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Original Article

A tract-based spatial statistics study of white matter integrity in epilepsy

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Abstract: Objective: To explore the changes of cerebral white matter diffusion tensor in epilepsy. Methods: This study was a retrospective study based on diffusion tensor imaging (DTI). Twenty-six epileptic patients and 42 normal controls matched for sex, age and handedness were enrolled in our research. Based on the method of tract-based spatial statistics (TBSS), we analyzed the changes of each relevant parameter index of DTI in white matter of the brain in all subjects, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). Results: In comparison with the control group, epileptic patients had decreased FA and elevated MD, AD, and RD in the anterior thalamic radiation, corticospinal tract, forceps major, forceps minor, cingulum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus and uncinate fasciculus ($P < 0.05$). Conclusion: Widespread white matter integrity was observed in epileptic patients, which may be the structural basis for the development of affective disorders, impaired cognition, and motor abnormalities.

Keywords: Epilepsy, diffusion tensor imaging, whiter matter, tract-based spatial statistic

Introduction

Epilepsy is a chronic recurrent disease, in which the sudden abnormal discharge of brain neurons leads to transient brain dysfunction [1]. According to the latest epidemiological data, there are over 70 million epileptic patients worldwide [2]. Due to the different sites of initiation and mode of transmission of abnormal discharges in the brain during seizures, their onset is complex and varied, and patients may present different symptoms such as loss of consciousness, limb convulsions, sensory abnormalities, and autonomic neuropathy. The diagnosis of epilepsy depends on the medical history, seizure symptoms and electroencephalogram (EEG). Routine magnetic resonance imaging (MRI) is widely taken for screening brain structural abnormalities in epileptic patients. However, the significant proportion of patients (mostly intractable, idiopathic, cryptogenic, and partial epilepsy) still have negative presentations to traditional imaging [3]. With the development of imaging equipment, new neuroimaging technology like 3D T1WI (T1-weighted imaging) and diffusion imaging have been increasingly applied to the study of brain microstructure of epileptic patients with negative conventional MRI examination [4, 5], which provide a new method for diagnosis and treatment of epileptic patients and to explore the pathogenesis of epilepsy.

Diffusion tensor imaging (DTI) is a new method developed from conventional diffusion-weighted imaging (DWI) [6]. Based on the anisotropy of diffusion motion of water molecules, DTI quantifies the measurement and direction of water diffusion in the three-dimensional space through the main parameters - fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD), and then reflects the fine structural and functional variations of living tissues [7, 8]. The analysis means taken for the DTI data post-processing include the region of interest (ROI), the voxel-based analy-

sis (VBA), and the tract-based spatial statistics (TBSS). In practice, the latter method is more comprehensive, accurate and sensitive than ROI and VBA [9].

The aims of this project were to explore the white matter integrity in epileptic patients from structural aspects by using DTI and TBSS, so as to further explore the potential pathophysiological changes in epilepsy.

Materials and methods

Subjects

In this retrospective study, we recruited 26 epileptic patients and 42 healthy volunteers matched for sex, age, education and handedness. Inclusion criteria: (1) diagnosis meets the guideline of International League Against Epilepsy (ILAE, 2017 edition) [10]; (2) age > 18 years; (3) right-handed; (4) MRI examination without contraindication. Exclusion criteria: (1) systemic diseases potentially affecting the central nervous system; (2) history of cranial-related diseases such as intracranial occupying lesions, cranial surgery, cerebrovascular accidents, intracranial infections, etc.; (3) history of psychiatric disorders; (4) claustrophobia or other inability to cooperate with the examination. The case group and the control group underwent neuropsychiatric examination before enrollment, so as to establish sound demographic profile and information about the examination, diagnosis, treatment and progress of the patient. The study was approved by the ethics committee of Suzhou Hospital Affiliated to Nanjing Medical University (K-2022-050-K01) and all subjects provided written informed consent.

