Evaluation of multiple voxel-based morphometry approaches and applications in the analysis of white matter changes in temporal lobe epilepsy

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Abstract. The purpose of this study was to compare multiple voxel-based morphometry (VBM) approaches and analyze the whole-brain white matter (WM) changes in the unilateral temporal lobe epilepsy (TLE) patients relative to controls. In our study, the performance of the VBM approaches, including standard VBM, optimized VBM and VBM-DARTEL, was evaluated via a simulation, and then these VBM approaches were applied to the real data obtained from the TLE patients and controls. The results from simulation show that VBM-DARTEL performs the best among these VBM approaches. For the real data, WM reductions were found in the ipsilateral temporal lobe, the contralateral frontal and occipital lobes, the bilateral parietal lobes, cingulated gyrus, parahippocampal gyrus and brainstem of the left-TLE patients by VBM-DARTEL, which is consistent with previous studies. Our study demonstrated that DARTEL was the most robust and reliable approach for VBM analysis.

1 Introduction

Voxel-based morphometry (VBM) is a computational quantitative magnetic resonance image (MRI) analysis technique which can detect the differences of the brain tissue composition between groups. Compared with the conventional region-of-interest (ROI) analysis, VBM is fully automated and unbiased, and is not restricted to the analysis of specific brain regions. VBM was first proposed by Ashburner and Friston [1], which allows a voxel-wise study of differences in tissue concentration throughout the whole brain between groups. An optimized VBM method was introduced by Good et al. [2], improving image registration and segmentation. More recently, the preprocessing steps of VBM have been improved with the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) registration method [3]. DARTEL was proposed by Ashburner as an

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alternative to the traditional registration measures in statistical parametric mapping (SPM), which can achieve more accurate inter-subject registration of brain images.

VBM has been applied to detecting the pathological changes in various diseases [4-6]. In particular, there have been lots of studies focusing on the application of VBM in temporal lobe epilepsy (TLE) [6-8]. TLE is one of the most frequent forms of partial epilepsy in adults, and is defined as a chronic neurological condition characterized by recurrent unprovoked seizures originating from temporal lobe. Many MRI studies have shown that structural abnormalities associated with TLE have been found in the hippocampus as well as other structures in extrahippocampal regions. Keller et al. [8] compared the standard and the optimized VBM for analysis of brain abnormalities in TLE, revealing that the optimized VBM might detect the subtle neuroanatomical changes that were not found in the standard VBM. According to previous studies, we found that most studies focused on finding gray matter (GM) atrophies in TLE patients, while a few studies on white matter (WM) abnormalities.

As DARTEL is a very recent technique used in VBM, only a few studies have applied this new method in VBM [9], and there has not been any studies detecting the structural changes in TLE with DARTEL. Yassa et al. [10] evaluated several registration approaches, concluding that DARTEL was a real improvement over the standard registration method. However, VBM-DARTEL was not compared with other VBM approaches in previous studies.

In our study, we first evaluated these VBM techniques (standard VBM, optimized VBM, and VBM-DARTEL) via simulated data to provide a ground truth. Then these VBM approaches were applied to the real data to detect the WM abnormalities between the unilateral TLE patients and controls. This is the first study to compare VBM-DARTEL with standard and optimized VBM and be applied to TLE, and the performance of these multiple VBM approaches was quantified in our study.

2 Materials and Methods

2.1 Simulation of Atrophy

Images with simulated atrophy can act as the gold standard for evaluating the relative merits of various VBM approaches. We employed 20 normal anatomical models from BrainWeb (http://www.bic.mni.mcgill.ca/brainweb/) and the algorithm developed by Karacali and Davatzikos, which automatically simulated anatomical deformations, was used to simulate the volumetric loss of 3D images [11]. To eliminate inter-individual differences, the 20 normal models were considered as the controls, and the corresponding images with simulated atrophies were the patients. We selected three regions (centered in the left hippocampus, the right frontal lobe and the right occipital lobe) to simulate atrophies (Fig. 1). The radius of the three regions was 5/5/2mm, and the atrophied degree was 25±1.62%, 10±1.75%, 25±1.62%, respectively. In addition, we add Gaussian noise to all the images (SNR=33).The acquisition parameters were as follows: TR/TE=22/9.2 ms, flip angle (FA) =30° and 1 mm isotropic voxel size.

