Regional Measurement of Hippocampal Atrophy in Alzheimer's Disease Using Optimized Manual ROI segmentation and Voxel Based Morphometry

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Purpose

Voxel based morphometry (VBM) has been increasingly applied to investigate differences in brain morphology between a group of patients and control subjects. VBM permits comparison of gray matter (GM) volume at voxel-level from the entire brain, thus is an efficient method for assessing regional differences. In addition, since the results are displayed on the standardized brain template, the exact brain region can be identified from the Atlas. However, despite its high efficiency, whether VBM can accurately depict atrophy of irregularly-shaped subcortical structures, such as hippocampus, is questionable. Since each individual image set is normalized to a standard template, the information may not be preserved during the procedure. The purpose of this study was 1) to assess the regional GM volume loss measured by VBM in AD compared to controls, and 2) to measure hippocampal volume using manually delineated volumetry and compare the results to VBM findings.

Methods

Twenty-three AD (mean age 70 ± 8 yo; male/female= 7/16, Mini-Mental State Exam [MMSE]= 22.2) and 20 cognitively normal elderly control subjects (mean age 69 ± 4 yo; male/female= 10/10) were included in this study. High-resolution axial view T1-weighted volumetric MR images (TE/TR = 10/700 ms, 24 cm × 24 cm field-of-view (FOV), matrix size of 128 × 256, 1.5 mm thickness) were acquired using a Siemens 1.5 T Magnetom scanner. To improve the VBM performance, a study-specific template and the probability maps were generated from the control subjects. The 20 sets of images were first normalized to the Montreal Neurological Institute (MNI) coordinate using a 12-parameter affine transformation, and smoothed with an 8 mm isotropic Gaussian kernel, then averaged to obtain the template. The second step was to create the probability maps for segmentation. The original images from each subject were segmented into GM, WM, and CSF. The brain extraction, based on erosions using MRIcro, was used to remove nonbrain tissues from the segmented images. Then the smoothed GM/WF/CSF maps were averaged to obtain the stereotactic customized probability maps. The VBM analysis was performed using the AnCova model in SPM, to measure and compare the GM volume between the 2 groups with 23 AD patients and 20 controls. The z-map was thresholded at P<0.001 uncorrected. The voxels with the highest z-values represented the region where GM volume was significantly different between these two groups. The ROI-based hippocampal volume was manual traced using an in-house program ROITOOL. This user–friendly program provides simultaneous views from 3 orthogonal planes for a better landmark referencing. The original images were resliced into contiguous coronal, 1.25-mm thick images oriented perpendicular to the intercommissural line, then loaded for analysis. After completing tracing the volume was automatically calculated in mm^3. The program also provides intracranial tracing based on skull-stripped brain analyzed by MRIcro. Normalized hippocampal volume to the intracranial volume was compared between AD and control groups.

Table1. Volumetric feature of AD patients and control

	AD	Normal
Number	23	20
Age (y)	70	69
MMSE	22.2	
VBM-GM (mm^3)	573(45.4%)	653(48.7%)
VBM-WM (mm^3)	357(28.3%)	392(29.3%)
VBM-CSF (mm^3)	331(26.3%)	295(22.0%)
VBM-TCV (mm^3)	1262	1341
ROI-TCV(mm^3)	1273	1345
ROI-HP(mm^3)	1.5(0.12%)	2.5(0.19%)

TCV:total cranial volume; HP: Hippocampus

Results

Table 1 shows the regional GM, WM, and CSF volume in the AD and control groups, and the percentage after normalizing to the intracranial volume. The AD group had a lower GM %, and a higher CSF% compared to controls. The total intracranial volumes analyzed using SPM and our own ROITOOL program were very close (p<0.0001). The hippocampal volume of AD patients was significantly lower than that of controls (P<0.001). The VBM analysis of group GM difference using voxel-wise two-sided t test are illustrated in Fig.1. The significant pixels were overlaid on the axial T1-weighted MR images. The regions, with cluster size and Voxel T and Z scores are summarized in Table 2. The region includes parahippocampal gyrus, anterior/posterior cingulate gyrus, insula, frontal lobe and middle temporal complex. Despite the high significance in manual ROI analysis, hippocampus was not revealed in the VBM.

Table 2. GM volume loss in AD patients compared to the age matched control

Region	Cluster size k	BA	Voxel T	*Z* score
posterior cingulate	6328	31	7.95	6.15
anterior cingulate	1216	25	6.54	5.38
Lt. parahippocampus	921	30	6.15	5.15
Rt. parahippocampus	1216		6.67	5.46
middle temporal	6141		7.32	5.82
Rt. Sup temporal	1522		6.66	5.45
Lt. Sup temporal	368	8	7.09	5.69
Rt. middle frontal	1854		8.57	6.45
Lt. superior frontal	372	8	7.09	5.69
Rt. Inferior frontal	253		6.79	5.53
Insula	6141	13	7.00	5.65

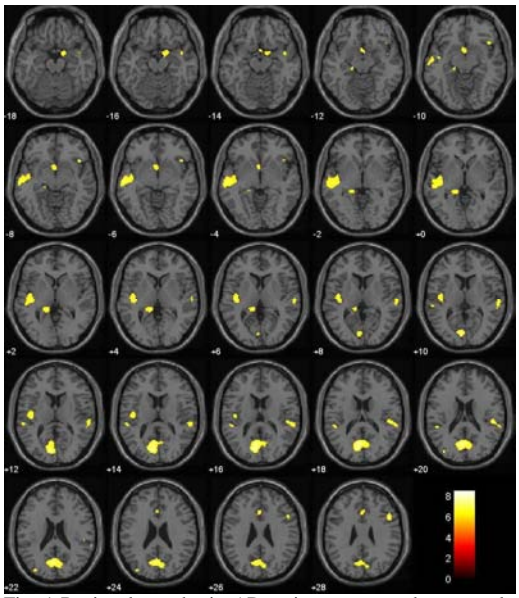

Fig. 1 Regional atrophy in AD patients compared to controls. Significance is set at uncorrected *P*< 0.001. The main regions were cingulate gyrus, middle temporal, frontal and insula.

Discussion

In this study, we applied VBM analysis and ROI-based volumetry to compare brain atrophy in mild to moderate AD patients with normal elderly controls. It is known that the medial temporal lobe, particularly the hippocampus, is the first area to develop AD pathology [Baron et al. Neuroimage 2001;14: 298–309]. Many studies have confirmed hippocampal atrophy in AD or even MCI (patients with mild cognitive impairment). In our series, we also found that the hippocampal volume in AD was significantly smaller than in controls using ROI-based volumetry. However, although our VBM results demonstrated that AD patients had a significant atrophy in middle temporal lobe, parahippocampus and insula, the hippocampus was not revealed. Since the shape of hippocampus was irregular and close to the temporal horn of ventricles, the information might be lost during the normalization and smoothing process in the VBM. A global shape deviation from that of the template might lead to registration inaccuracy during normalization, also unevenly distributed atrophic changes in the hippocampus might be attenuated by the smoothing step. In contrary, the individual differences could be well accounted for when applying ROI-based analysis. However, VBM analysis was efficient. In addition to temporal regions, the AD patients also demonstrated significant atrophy in anterior and posterior cingulate, and also the frontal lobe. These regions were reported in the literature. The information provided by manual volumetry and VBM are complementary. While VBM can be applied to assess global atrophy efficiently, manual volumetry is needed to study irregularly-shaped subcortical structures.