Data collection

MRI was performed using a 3 Tesla MRI-Scanner (Skyra, Siemens, Erlangen, Germany) with an 8-channel head coil. The imaging sequences were as follows: T1-weighted, T2-weighted, liquid attenuation inversion recovery, diffusion-weighted and planar echo imaging sequence. The specific parameters of this MRI scan were as follows: a total of 32 sets of images (32 diffusion-sensitive gradient directions) with a diffusion-sensitivity coefficient b value of 1000 s/ram^2 and a set of non-diffusion-weighted images with a diffusion-sensitivity coefficient b value of 0 s/ram^2. Repetition time = 5400 ms; echo time = 93 ms; slice gap = 0; layer thickness = 4.0 mm; number of layers = 40; field of view = 220 mm × 220 mm; matrix size = 122 × 122; number of excitations = 1; flip angle = 90. Twenty-four hours before cranial MRI examination, none of the patients underwent seizures. Subjects' imaging data were evaluated by 2 experienced radiologists and neurologists without access to clinical information.

Preprocessing

DTI data preprocessing was performed using FSL software. This included the following steps: (1) Convert the measured raw DICOM data to NIFTI format using dcm2nii and check the data quality; (2) Eliminate head movement as well as deformation caused by eddy currents in the course of inspection, and adopt linear registration alignment to B0 image; (3) Adjust the original gradient direction according to the changes in eddy current correction; (4) Obtain brain mask to remove non-brain tissue, improve the accuracy of spatial alignment, and limit the analysis range to reduce the amount of operations; (5) Calculate the tensor and also obtain the relevant scalar metrics such as FA, MD, AD, and RD.

Tract-based spatial statistics

FSL software was conducted to align individual FAs to the standard space using linear and nonlinear alignments. Next, on the basis of all FAs aligned to the standard space, the average FA map and white matter skeleton were constructed. FA greater than 0.2 was set as the threshold for screening the FA skeleton. Each subject's white matter fibers were aligned to the average FA template fiber skeleton image. Then the FA fiber skeleton map was extracted and superimposed on the respective structural image, and the spatial location coordinates were converted to MNI space for automatic anatomical localization. Average diffusion metrics (FA, MD, AD and RD) were extracted from the white matter skeleton of each subject. Two sample *t* tests were performed for the comparison of two groups using the Glm tool. The permutation test with 5000 permutations was used for statistics. Multiple comparisons were corrected using the TFCE method, and a modified *P* value 0.05 was used as a significant

Table 1. Demographic data of epilepsy patients and healthy controls

Characteristic	Patients (n = 26)	Controls (n = 42)	t/χ^2 values	*P* values
Gender (male/female)	9/17	29/13	0.098	0.79
Age (years)	31.88±6.48	30.17±5.50	1.169	0.25
Education (years)	14.62±2.52	13.88±2.40	1.204	0.23
Handness	Right	Right	/	/
Duration of epilepsy (years)	4.35±2.83	/	/	/
Antiepileptic treatment (%)	100	/	/	/

threshold. Finally, *JHU White Matter Tractography Atlas* was used to identify the clumps with significant differences, and the results were visualized using the inflated clumps.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 statistics software. The normally distributed measured data expressed as $\bar{x} \pm s$ was compared by independent sample *t* tests. The count data expressed as frequencies or percentages were compared using χ^2 test. $P < 0.05$ shows statistical significance.

Results

Subjects' baseline information

There were no statistical differences in gender ($\chi^2 = 0.098$, $P = 0.79$), age ($t = 1.169$, $P = 0.25$), education ($t = 1.204$, $P = 0.23$) and handedness between the 26 epileptic patients and 42 healthy controls for comparison (**Table 1**). Subjects recruited for this study were adults ranging in age from 19 to 45 years, to avoid interference with the results of the experiment by brain growth and development. Patients in the epilepsy group received routine antiepileptic drugs, with a course of 1-12 years and an average disease duration of about 4 years.

Group differences in FA and MD

Statistical analysis showed that there were significant differences in all diffusion indicators among the groups. Compared with healthy controls, FA decreased significantly while MD increased significantly in patients with epilepsy. The brain regions with intergroup differences were anterior thalamic radiation, corticospinal tract, cingulum, forceps major, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus and uncinate fasciculus (P = 0.002) (**Tables 2** and **3**; **Figures 1** and **2**).