2.2 Subject and Data Acquisition

The study group consisted of 20 left-TLE patients (age: 33.2±8.1 years; 9 males), 20 right-TLE patients (age: 34.1±7.2 years; 9 males) and 20 controls with no history of neurological or psychiatric symptoms (age: 32.2±6.2 years; 9 males). All of these groups were matched in age and gender. The laterality of the seizures origin was determined based on medical history, ictal EEG and hippocampal atrophy observed on MRI. Written informed consent was obtained from each subject before the study.

T1-weighted MRI scans were obtained using a 3 Tesla scanner with following parameters: TR/TE/TI = 7/3/400 ms, slice thickness = 1.6 mm, FA= 15°, matrix size = 256×256, field of view (FOV) = 24×24 cm^2, yielding axial slices with in-plane resolution of 1×1 mm^2.

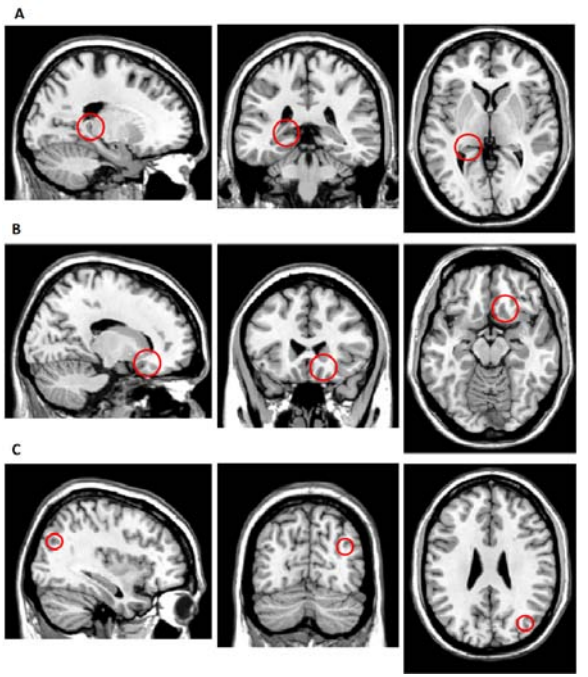

Fig. 1. Landmarks for simulated atrophies centered in (A) the left hippocampus, (B) the right frontal lobe and (C) the right occipital lobe.

2.3 Image Preprocessing

All the 3D T1-weighted images were brain extracted to exclude the non-brain tissues and reoriented with the origin set close to the anterior commissure (AC). All these images were then preprocessed with multiple VBM approaches detailed as follows. Preprocessing steps were performed by using Statistical Parametric Mapping (SPM8)

(http://www.fil.ion.ucl.ac.uk/spm, Wellcome Department of Cognitive Neurology, London, UK, 2008) on a Matlab 7.6 platform (MathWorks, Natick, MA, USA).

The methodology of the standard VBM was proposed by Ashburner and Friston in 2000 [1], which was used to detect the differences in tissue density between groups. All the skull-stripped and reoriented images were spatially normalized to the Montreal Neurological Institute (MNI) space by minimizing the residual sum of squared differences between structural MRI and the ICBM 152 template image. The data were then resampled to $1.5\times1.5\times1.5$ mm^3. All these images were partitioned into GM, WM and CSF using the unified segmentation algorithm with bias correction incorporated in [12]. WM images were then smoothed with an 8-mm smoothing kernel.

The optimized VBM method customized a study-specific template obtained from all the subjects. Each reoriented image was normalized to MNI template and resliced to 1.5-mm isotropic voxels. Then, they were smoothed with an 8-mm Gaussian kernel. The whole-brain template was created by averaging all these images. The reoriented images were then normalized to the customized template and resliced to $1.5\times1.5\times1.5$ mm^3. After that, the unified segmentation algorithm [12] was performed. The segmented WM images were smoothed with 8-mm FWHM and the average image was the specific WM template. The reoriented images were segmented in native space. Each segmented WM image was normalized to the study-specific WM template with the normalization parameters applied to the reoriented images. Then, these normalized images were segmented again. Furthermore, modulation was alternative to correct for volume changes, creating the Jacobian scaled warped WM images. These images were then smoothed with an 8-mm Gaussian filter.

