Voxel-Based Morphometric Study of Brain Regions from Magnetic Resonance Images in Temporal Lobe Epilepsy

Matineh Shaker[1], Hamid Soltanian-Zadeh[1,2]
[1] *Control and Intelligent Processing Center of Excellence, Department of Electrical and Computer Engineering, University of Tehran, Tehran, Iran*
m.shaker@ece.ut.ac.ir, hszadeh@ut.ac.ir
[2] *Image Analysis Lab., Department of Radiology, Henry Ford Hospital, Detroit, Michigan, USA*
hamids@rad.hfh.edu

Abstract

The aim of this study was to analyze the brain structures in temporal lobe epilepsy (TLE) using 3D T1-weighed magnetic resonance images (MRI). We used a method of voxel-based morphometry (VBM) with the unified segmentation framework to examine the effects of TLE on specific brain structures in 22 patients. Also, 18 healthy control subjects were included in this study for group comparison. We accomplished GM segmentation, spatial normalization, and intensity non-uniformity correction in the same model. Besides, removal of nonbrain voxels and compensation of spatial normalization effects were performed in this study. Student's t-test statistical models of differences between gray matter concentration (GMC) of patients and controls were obtained using a general linear model (GLM). Compared to controls, TLE presented GMC reduction in hippocampus, amygdala, and entorhinal cortex. Comparison of abnormal areas detected by VBM method and manual delineation of these structures confirms the obtained results.

1. Introduction

Many neurodegenerative diseases exhibit volume and shape changes in specific brain regions. Neuroanatomical changes may be mild, and undetectable by visual inspection. Therefore, automatic methods for evaluation of the brain structures' changes are useful for the diagnosis and prognosis of neurological disorders [1,2]. These studies have clinical values in deciding about surgeries and treatment evaluations as well as diagnosis stages. Volumetric MRI studies of the brain structures in temporal lobe epilepsy (TLE) have shown brain abnormalities associated with this disease.

Voxel-based morphometry (VBM) is an automated technique that performs voxel-wise statistical analysis of magnetic resonance (MR) images that have been spatially normalized to a stereotaxic space to identify regional differences in gray matter (GM) between groups of subjects [3]. The main idea behind VBM analysis is the statistical comparison of GM and WM partitions obtained by segmentation.

Among all of the brain structures, those in the temporal lobe of the brain are most affected by TLE. In this study, we focused on hippocampus, amygdala, and entorhinal cortex. There are vast numbers of studies which examine the changes in hippocampus shape and volume in TLE. Also, some of the studies evaluate the changes in amygdala. To our knowledge, very limited numbers of studies included entorhinal cortex in the analysis.

The present paper is organized as follows. In Section 2, the specifications of data and image acquisition protocol are described. Also, we discuss about VBM method with unified segmentation framework and its advantages. Section 3 presents the MR data analysis details and results. Finally, Section 4 concludes the paper.

2. Materials and methods

2.1. Image acquisition and subjects

Two groups of subjects were used in this study. The first group were 22 TLE patients (14 females, 8

males), with an age average and standard deviation of 38 and 12 years, respectively. Their MR images were acquired using a General Electric 3 Tesla Signa system (GE Medical System, Milwaukee, WI).

All patients underwent coronal T1-weighted MRI study using a spoiled gradient-echo (SPGR) sequence with $TR/TI/TE = 7.6/1.7/500ms$, flip angle= 20°, field of view (FOV) $= 200\times 200mm^2$, matrix size= 256×256, pixel size= $0.781\times 0.781mm^2$, and slice thickness= $2.0mm$.

The second group of subjects were 18 healthy controls (4 females, 14 males), with an age average and standard deviation of 40 and 11 years, respectively. Their MR images given from IBSR website [4], were the coronal T1-weighted images with matrix size= 256×256, pixel size= $0.94\times 0.94mm^2$, and slice thickness= $1.5mm$.