Group differences in AD and RD

Our study found 4 independent voxel clusters with significantly elevated AD in comparison between the two groups. The information about voxel clusters and the comparison of AD values are detailed in **Table 4**. In comparison with the healthy controls, epileptic patients showed significantly higher AD values in the anterior thalamic radiation, corticospinal tract, cingulum, forceps major, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus and uncinate fasciculus, as well as a widespread increase in RD values (**Tables 4** and **5**; **Figures 3** and **4**).

Discussion

Epilepsy was once thought to be a major gray matter disease. Recent advances in imaging techniques enable non-invasive quantification of white matter integrity in the brain, and the changes in specific areas especially the integrity of global white matter have been identified in the study of epileptic patients. Therefore, in recent years, we have recognized that epilepsy affects the whole white matter network of the brain, which is typically characterized by the loss of white matter microstructure and the interruption of network connection [11, 12]. Epileptogenic foci and their abnormal neuronal discharges, and the use of antiepileptic drugs can lead to metabolic and physiological changes in brain tissue [13, 14]. For example, the microstructure of white matter such as axonal degeneration, myelin demyelination or extracellular edema. This series of changes resulted in the increase of free water molecules in tissues and the expansion of extracellular space, thus changing the degree of diffuse movement of

Table 2. Fractional anisotropy (FA)-epilepsy patients vs. healthy controls

Cluster Index	Voxels	MIN P	MNI		
			X (vox)	Y (vox)	Z (vox)
1	57754	0.002	103	158	59
JHU White-Matter Tractography Atlas			Average probability	Significance	
Anterior thalamic radiation L			2.15514	0.002	
Anterior thalamic radiation R			1.82702	0.002	
Corticospinal tract L			0.792776	0.002	
Corticospinal tract R			0.565727	0.002	
Cingulum (cingulate gyrus) L			0.262285	0.002	
Cingulum (cingulate gyrus) R			0.138172	0.002	
Forceps major			0.82654	0.002	
Forceps minor			3.5965	0.002	
Inferior fronto-occipital fasciculus L			1.5196	0.002	
Inferior fronto-occipital fasciculus R			1.35624	0.002	
Inferior longitudinal fasciculus L			0.957406	0.002	
Inferior longitudinal fasciculus R			0.562922	0.002	
Superior longitudinal fasciculus L			1.61608	0.002	
Superior longitudinal fasciculus R			1.41673	0.002	
Uncinate fasciculus L			0.62626	0.002	
Uncinate fasciculus R			0.373913	0.002	
Superior longitudinal fasciculus (temporal part) L			0.723257	0.002	
Superior longitudinal fasciculus (temporal part) R			0.537002	0.002	

Table 3. Mean diffusivity (MD)-epilepsy patients vs. healthy controls

Cluster Index	Voxels	MIN P	MNI		
			X (vox)	Y (vox)	Z (vox)
1	65710	0.002	82	153	85
JHU White-Matter Tractography Atlas			Average probability	Significance	
Anterior thalamic radiation L			1.5095	0.002	
Anterior thalamic radiation R			1.14718	0.002	
Corticospinal tract L			0.750403	0.002	
Corticospinal tract R			0.514123	0.002	
Cingulum (cingulate gyrus) L			0.35334	0.002	
Cingulum (cingulate gyrus) R			0.0841881	0.002	
Forceps major			0.644209	0.002	
Forceps minor			2.91481	0.002	
Inferior fronto-occipital fasciculus L			1.59661	0.002	
Inferior fronto-occipital fasciculus R			1.58977	0.002	
Inferior longitudinal fasciculus L			1.19647	0.002	
Inferior longitudinal fasciculus R			0.716375	0.002	
Superior longitudinal fasciculus L			2.09448	0.002	
Superior longitudinal fasciculus R			1.60081	0.002	
Uncinate fasciculus L			0.569533	0.002	
Uncinate fasciculus R			0.272211	0.002	
Superior longitudinal fasciculus (temporal part) L			0.954406	0.002	
Superior longitudinal fasciculus (temporal part) R			0.578177	0.002	