In VBM-DARTEL method, each reorientated image was first segmented into GM, WM and CSF in native space and then Procrustes aligned GM and WM images were generated by a rigid transformation. The resolution of the aligned images was specified as $1.5\times1.5\times1.5$ mm^3. The study-specific GM/WM templates were then created by the aligned images from all the patients and controls. The procedure began with the generation of an original template computing the average of all the aligned data, followed by the first iteration of the registration on each subject in turn. Thus, a new template was created and the second iteration began. After six iterations, the template was generated, which was the average of the DARTEL registered data. During iterations, all images were warped to the template yielding a series of flow fields that parameterized deformations, which were employed in the modulation step. Since the previous processing was in native space, it was a requirement to transform all the normalized, modulated data into MNI space. After the space transformation, all these images were smoothed with an 8-mm FWHM isotropic Gaussian kernel.

2.4 Statistical Analysis

Based on the general linear model, statistical parametric maps were created to identify brain regions with significant changes in patients relative to controls. As the simulated data, all the preprocessed WM images were analyzed with paired *t* test. An absolute threshold of 0.1 was used in the analysis. Since the images of controls and patients are from identical subjects, covariates (such as total intracranial volume (TIV), age and

gender) were not considered in this model. The performance of the three VBM approaches was quantitatively evaluated by the ratio which was calculated by dividing the number of true positive voxels by the number of all the detected voxels with increasing *t* values. As the real data, the processed WM images were analyzed using two-sample *t*-test. The absolute threshold was set to 0.1. TIV, age and gender were incorporated in the design as nuisance covariates. The statistical parametric maps were thresholded at a *p* value of <0.05 by False Discovery Rate (FDR) to correct for multiple comparisons, and the extent threshold was set to 20.

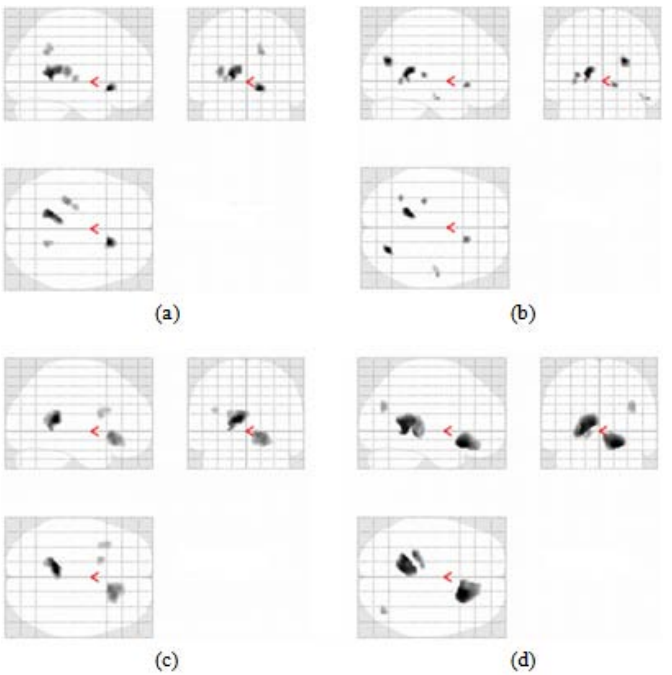

Fig. 2. Significant WM atrophies detected by (a) standard VBM, (b) optimized VBM (unmodulated), (c) optimized VBM (modulated), and (d) VBM-DARTEL using simulated data ($p < 0.05$, corrected for multiple comparisons using FDR, cluster size > 20 voxels).

3 Results

As the simulated data, significant WM atrophies detected by VBM approaches were shown in Fig. 2. We can see that all the VBM approaches have detected more or less degree of significant atrophies in the regions under the ground truth. With standard VBM (Fig. 2a), WM density changes were detected, but some false positive regions were also found. Using optimized VBM without modulation (Fig. 2b), less false positive regions were seen in the WM compared with standard VBM. For modulated

data (Fig. 2c), the optimized VBM method examined more significant atrophies in WM, and fewer false positive regions were presented. With VBM-DARTEL (Fig. 2d), most true positive regions and least false positive regions displayed. The two regions with 5-mm radius were detected in each VBM method. However, the detected area of the region with 10% atrophy degree was smaller in each VBM approach except VBM-DARTEL. In addition, the atrophied region simulated with 2-mm radius and 25%-atrophy was only detected by VBM-DARTEL. Hence, a conclusion can be drawn that VBM-DARTEL is more robust and reliable than other VBM methods.

