Tract Based Spatial Statistical Analysis of Diffusion Parameters in Temporal Lobe Epilepsy

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Abstract

Temporal lobe epilepsy (TLE) is a neurological disease that involves parts of the brain. Majority of TLE patients suffer from refractory seizures. Therefore, determining damaged areas of the brain and the seizure focus are important in TLE. The purpose of this paper is to estimate the level of damage in the brain fiber tracts using diffusion tensor magnetic resonance imaging (DT-MRI). For the evaluation of the fiber tracts, a variety of diffusion anisotropy indices (DAI's) are proposed such as fractional anisotropy (FA), mean diffusivity (MD), and ellipsoidal area ratio (EAR). Here, in addition to the widely used index (FA), a newly proposed index (EAR) is also estimated because of its higher contrast to noise ratio (CNR) and signal to noise ratio (SNR) compared with the other DAI's in the high noise levels that occur in practice. Tract based spatial statistics (TBSS) method is employed for the evaluation of the fiber tracts throughout the brain based on the above DT-MRI indices. This method is applied to five patients with TLE in comparison with five normal control subjects. In the patient group, significant reduction of FA and EAR in temporal lobes is found. Also, abnormality is observed in the corpus callosum and inferior frontal gyrus. In addition, decreased FA and EAR in the hippocampus is marginally detected. In conclusion, DT-MRI indices provide complementary information for the diagnosis of TLE where EAR provides a higher sensitivity than FA.

Keywords: Diffusion Tensor Magnetic Resonance Imaging, Temporal Lobe Epilepsy, Ellipsoidal Area Ratio, Tract Based Spatial Statistics.

1. Introduction

Temporal lobe epilepsy (TLE) is a neurological disease that involves parts of the brain including the white matter fiber tracts. Majority of the TLE patients suffer from refractory seizures that cannot be remedied by medications. For seizure freedom or significant reduction of seizure frequency, resection of the seizure focus can be useful in majority of the patients. Therefore, finding the damaged fiber tracts is important for the diagnosis and therapeutic intervention [1, 2]. There are different methods based on diffusion tensor magnetic resonance imaging (DT-MRI) to determine the seizure focus. Majority of these methods have focused on using regions of interest (ROIs) that are subjective [3]. To alleviate this subjectivity, we analyze the diffusivity of the entire brain in this work.

The DT-MRI data can be used to determine the orientation and integrity of fibers in white matter. Diffusion is isotropic if diffusion in all directions is identical. In white matter, cell membranes and myelin sheets restrict diffusion perpendicular to the main axis of fibers, therefore, diffusion is anisotropic. For analysis, anisotropy indices are used that are scalar representations of the original diffusion tensor space. To this end, a variety of anisotropy indices are proposed including mean diffusivity (MD), fractional anisotropy (FA), and ellipsoidal area ratio (EAR) [4-6], where EAR is the most recently proposed index.

In this work, we employ a recently proposed analysis method called tract based spatial statistics (TBSS) and a recently proposed DT-MRI index (EAR) to identify damaged fiber tracts throughout the entire brain.

Previous studies of TLE have analyzed the FA and the MD maps. They have shown changes in the hippocampus, limbic system, temporal lobes, inferior frontal lobe, and arcuate fasciculus. The abnormality is identified by the FA decrease and the MD increase in the involved tissues [1, 3]. However, the previous studies have the following limitations. The MD maps show average magnitude of diffusion in each voxel. A voxel with three equal eigenvalues have the same MD as a voxel with unequal eigenvalues but the same average. Therefore, the sensitivity

of the MD maps to anisotropy is less than the FA maps. The limitation of the FA maps is sensitivity to noise which can introduce bias into the quantification of the diffusion anisotropy when using this index. To overcome these limitations, we use the EAR maps which are more robust to the noise effects [6].

The TBSS is a tract-based method that can be used to determine the abnormal fiber tracts in the brain. Diseases such as epilepsy, schizophrenia, and Alzheimer involve regions of white matter and gray matter. It is an appropriate method for investigating damaged fibers in these diseases [7].

We use TBSS in this study to analyze the EAR maps. It is included as a part of the FSL software package. In this method, diffusion anisotropy indices (DAI's) are calculated and then skeleton is extracted from them. The skeleton can be used to compare the patient fiber tracts and normal control data.