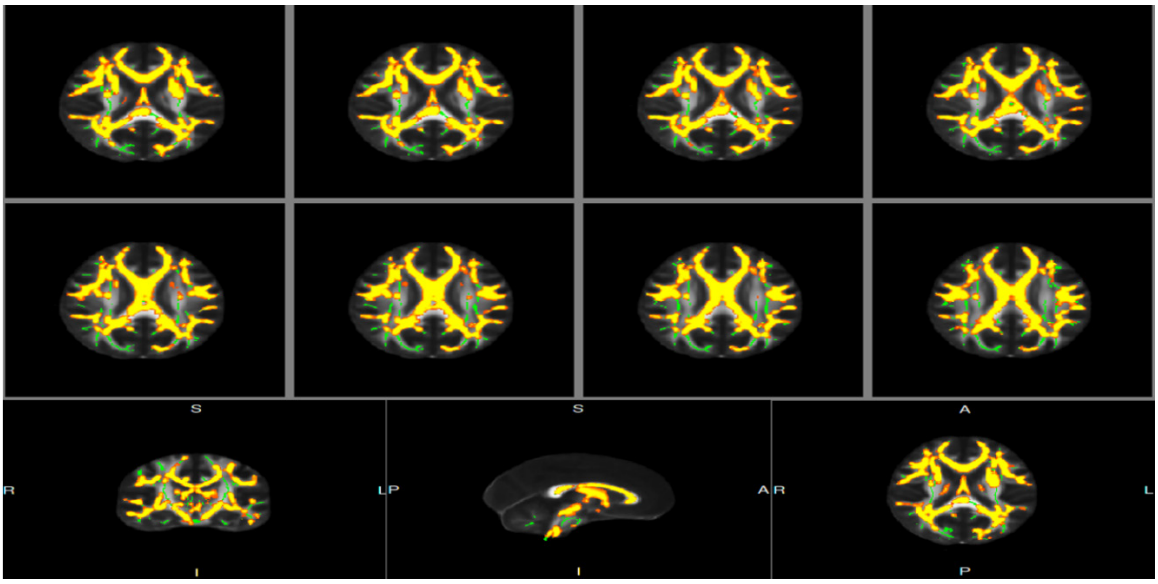

Figure 1. Tract-based spatial statistic results of fractional anisotropy (FA) images between epilepsy patients and healthy controls. Green represents mean skeleton of all participants; red and yellow represents regions with decreased FA in epilepsy patients ($P < 0.05$, TFCE corrected for multiple comparisons).