The ratio of the true positive voxels in the detected regions with increasing *t* values was calculated to quantitatively evaluate the performance of VBM approaches (Fig. 3). For the same *t* threshold, the higher the ratio is, the better the performance is. It is clear that with the *t* value increased, the ratio increased and reached 100% fastest with VBM-DARTEL method, indicating that VBM-DARTEL performed best. The order of the performance of these VBM approaches is: VBM-DARTEL > optimized VBM (modulated) > optimized VBM (unmodulated) > standard VBM.

As the real data, significantly reduced WM concentrations were detected by the standard VBM protocol in the left-TLE patients (Fig. 4 (a)) but not by the optimized VBM without modulation. For VBM-DARTEL and the optimized VBM with modulation, which contained a modulation step, WM volume reductions were found in the left-TLE patients (Fig. 4 (b), (c)). Fig. 4 shows that the locations of significant regions detected by standard VBM are more widely distributed. The distributions of significant atrophies detected by optimized VBM (modulation) and VBM-DARTEL were similar but obviously larger extents were found using VBM-DARTEL.

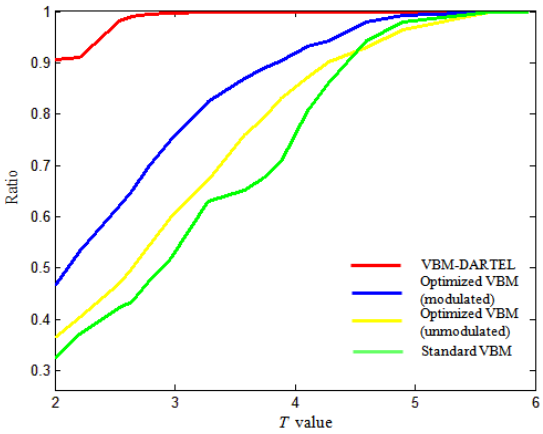

Fig. 3. The performance evaluated by the ratio of true positive voxels in the detected regions with increasing *T* values.

Concluded from the simulation, VBM-DARTEL is more robust and reliable than other VBM approaches. Using VBM-DARTEL, the left-TLE patients showed WM volume decreases predominantly focused in the ipsilateral temporal lobe, the

contralateral frontal and occipital lobes, the bilateral parietal lobes, cingulated gyrus, parahippocampal gyrus and brainstem (Table. 1). However, no significant WM concentration/volume reductions were examined in the right-TLE patients.

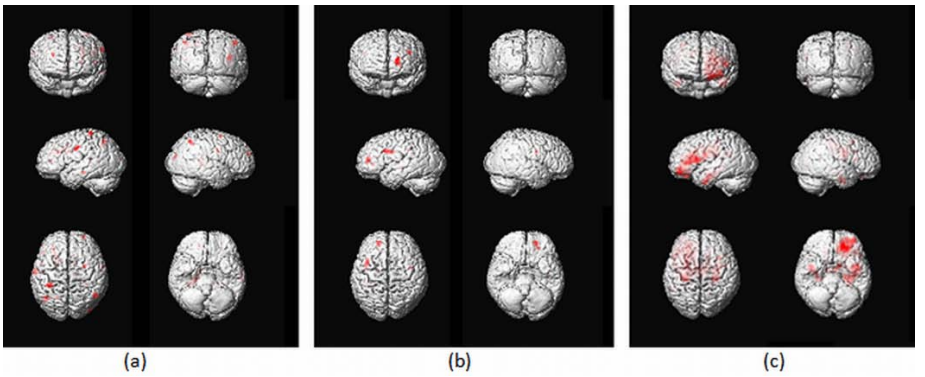

Fig. 4. Regions with significantly reduced white matter concentration/volume in the left-TLE patients (p<0.05, corrected for multiple comparisons using FDR) relative to controls by (a) standard VBM, (b) optimized VBM with modulation, and (c) VBM-DARTEL.

Table 1. Significant reductions in white matter detected in the left-TLE patients versus controls by VBM-DARTEL (p<0.05, corrected for multiple comparisons using FDR, cluster size > 20).