2.2. Standard VBM

The standard VBM method consists of multiple stages. At its simplest case, preprocessing of data in VBM involves spatially normalizing images into a common stereotactic space. This is obtained by registering each of the images to the same template image by estimating the 12-parameter affine transformation. This is followed by the segmentation of GM from MR images based on voxel intensities. The next step is smoothing the GM segments with Gaussian kernels to reduce the image noise. In addition, by the central limit theorem, smoothing of the data will render the errors more normal in their distribution and ensure the validity of inferences based on parametric tests [5].

2.3. Unified Segmentation Framework

There are some problems with the standard VBM that lead to establishing modified procedures. In the standard VBM method, the images should be registered with tissue probability maps that represent the prior probability of different tissue classes. Then, Bayes rule can be used to combine these priors with tissue type probabilities acquired from voxel intensities. This process is circular, because registration needs an initial tissue classification and tissue classification needs an initial registration. This circularity can be resolved by a unified segmentation framework presented in [6], which combines both procedures in a single model. The advantage of this model is that it is more accurate and makes better use of the information existing in the data.

Thus, we accomplish GM segmentation, and spatial normalization in the same model as well as intensity non-uniformity correction. Also, for reducing the effect of nonbrain regions on the GM segmented images, all of the GM images are eroded to remove nonbrain voxels from the skull, scalp, and venous sinuses. This erosion is followed by a conditional dilation.

Another problem of the standard VBM method is that spatial normalization may cause some specific regions of the brain to expand and other regions to shrink. This effect can be compensated by multiplying voxel values of spatially normalized GM images by relative volume of GM before and after normalization. Indeed, this is a modulation procedure. The changes of the regions in the normalized image in relation to the original image make a deformation field. The gradient of this deformation field is its Jaccobian matrix and consists of the following matrix in the 3D space.

$$\begin{bmatrix} \frac{dx}{dx'} & \frac{dx}{dy'} & \frac{dx}{dz'} \\ \frac{dy}{dx'} & \frac{dy}{dy'} & \frac{dy}{dz'} \\ \frac{dz}{dx'} & \frac{dz}{dy'} & \frac{dz}{dz'} \end{bmatrix} \quad (1)$$

where $[x\ y\ z]$ and $[x'\ y'\ z']$ are the vectors of the coordinate in the original and normalized images, respectively. Thus, we can use the determinant of the Jaccobian matrix as a measure of relative volumes of the GM before and after normalization.

2.4. Statistical inference

The normalized, smoothed, segmented data were analyzed by employing the framework of the general linear model (GLM) [7], which is a statistical linear model written as:

$$Y = XB + U \quad (2)$$

where Y is a matrix with series of multivariate measurements, X is a matrix that might be the design matrix, B is a matrix containing parameters that should be estimated, and U is a matrix containing errors or noise. The GLM incorporates a number of different statistical models like *t*-test. A t-test is any statistical hypothesis test in which the test statistic has a Student's *t* distribution [8].

Analysis of the data from multiple subjects usually proceeds in making inferences about the population of the subjects. This is an example of random-effects (RFX) analysis [9], where contrast images from each subject are used as summary measures of the subject response.