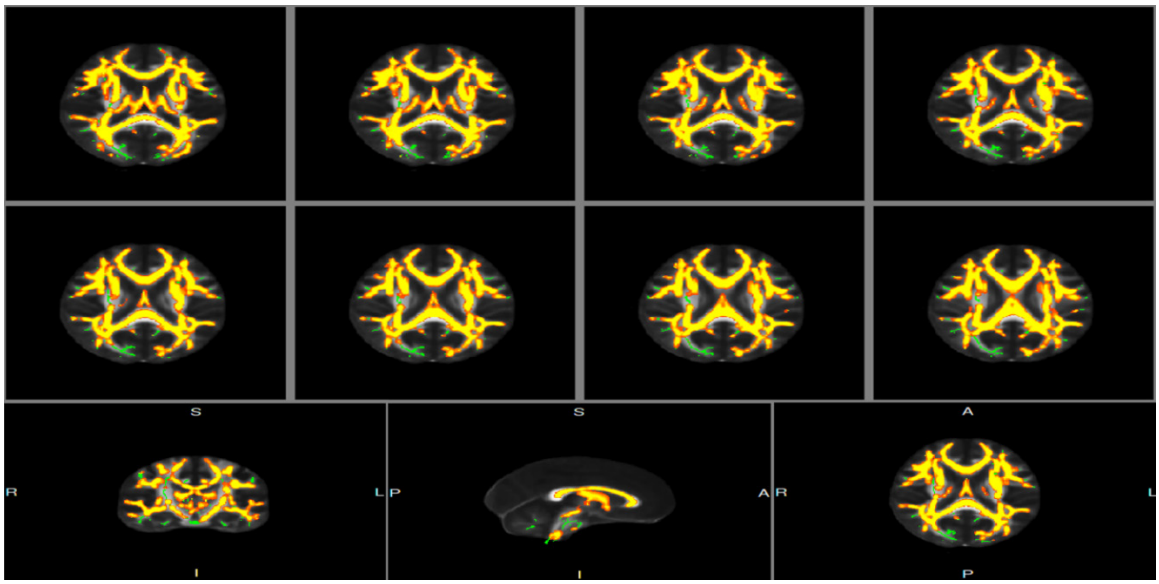

Figure 2. Tract-based spatial statistic results of mean diffusivity (MD) images between epilepsy patients and healthy controls. Green represents mean skeleton of all participants; red and yellow represents regions with increased MD in epilepsy patients ($P < 0.05$, TFCE corrected for multiple comparisons).

water molecules. DTI uses the anisotropic principle of water molecule diffusion movement to indirectly reflect the subtle structural and functional changes in living tissues. It can be used for epilepsy diagnosis, clinical staging, drug efficacy and mechanism analysis [15-17]. In this study, the difference of DTI parameter between epileptic patients and healthy controls was examined by TBSS, and the white matter structure integrity of epileptic patients was investigated.

From the above results, the decrease of FA in the epileptic patients and the increase of MD, AD and RD agreed with the results of many previous studies [18-20]. FA values are used to

Table 4. Axial diffusivity (AD)-epilepsy patients vs. healthy controls

Cluster Index	Voxels	MIN P	MNI		
			X (vox)	Y (vox)	Z (vox)
1	59	0.049	73	173	63
2	84	0.049	115	157	89
3	832	0.034	80	102	84
4	17414	0.001	117	91	97
JHU White-Matter Tractography Atlas			Average probability	Significance	
Cluster 1					
Anterior thalamic radiation R			11.7627	0.049	
Forceps minor			9.37288	0.049	
Inferior fronto-occipital fasciculus R			8.23729	0.049	
Uncinate fasciculus R			7.0339	0.049	
Cluster 2					
Anterior thalamic radiation L			14.1786	0.049	
Forceps minor			0.928571	0.049	
Inferior fronto-occipital fasciculus L			6.32143	0.049	
Superior longitudinal fasciculus L			0.392857	0.049	
Uncinate fasciculus L			4.54762	0.049	
Cluster 3					
Anterior thalamic radiation L			4.91346	0.034	
Anterior thalamic radiation R			4.18149	0.034	
Cluster 4					
Anterior thalamic radiation L			0.20696	0.001	
Anterior thalamic radiation R			0.292581	0.001	
Corticospinal tract L			1.46595	0.001	
Corticospinal tract R			1.44321	0.001	
Cingulum (cingulate gyrus) L			0.0548409	0.001	
Cingulum (cingulate gyrus) R			0.022568	0.001	
Forceps major			1.06368	0.001	
Forceps minor			0.691283	0.001	
Inferior fronto-occipital fasciculus L			1.53503	0.001	
Inferior fronto-occipital fasciculus R			2.38061	0.001	
Inferior longitudinal fasciculus L			1.92512	0.001	
Inferior longitudinal fasciculus R			1.08344	0.001	
Superior longitudinal fasciculus L			3.44659	0.001	
Superior longitudinal fasciculus R			2.00919	0.001	
Uncinate fasciculus L			0.114965	0.001	
Uncinate fasciculus R			0.0522568	0.001	
Superior longitudinal fasciculus (temporal part) L			1.61973	0.001	
Superior longitudinal fasciculus (temporal part) R			0.529574	0.001	

measure the ability of water molecules to diffuse in tissue in a directional manner. Loss of white matter fiber myelin, impaired axon cell membrane integrity, and axonal transport velocity all affect FA values [21]. Damage to white matter fiber structure in epilepsy reduces the degree of anisotropy of water molecule dispersion, as evidenced by a decrease in FA value. The MD value is used to evaluate the non-directional diffusion capacity of water molecules within a single voxel. The expansion of the intercellular space and the increase in free water molecules result in an increase in the MD value. Changes associated with epilepsy have

