	3.89	16 60 -9	453
L inferior frontal gyrus	0.023	3.63	-35 8 26	571
R inferior frontal gyrus	0.019	3.85	49 29 8	251

T*: $P < 0.05$, corrected using False Discovery Rate (FDR); L: left; R: right; coordinates in Talairach space.