Anatomical location	Side	Talairach coordinates			p(FDR-corr)	t	Cluster
		x(mm)	y(mm)	z(mm)			
Cingulate gyrus	L	0	-9	31	0.024	5.07	25173
		-12	-36	34	0.027	3.17	90
Superior temporal gyrus	L	-37	-1	-18	0.024	4.40	3911
ParaHippocampal gyrus	R	34	-8	-20	0.024	3.74	1482
Inferior frontal gyrus	R	45	17	13	0.025	3.38	113
Inferior parietal lobule	L	-49	-44	26	0.026	3.22	149
Middle occipital gyrus	R	34	-67	7	0.036	2.85	45
Precuneus	R	15	-47	49	0.037	2.83	32
Transverse temporal gyrus	L	-37	-33	14	0.038	2.80	28
Brainstem	R	10	-15	-3	0.039	2.79	54

4 Discussion and Conclusions

In the present study, the performance of various VBM approaches (standard VBM, optimized VBM and VBM-DARTEL) was first evaluated by simulation, concluding that VBM-DARTEL performed the best and the optimized VBM with modulation came second. In the left-TLE patients, WM reductions were found in the ipsilateral temporal lobe, the contralateral frontal and occipital lobes, the bilateral parietal lobes,

cingulated gyrus, parahippocampal gyrus and brainstem by VBM-DARTEL. To the best of our knowledge, this is the first study to quantitatively evaluate VBM-DARTEL with standard and optimized VBM methods.

Previous studies [10] evaluated several registration approaches, concluding that DARTEL was a real improvement over the standard method. Keller et al. [8] revealed that the optimized VBM might detect more subtle neuroanatomical changes than standard VBM. In our study, VBM-DARTEL showed the best performance, next came the optimized VBM with modulation, which was a support to previous study.

There are many factors which may affect the results. First, voxels alignment is concernful in the preprocessing. Compared with other VBM methods, registration in DARTEL involves simultaneously minimizing the sum of squares difference between source and target images as well as the linear elastic energy of the deformations. While the normalization in SPM estimates nonlinear deformations by the linear combination of discrete cosine transformations, DARTEL provides high dimensional warping. Second, modulation is an important step in VBM. After nonlinear normalization, the volume of some regions may change. Modulation is the step to preserve the volume of a particular tissue within a voxel. With modulation, it is allowed to detect the volume changes. Third, template may also affect the results. In standard VBM, the template is ICBM 152 template. In optimized VBM, the template is generated by averaging the smoothed images from all subjects, which was matched with the study group. In DARTEL, the template is also created from all the subjects, but the procedure is iterative, which may improve the results. Many previous studies [8] have demonstrated the study-specific template might obtain more accurate results.

Some studies reported WM reductions of TLE patients in temporal lobe, frontal lobe and the corpus callosum [7]. Mueller et al. [8] found WM reductions in parietal lobe, parahippocampal gyrus and brainstem. Our results were consistent with these studies. Besides, our results from VBM-DARTEL showed more significant reductions in cingulated gyrus and occipital lobe, which was also detected in GM atrophy by Keller et al. [6]. Thus, our results have demonstrated the validity of VBM-DARTEL.

In our study, no significant WM atrophies were observed in the right-TLE patients. Coan et al. [13] reported that the atrophied progression was less intense in the right-TLE. Besides, less atrophies of hippocampus were observed in the right-TLE patients on MR images, suggesting that there might be less atrophy.

In the present study, some issues are still to be addressed. First, although VBM-DARTEL performed best among various VBM approaches, it has some disadvantages when compared with variable velocity models. The constant velocity vector field employed in DARTEL makes the model parameterization less suited to computational anatomy studies [3]. Second, the scanning parameters of simulated and real data were different, which might cause differences in the evaluation. However, the results from both simulated and real data revealed that VBM-DARTEL performs best, indicating VBM-DARTEL is appropriated to these two models.

The current study has some limitations. First, the images are resliced from $1\times1\times1$ mm^3 to $1.5\times1.5\times1.5$ mm^3 during the preprocessing step because of a memory problem in VBM-DARTEL. Thus, the atrophied size might be affected. Second, the TLE

patient group was heterogeneous without subgroup stratification and no consideration of medication was included, which is to be considered in the future.

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