Table 5. Radial diffusivity (RD)-epilepsy patients vs. healthy controls

Cluster Index	Voxels	MIN P	MNI		
			X (vox)	Y (vox)	Z (vox)
1	73649	0.002	78	156	81
JHU White-Matter Tractography Atlas			Average probability	Significance	
Anterior thalamic radiation L			1.63766	0.002	
Anterior thalamic radiation R			1.38011	0.002	
Corticospinal tract L			0.648889	0.002	
Corticospinal tract R			0.451058	0.002	
Cingulum (cingulate gyrus) L			0.306318	0.002	
Cingulum (cingulate gyrus) R			0.162324	0.002	
Forceps major			0.786406	0.002	
Forceps minor			2.93337	0.002	
Inferior fronto-occipital fasciculus L			1.53792	0.002	
Inferior fronto-occipital fasciculus R			1.45657	0.002	
Inferior longitudinal fasciculus L			1.06447	0.002	
Inferior longitudinal fasciculus R			0.649255	0.002	
Superior longitudinal fasciculus L			1.80328	0.002	
Superior longitudinal fasciculus R			1.40314	0.002	
Uncinate fasciculus L			0.551331	0.002	
Uncinate fasciculus R			0.325802	0.002	
Superior longitudinal fasciculus (temporal part) L			0.819292	0.002	
Superior longitudinal fasciculus (temporal part) R			0.507176	0.002	

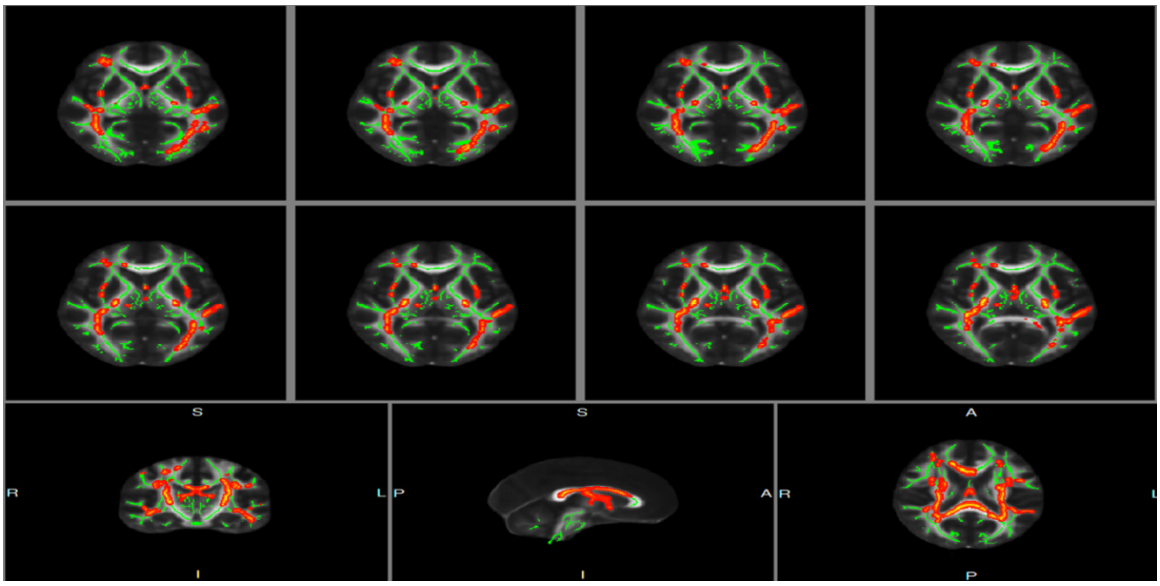

Figure 3. Tract-based spatial statistic results of axial diffusivity (AD) images between epilepsy patients and healthy controls. Green represents mean skeleton of all participants; red and yellow represents regions with increased AD in epilepsy patients ($P < 0.05$, TFCE corrected for multiple comparisons).

