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White matter impairment in the basal ganglia-thalamocortical circuit of drug-naïve childhood absence epilepsy☆

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Summary
Purpose: It is unknown whether white matter abnormalities exist in childhood absence epilepsy (CAE), a syndrome of idiopathic epilepsy (IGE). Diffusion tensor imaging (DTI) can noninvasively quantify white matter integrity. This study used DTI to investigate abnormal changes in white matter of untreated CAE patients.
Methods: Subjects included nine patients with untreated CAE and nine age-and sex-matched healthy controls. Diffusion tensor imaging parameters were voxel based and statistically compared between patients and controls. The correlations between DTI parameters in regions of interest (ROIs) and age of seizure onset or duration of epilepsy were analyzed.
Results: Untreated CAE patients had a significantly higher fractional anisotropy (FA) value in the bilateral thalamus, anterior corpus callosum and upper brainstem, while also displaying a lower FA value in prefrontal white matter, anterior cingulate, and bilateral posterior limbs of the internal capsule compared to control subjects. An increase in mean diffusivity (MD) value was observed in parietal lobe white matter, prefrontal white matter, and posterior cerebellar hemispheres, in addition to subcortical structures including bilateral putamen and posterior limb of internal capsule. MD significant correlations between ROI diffusion parameters and the duration of the disease or the age of onset.

☆ The research was conducted at West China Hospital, SiChuan University.

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Conclusions: The results showed white matter integrity impairment in the basal ganglia-thalamocortical circuit of drug-naïve CAE patients. These abnormalities in white matter may be related to increased cortical excitability and cause cognitive, linguistic, and behavioral/emotional deficits both during and between seizures.

Introduction

Childhood absence epilepsy (CAE) is the most common childhood-onset epilepsy syndrome, and it has a broad range of untreated cognitive, linguistic, and behavioral/emotional comorbidities (Caplan et al., 2008). Unfortunately, the fundamental mechanisms of altered brain function and impaired attention in CAE are not yet known (Li et al., 2009). However, recent studies have reported white matter abnormalities in Idiopathic Generalized Epilepsy (IGE), including IGE with Generalized Tonic–Clonic Seizures (GTCS) (Li et al., 2010), and juvenile myoclonic epilepsy (JME) (Deppe et al., 2008; O'Muircheartaigh et al., 2011). Diffusion tensor imaging (DTI) can noninvasively quantify white matter integrity and has emerged as a useful tool for measuring subtle white matter changes associated with epilepsy (Yogarajah and Duncan, 2008). The main parameters of DTI are mean diffusivity (MD), which reflects the amplitude of water diffusion, and fractional anisotropy (FA), which reflects the directionality of water diffusion (Kingsley, 2006). Although research has not yet established white matter integrity in untreated CAE patients, voxel-based morphometry (VBM) studies have found volume changes in frontal and temporal lobes as well as the amygdala in CAE subjects (Caplan et al., 2009; Cohen et al., 2009). In addition, magnetic resonance spectroscopy (MRS) data have demonstrated neuronal dysfunction in the thalami of patients with CAE (Fojtikova et al., 2006). Taken together, these findings indicate that white matter abnormalities may be detected in CAE.

In the current study, we applied DTI to a homogeneous group of newly diagnosed and untreated children with CAE to determine whether the DTI parameters (including FA and MD) would change in CAE compared to those associated with healthy age- and sex-matched controls. We also investigated the influence of clinical factors on white matter integrity in CAE, including epilepsy duration and age of epilepsy onset.

Materials and methods

Subjects

This study recruited drug naïve CAE patients from the epilepsy clinics at the West China Hospital for Neurology of Sichuan University. Diagnosis of CAE was established according to the diagnostic scheme published by the International League Against Epilepsy in 2001 (Engel, 2001). All patients and controls underwent initial neuroimaging to ensure that there were no structural abnormalities. Patients with mental disorders or cognitive handicaps were excluded. Data was collected from nine patients (Table 1), including four males and five females, aged 5–12 years (mean 9), with a CAE onset age of 4–9 years (mean 7.3) and nine healthy controls. None of the patients used antiepileptic medications. Both patients and healthy age- and sex-matched controls were right-handed and gave written informed consent for the study. This research was approved by a responsible governmental agency at the Sichuan University.