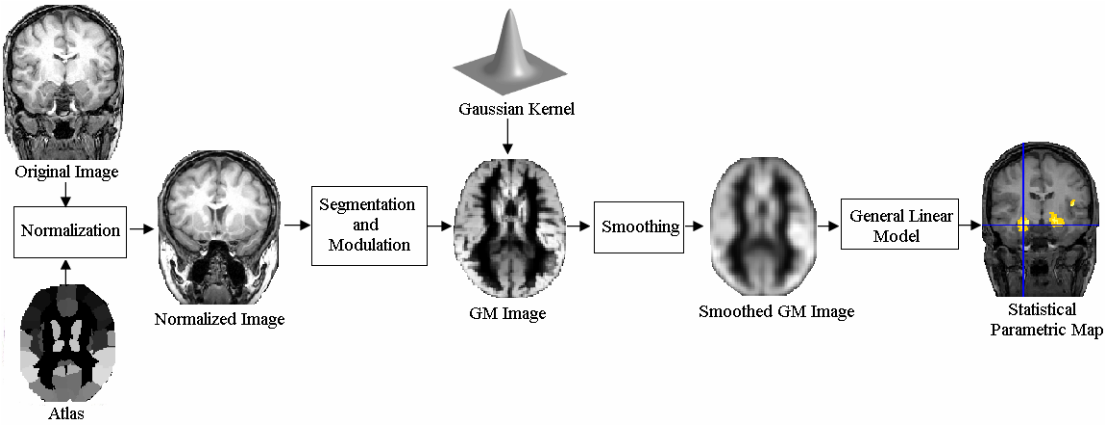

Figure 1. Block diagram showing different steps of the VBM method.

3. Data analysis and results

Structural MRI data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk). We accomplished the VBM method with the unified segmentation framework for an investigation of the data using the steps described in the previous section. The images were normalized to the Montreal Neurological Institute (MNI) T1-weighted template using 12 parameter affine transformation. The algorithm works by minimizing the sum of the squared errors between each image and the template. Also, the images were corrected for the intensity non-uniformity effects.

After segmentation of GM and modulation procedure for correcting volume changes, an 8mm×8mm×8mm full-width half-maximum (FWHM) isotropic Gaussian kernel was used to smooth the GM partitions for subsequent statistical analysis.

Then, Student's t-test statistical models of differences between GM concentrations of patients and controls were obtained using a general linear model (GLM). This led to voxel by voxel comparison of images in the two groups. The voxel-wise statistical threshold was at a value of $P < 0.005$ in the statistical t-test. The block diagram of these methods is presented in Figure 1.

After applying VBM to the data, the corresponding statistical parametric maps (SPMs) are created. Figures 2 and 3 show the results of overlaying these maps on the original images. In Figure 2, the abnormal regions that contain entorhinal cortex are exhibited. We have used the coronal view for showing this structure, because this is the only view that can show the entorhinal cortex properly. Figure 3 provides abnormal regions in axial, sagittal, and coronal views and highlights them to illustrate that these regions are mostly related to the hippocampus and amygdala. For further confirmation, we have used manual segmentation of these structures performed by an expert. The results show that all of these three structures have been affected by TLE.

4. Conclusion

In the present work, we used a VBM method with unified segmentation framework to discover the brain structures that are mostly affected by TLE. MR images of two groups (TLE patients and healthy controls) were used for the comparison. The results show that GM concentration in the hippocampus, amygdala, and entorhinal cortex decreases dramatically. Also, the results show some subtle changes in other brain regions. As the focus in this study was on the temporal lobe structures, we did not present details of the other parts.

As described earlier, VBM method has serial modules where the result of each stage will be used for the next one. So, the errors of each part will propagate to the entire procedure and this may lead to inexact results in some cases. By improving the accuracy of each of these modules, specially, for the GM segmentation step, we can achieve more accurate results.

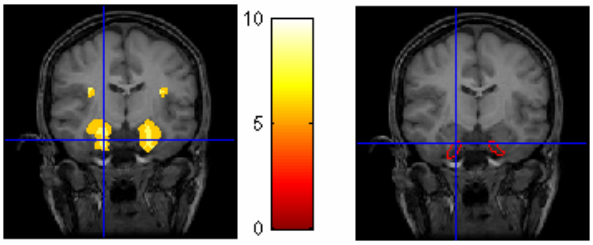

Figure 2. GMC reduction in regions including entorhinal cortex in the coronal view. Left: VBM results. Right: Manual segmentation