been observed in both animal and human studies, with the MD value typically exhibiting an early decline, a gradual return to normal, and then a chronic increase [22]. The AD value represents the degree of water molecules diffusion parallel to the direction of fiber bundle travel, and therefore the elevated value is associated with axon injury [19]. The RD value is the

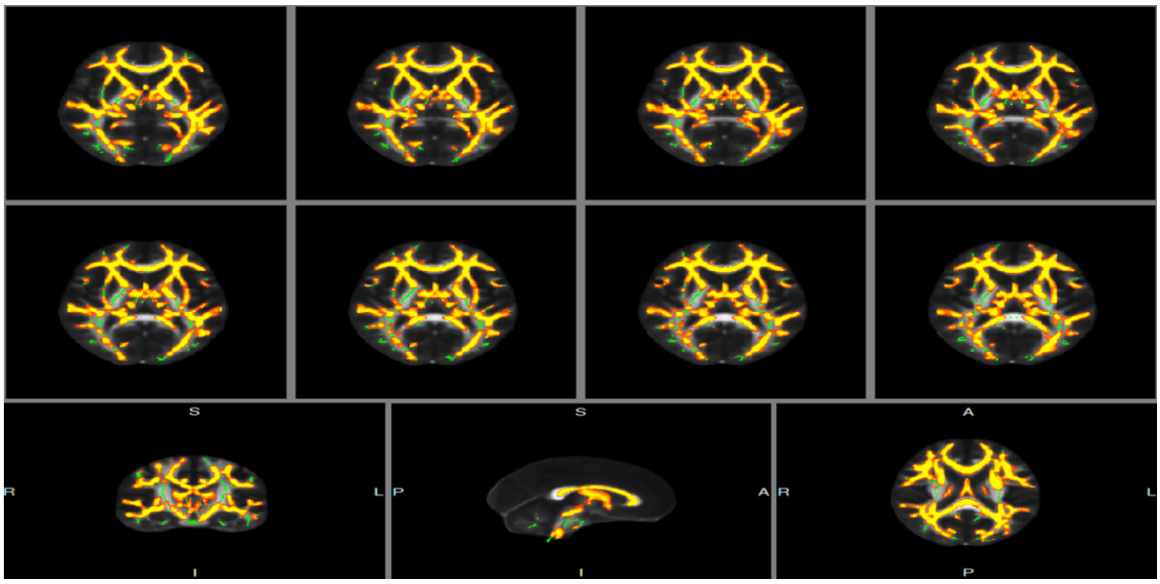

Figure 4. Tract-based spatial statistic results of radial diffusivity (RD) images between epilepsy patients and healthy controls. Green represents mean skeleton of all participants; red and yellow represents regions with increased RD in epilepsy patients ($P < 0.05$, TFCE corrected for multiple comparisons).

degree of water molecules diffusion perpendicular to the direction of fiber bundle travel, and its increase is associated with demyelination or myelin phospholipid abnormalities [23]. Thus, the above 4 diffusion index anomalies indicate the microstructural changes of white matter fiber bundles in epileptic patients, which can hardly be monitored in conventional MRI sequences [24]. However, the specific pathophysiological mechanisms of DTI parameter changes in epileptic patients are not clear, but it can be explained form the following aspects: the initial epileptogenic lesions prior to seizures, the direct effects of axonal damage on ipsilateral white matter, the remote effects of recurrence transmitted through the white matter portion of the epileptic network [25] and the plasticity of brain development and structural changes of white matter. In spite of these mechanical uncertainties, clinical understanding of different types of epilepsy requires knowledge of the location and range of white matter fiber damage in the brain. This information will help to understand the potentially deleterious effects of recurrent epilepsy and may serve as a quantitative biomarker for future therapeutic research.