Most functions in the human brain are carried out in connective networks. As such for detecting the abnormalities in the TLE patients, we should not focus only on the temporal lobes; we should consider all of the damaged fiber tracts in the whole brain. In this work, diffusion abnormalities in all regions of the brains of the TLE patients are evaluated using the EAR maps extracted from DT-MRI.

2. Materials and Methods

2.1. Subjects

We studied DT-MRI data of 5 patients with TLE and 5 normal control subjects. Data were acquired with 26 gradient directions. Forty slices with 2.6 mm thickness were acquired with a 256×256 matrix size.

2.2. TBSS Analysis

The MRI scans are in the DICOM format. First, the DICOM images are processed in the DTIstudio to estimate the eigenvalues and the FA maps. The EAR maps cannot be calculated in the DTIstudio. Therefore, they are made using the codes we have developed in Matlab. For this purpose, we use the following equation.

$$EAR = 1 - \left(\frac{1}{3} \times \frac{1}{\lambda_1^{2p}} \left(\lambda_1^p \lambda_2^p + \lambda_3^p \lambda_2^p + \lambda_1^p \lambda_3^p\right)\right)^{\frac{1}{p}} \quad (1)$$

where p is a constant. The estimation has the least error in the sense of the *knud thomsen approximation* [6] when $p \approx 1.6075$. In addition, λ_1, λ_2, λ_3 are the eigenvalues of the diffusion tensor and λ_1 is the largest eigenvalue [6].

After EAR calculation, the next step is noise reduction using morphological operators and masking. The resulting images are saved in ANALYZE format and then changed to 4D Nifti-File for using in FSL.

The TBSS method involves several steps as follows. In the first step, the EAR images are eroded slightly and the last slices changed to zero to remove the outliers. Afterwards, every EAR image is aligned to every other one where the most representative one is identified and used as the target image. This target image is then affine-aligned into the MNI152 standard space, and every image is transformed into the 1×1×1mm MNI152 space by combining the nonlinear transform to the target EAR image with the affine transform from that target to the MNI152 space. A mean EAR image is generated by averaging all EAR maps and a group skeleton is automatically constructed from the maps. In brief, this process involves finding the main tract direction and reducing it to a tube or sheet. This process is described in detail in [7].

The skeleton is a representation of the main fiber tracks. Next, the locally highest EAR values are projected onto this skeleton. A distance map automatically weights the search area by the distance from the individual voxel to the skeleton. For each subject (patients and controls), an individual EAR skeleton is produced and analyzed in a group comparison of patients versus controls respectively using the FSL function "randomize" with 500 permutations. The resulting statistical maps are corrected for multiple comparisons at the cluster level with a p value of 0.05 and superimposed on the mean EAR map and the group skeleton.

The FA map is widely used to compare patients and controls in group analysis. Therefore, we apply the TBSS analysis on the FA maps in addition to the EAR maps.

3. Experimental Results

3.1. FA Results

Experimental results presented in Fig. 1 show FA decrease in the temporal lobes. Prominent regions in the temporal lobes are the inferior temporal gyrus, the middle temporal gyrus, and the superior temporal gyrus. Changes in the left temporal lobe are more than those in the right temporal lobe. Abnormal regions in the middle frontal gyrus and superior frontal gyrus are also detected. Table 1 lists the damaged fiber tracts. The parahippocampal gyrus is one of the damaged regions. The FA has also been reduced in the anterior corpus callosum. Clusters of decreased FA are observed in the postcentral gyrus. No FA increase is found in the patient group compared to the normal group.

3.2. EAR Results

The TBSS analysis has detected areas of decreased EAR in the temporal lobes similar to the FA results (Fig. 2). Significant reduction of the EAR is detected in the inferior temporal gyrus, the middle temporal gyrus, and the superior temporal gyrus. The EAR reduction is also found in the crus of the fornix. Changes in the volume of the hippocampus are marginally detected on the parahippocampal gyrus. In addition, the EAR is reduced in the anterior thalamus. The corpus callosum is abnormal in both of the right and left sides. However, the EAR reduction is prominent in the left side compared to right side. All abnormal regions show decreased EAR; none of the abnormal regions show increased EAR.