Image acquisition

All subjects were scanned in a 3 T MRI scanner (EXCITE, GE Milwaukee, USA) with an eight-channel-phased array head coil. Anatomical T1-weighted images were acquired using a three-dimensional (3D)-spoiled gradient recalled (SPGR) sequence, generating 156 axial slices (thickness: 1 mm (no gap), TR = 8.5 ms, TE = 3.4 ms, FOV = 24 cm × 24 cm, flip angle = 12°, matrix = 512 × 512). The DTI acquisition used a single-shot spin-echo planar imaging sequence. Fifty 3 mm thick contiguous slices were acquired without gap. The other imaging parameters were: TR = 10,000 ms, TE = 79.7 ms, number of excitations (NEX) = 2, matrix size = 256 × 256, FOV = 24 cm × 24 cm. At each slice position, except for S0 ($b = 0\,s/mm^2$), a single b-value ($b = 1000\,s/mm^2$) was applied to 19 non-collinear gradient directions.

Image processing

For DTI images, head motion was removed by aligning 19 diffusion-weighted scans to the un-weighted B0 image ($b = 0\,s/mm^2$) using the SPM8 software package (statistical parametric mapping http://www.fil.ion.ucl.ac.uk/spm). Eddy current distortions were corrected by affine registration to the reference B0 image. The Diffusion Toolkit 0.6 (http://trackvis.org/dtk/) provided three eigenvalues (λ_1, λ_2, λ_3) and the values of MD and FA. Using the Montreal Neurological Institute (MNI) echo-planar imaging template in SPM8, these maps were normalized on an individual level, and interpolated into isotropic voxels (2 mm × 2 mm × 2 mm). Finally, maps were spatially smoothed by convolution with an isotropic Gaussian kernel (FWHM = 6 mm) that was processed to improve the signal-to-noise ratio (SNR). To detect differences in MD and FA values between patients and controls, the two-sample t-test was adopted in SPM, with a statistical significance level of $P < 0.05$ (FDR corrected).

Correlational analyses were performed within the patient group to investigate the potential relationships between the significantly altered diffusion parameters and the clinical features. For the FA parameter, six ROIs, which had the maximum FA value difference between groups, were chosen in bilateral thalamus (−15, −23, 9; 14, −23, 10), anterior corpus callosum (−7, 28, 0; 7, 28, 0) and posterior limb of internal capsule (−27, −15, 12; 20, −7). All the ROIs were composed of 27 voxels around the peak. For every subject, the FA value of each ROI was extracted using the following procedure: First, the FA image was loaded by MATLAB software, and the FA value of one ROI was obtained; Second, the values of the ROIs' extraction were manually checked and confirmed and; Third, the average value of the 27 voxels was obtained for each subject. This same procedure was used for MD images, and the averaged MD values of ROIs (bilateral parietal lobe white matter [−16, −18, 58; 15, −23, 58], putamen [−26, 8, 2; 27, 1, 2] and left posterior limb of internal capsule [−18, −4, 2]) were extracted from each subject. Finally, Pearson correlation analyses were performed between the diffusion parameters and the clinical features of each ROI, which included epilepsy duration and age of CAE onset.

Table 1 Clinical patient details based upon ILAE diagnostic categories.

ID no.	Age (y)	Sex	Seizure onset age (y)	Duration of epilepsy (y)	Seizure type and frequency (times/d)	Frequency of GSW (Hz) and accompanied symptoms	
						Frequency (Hz)	Accompanied symptoms
1	12	F	9	3	Absence, 0—12/d	3	Absence
2	12	F	8	4	Absence, 2—6/d	3—3.5	Absence
3	5	M	4	1	Absence, 15—35/d	3	Absence
4	8	F	7	1	Absence, 6—7/d	3	Absence
5	10	F	8	2	Absence, 3—20/d	3	Absence
6	11	M	9	2	Absence, 1—5/d	3—3.5	Absence
7	8	F	7	1	Absence, 0—6/d	3	Absence
8	8	M	7	1	Absence, several	3	Absence
9	7	M	7	0.5	Absence, 9—15/d	3	Absence

GSW: generalized spike wave; F: Female; M: Male; y: Years.