According to our results, white matter damage in epileptic patients is diffuse and bilaterally symmetric. Extensive damage suggests that previous regional based studies may have underestimated the extent of white matter damage. The white matter fibers involved in epileptic patients in our study included anterior thalamic radiation, corticospinal tract, forceps major, forceps minor, cingulum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus and uncinate fasciculus. These white matter fiber bundles involve commissural fibers, association fibers and projection fibers. Commissural fibers connect both sides parts of the hemisphere that are functionally identical. The corpus callosum transmits information through the midline of the brain, which is the largest commissural fiber. The forceps minor is located at the knee of the corpus callosum and is responsible for connecting the anterior frontal lobes of both hemispheres, while the forceps major is located at the pressure and is responsible for connecting the bilateral parietal cortex. Partial epileptic activity in the cerebral hemisphere can cause global epilepsy because it can spread to the contralateral hemisphere through the corpus callosum [26]. Abnormalities of the corpus callosum explain why white matter brain damage is involved bilaterally in patients with mesial temporal sclerosis even if only unilateral lesions are present [27]. Association fibers connect different parts of the cerebral cortex in the ipsilateral hemisphere. The superior longi-

tudinal fasciculus is the largest contact fiber and it's also an important brain region for language expression and comprehension by connecting the frontal, parietal, occipital and temporal lobes [28]. In addition, uncinate fasciculus connects frontal and temporal lobe, which is closely related to executive ability [29]. The cingulate gyrus is a part of the limbic cortex involved in functions such as memory and emotion. Extensive damage to the association fibers like cingulate tract, frontal white matter and temporal white matter suggests that epilepsy is closely related to both limbic system and default mode network. Projection fibers connect the cerebral cortex to the subcortical centers and the spinal cord. Damage to corticospinal tract, the most important motor conduction tract in the brain, may be associated with motor symptoms such as limb tonicity and convulsions in patients with epilepsy [30]. The lesions of the aforementioned fiber tracts involve the limbic system, default network, pyramidal tract and other central nervous systems, providing a pathophysiological basis for the accompanying affective disorders, impaired cognitive and executive functions, and motor-related symptoms in epileptic patients.

In our study, subjects were predominantly young and middle-aged people, with a short average disease duration of approximately 4 years. Diffuse white matter microstructural damage was observed in these patients, indicating that white matter injury has already occurred at a relatively early stage of the disease. Similarly, several significant lesions of white matter microstructures were found in children with new-onset epilepsy [31]. The etiologic mechanisms of cerebral white matter diffusion abnormalities and how the integrity progress with the course of the disease is still controversial. It is reported that the degree of white matter integrity in patients with epilepsy is positively correlated with the course of the disease [32]. With the extension of the disease, the damaged white matter bundles gradually reorganized [19]. However, it has also been reported that the white matter integrity of seizure patients in the remission period is not different from controls [33], suggesting that the damage may be reversible. It may be because the study focused on children whose brain is still developing. The limitation of this study is that there is no correlation analysis with the disease duration to investigate the white matter change accompanied with disease progress. The longitudinal design should be carried out in epileptic patients in the future. In addition, due to the small sample size of this study, no further intragroup comparison was conducted among epileptic patients in this study. Some studies have shown that there is no significant difference in white matter microstructural damage among different epilepsy subgroups [34]. However, patients with left temporal lobe epilepsy showed wider and more severe white matter damage than the right lesions [35]. In the future, the sample size is further expanded to confirm whether there is a difference in the microstructural change of the white matter in different types of epileptic patients.

In conclusion, this study compared the white matter skeleton of epileptic patients and healthy subjects using the TBSS method, and bilateral symmetric white matter white matter abnormality was recognized in the epileptic patient. Diffuse white matter damage may occur in the early stage of the disease and may be the structural basis for the development of affective disorders, cognition impairment, and motor abnormalities in epileptic patients.

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Disclosure of conflict of interest

None.

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