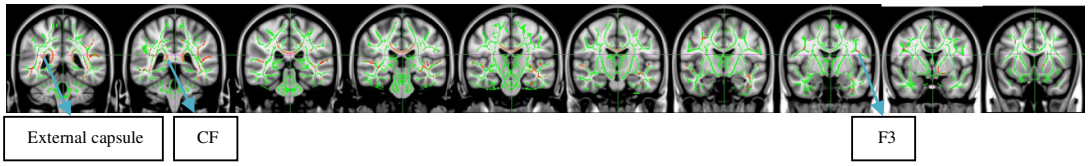

Fig. 1. The results of the TBSS analysis of the FA maps: The mean FA skeleton is shown in green, the red regions demonstrate the damaged fiber tracts, and background is the MNI152 atlas.

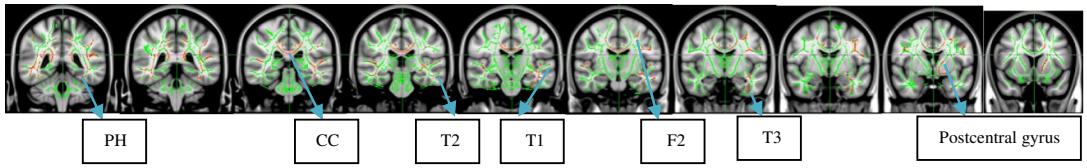

Fig. 2. The results of the TBSS analysis of the EAR maps: The skeleton is shown in green, the red regions represent the damaged fiber tracts, and the background is the MNI152 atlas.

Table 1. The TBSS analysis results for the left hemisphere.

EAR reduction	FA reduction
Inferior temporal gyrus (T3)	Inferior temporal gyrus (T3)
middle temporal gyrus (T2)	middle temporal gyrus (T2)
superior temporal gyrus (T1)	superior temporal gyrus (T1)
corpus callosum (CC)	crus of fornix (CF)
external capsula (EC)	Inferior frontal gyrus (F3)
parahippocampal gyrus (PH)	superior frontal gyrus (F2)
crus of fornix (CF)	corpus callosum (CC)
Inferior frontal gyrus (F3)	external capsula
superior frontal gyrus (F2)	parahippocampal gyrus (PH)
post-central gyrus (PCG)	

Table 2. The TBSS analysis results for the right hemisphere.

EAR reduction	FA reduction
Inferior temporal gyrus	middle temporal gyrus
middle temporal gyrus	superior temporal gyrus
superior temporal gyrus	corpus callosum (CC)
anterior corpus callosum	external capsula
external capsula	crus of fornix (CF)
crus of fornix (CF)	Inferior frontal gyrus
Inferior frontal gyrus	parahippocampal gyrus (PH)
corpus callosum (CC)	

Quantitative results of the TBSS method are shown in Fig. 3. It is clear from this figure that the FA and EAR are reduced in the damaged fibers. The blue bars show the control group and the red bars show the patient group. The peak value of each bar is obtained by averaging the FA and EAR values in the regions of brain that are identified as the abnormal regions. As shown in Fig. 3, the average of the EAR changes is 0.23 and its standard deviation is 0.01. However, the average of the FA changes is smaller (0.09) and its standard deviation is the same (0.01).

The abnormal regions in the left hemisphere are more than those in the right hemisphere. This suggests that most of the TLE patients in this research suffer from damages in the left side of the brain. The differences between the control

and patient groups in the EAR maps are more than in the FA maps. Therefore, the EAR is superior to the FA for the diagnosis of the damaged areas in TLE. The results in Fig. 3 are consistent with the findings of the previous work in [1].