Results

White matter alterations

The quantitative analysis of diffusion parameters revealed that CAE patients had significantly lower FA values in prefrontal white matter, parietal lobe white matter, anterior cingulate, and bilateral posterior limbs of the internal capsule compared to controls (Fig. 1A—C). Moreover, patients also displayed significantly higher FA values in the bilateral thalamus, anterior corpus callosum, and upper brainstem (Fig. 1D—F) compared to their control counterparts. Our results also found increased MD values in the parietal lobe and prefrontal white matter, posterior cerebellar hemisphere, and subcortical structures such as bilateral putamen and posterior limb of internal capsule in patients (Fig. 2). No other significant differences in white matter integrity between patients and controls were detected.

Correlation analysis

Pearson correlational analyses failed to detect any significant relationships between the FA of the ROIs (bilateral thalamus, posterior limb of internal capsule and anterior corpus callosum) and the duration or age of disease onset. In addition, we did not establish a significant correlation between MD value in ROIs and CAE duration or age of onset.

Discussion

The present study found that untreated CAE patients exhibited changes in white matter integrity in the basal ganglia-thalamocortical circuit compared to healthy controls. In addition, the data failed to support the existence of any relationship between either the duration of the disease or the age of onset and the ROI diffusion parameters. These results indicate that the involvement of these regions in specific cortical and subcortical networks may be related to the pathomechanisms of seizure generation and the cognitive, linguistic, and behavioral/emotional neurological deficits observed in CAE patients.

The cortical and subcortical network involvement in CAE patients has previously been supported by EEG-fMRI studies (Li et al., 2009; Berman et al., 2010). For example, in drug-naïve CAE patients, generalized spike wave discharges (GSWDs) were associated with a bilateral increase in the BOLD signal in the medial thalamus and regional decreases in the BOLD signal of parietal areas, the precuneus, and the caudate nucleus (Moeller et al., 2008). On the other hand, MRS data has clearly indicated neuronal dysfunction in the thalami of patients with CAE (Fojtikova et al., 2006). Additional findings from a VBM study show decreased white matter in the extranuclear subcortical area and in the basal forebrain of CAE individuals (Chan et al., 2006). Moreover, another VBM study found that CAE patients had significantly smaller gray matter volumes of the left orbital frontal gyrus as well as both left and right temporal lobes compared with the control group (Caplan et al., 2009). Bilateral thalamic atrophy is also found in CAE patients (Chan et al., 2006; Pardoe et al., 2008; Bernhardt et al., 2009).

Our previous EEG-fMRI work indicated that the basal ganglia-thalamocortical circuit was functionally involved in CAE patients (Li et al., 2009). Consistent with these results, our current data show changes in white matter integrity of the basal ganglia-thalamocortical circuit, including significantly higher FA value of the bilateral thalamus in untreated CAE patients. The high strength of thalamus-to-cortex coupling has been found during absence seizures, and the coupling of thalamus-to-cortex may facilitate propagation and maintenance of seizure activity (Sitnikova et al., 2008). Therefore, these structural abnormalities may be related to an increased cortical excitability in CAE pathophysiology.

Our results also showed that FA values were remarkably increased at the anterior of the corpus callosum (CC) in CAE patients. The CC represents the most important connection for the inter-hemispheric propagation of epileptic activity. Subsequently, a corpus callosotomy is considered an effective surgical treatment for medically intractable generalized seizures (Jenssen et al., 2006; Sunaga et al., 2009; Tanriverdi et al., 2009). Recently, the posterior portion of the CC