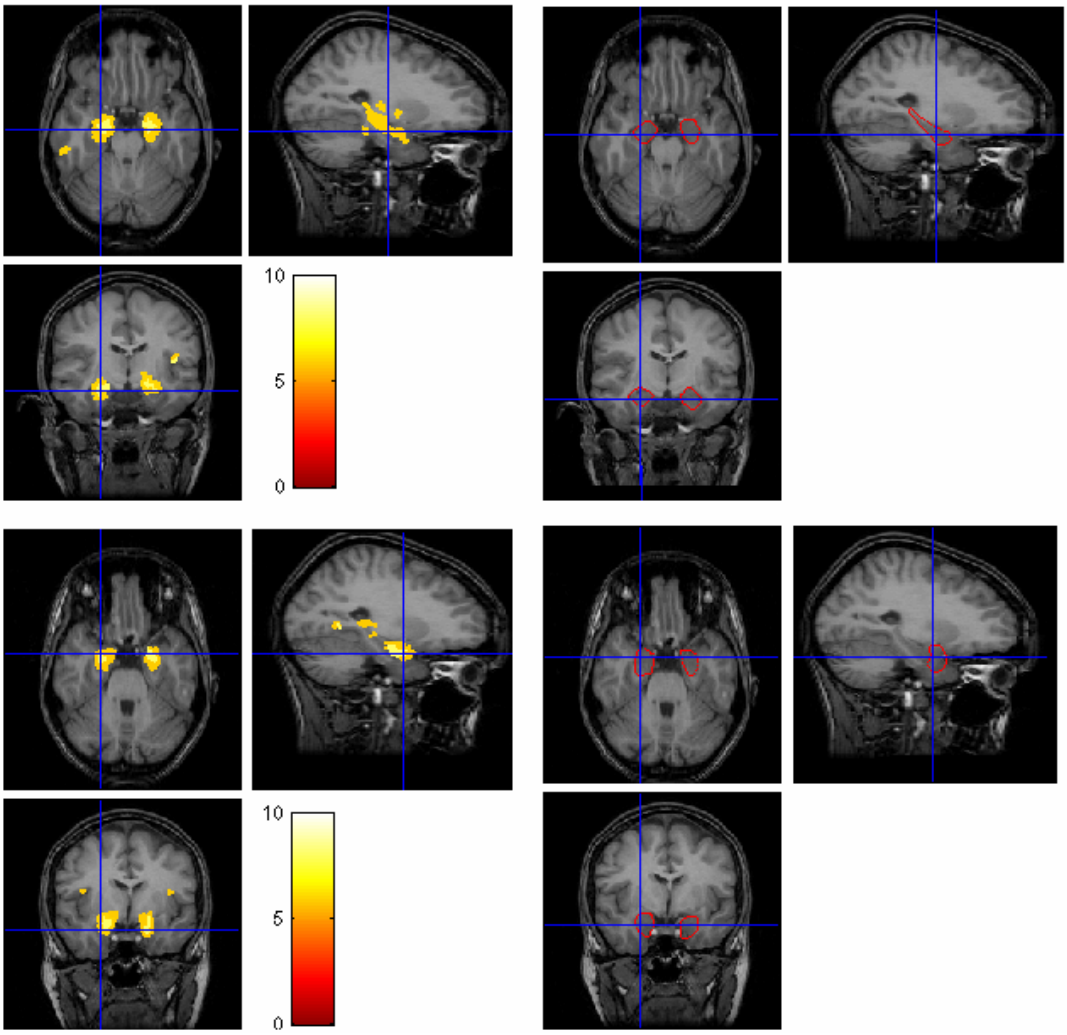

Figure3. Regions showing GM concentration reduction in the axial, sagittal, and coronal views due to TLE. Top rows (left): Regions in which GMC reduction of hippocampus is obvious. Top rows (right): Manual segmentation of hippocampus. Bottom rows (left): Regions in which GMC reduction in amygdala is obvious. Bottom rows (right): Manual segmentation of amygdala.

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