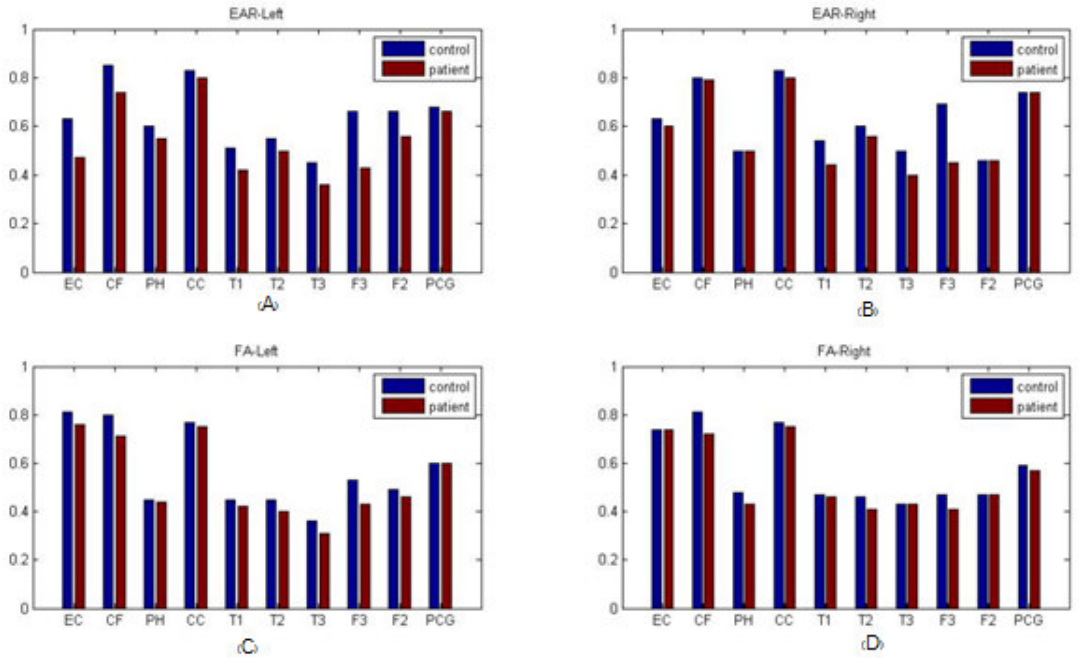

Fig. 3. The results of the TBSS analysis of the EAR and FA maps: The mean EAR values for the patient and control groups are compared for the left hemisphere in (A) and for the right hemisphere in (B). The mean FA values for the patient and control groups are compared for the left hemisphere in (C) and for the right hemisphere in (D).

4. Discussion

In this work, FA and EAR reductions are detected in the temporal lobes, the corpus callosum, and the inferior frontal gyrus of the TLE patients. We are the first to investigate the EAR maps for the analysis of the DT-MRI data of the TLE patients. We have compared the TBSS analysis results of the FA and EAR maps. This work is motivate by the superiority of the contrast to noise ratio (CNR) and signal to noise ratio (SNR) of the EAR maps compared to those of the FA maps. For the TBSS analysis, the image contrast is critical to the detection of the damaged fibers [5].

Comparing the experimental results of the TBSS analysis of the FA and EAR maps, it is concluded that the EAR results are more appropriate than the FA results for TLE. More damaged fiber tracts are identified by the EAR than the FA.

The findings of our study indicate that the parahippocampal gyrus is abnormal in patient group (Figs. 1, 2). This may be attributed to the changes in the hippocampus volume in the TLE patients. This is consistent with previous ROI-based studies that have shown the hippocampus volume changes [6]. In addition, clusters of FA and EAR reduction are found in the inferior temporal gyrus, the middle temporal gyrus, and the superior temporal gyrus [8]. The inferior frontal gyrus is one of the regions with reduced FA and EAR in the TLE patients. This may be due to the changes in the tract between the temporal and frontal lobes [9]. The FA and EAR values are also decreased in the anterior corpus callosum [10]. Moreover, the FA and EAR reduction is found in the external capsule [11-13]. The changes in the FA and EAR values are detected more on the left hemisphere than the right hemisphere. All changes correspond to reductions in the FA and EAR values. No increase in these indices was reported.

5. Conclusion

This work has shown that there are clusters of abnormal diffusivity in a large brain network in the TLE patients. Prominent EAR changes were observed in the temporal lobes and the inferior frontal gyrus. Another involved region was the corpus callosum. The results obtained from the EAR maps are generally consistent with those of the FA maps. However, the robustness of the EAR maps to noise is more than the FA maps. Therefore, the EAR maps are most appropriate for the identification of the thin abnormal regions compared to the other DAI maps like the FA maps.

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