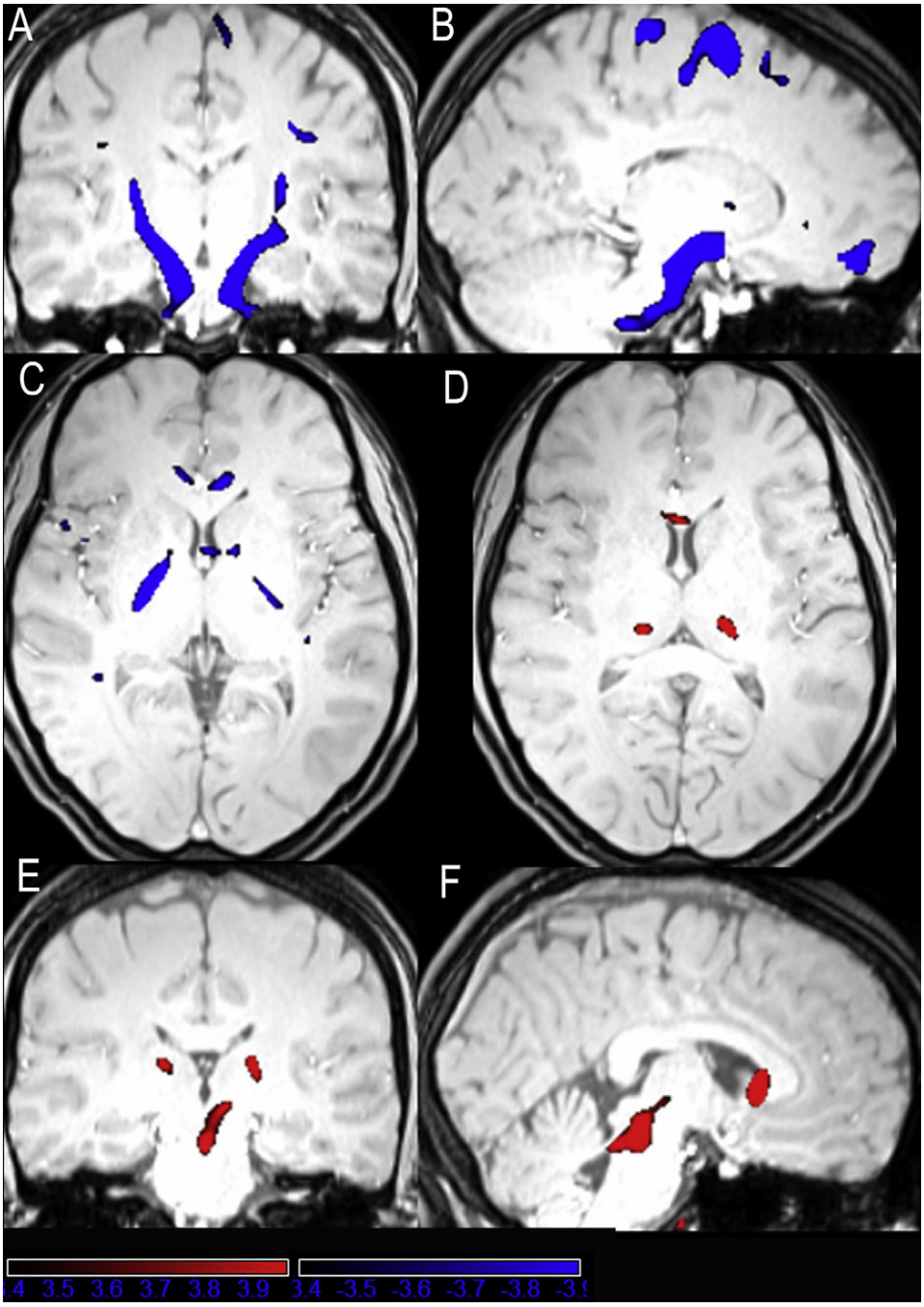

Figure 1 FA value changes in untreated CAE patients compared to healthy controls. The colored voxels indicate brain regions where the FA value was significantly increased (red)or reduced (blue), in untreated CAE patients compared to controls (A—F). The statistical significance level was set to $P < 0.05$ (FDR corrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

displayed reduced FA values in mixed group epilepsy patients, including those with generalized epilepsy (Hutchinson et al., 2010). In an animal model of absence epilepsy, WAG/Rij rats and GAERS (Genetic Absence Epilepsy Rat from Strasbourg), exhibited a localized decrease in FA in the anterior corpus callosum of the white matter pathway interconnecting bilateral cortical regions most directly involved in GSWDs (Chahboune et al., 2009). Moreover, our study also showed FA alterations in the upper brainstem. These regions are involved in midline arousal systems (Blumenfeld et al., 2009), and their activity may be related to the pathomechanisms of seizure propagation and the impaired consciousness associated with this form of generalized epilepsy.

The basal ganglia play an important role in the regulation of absence seizures (Deransart et al., 1998),

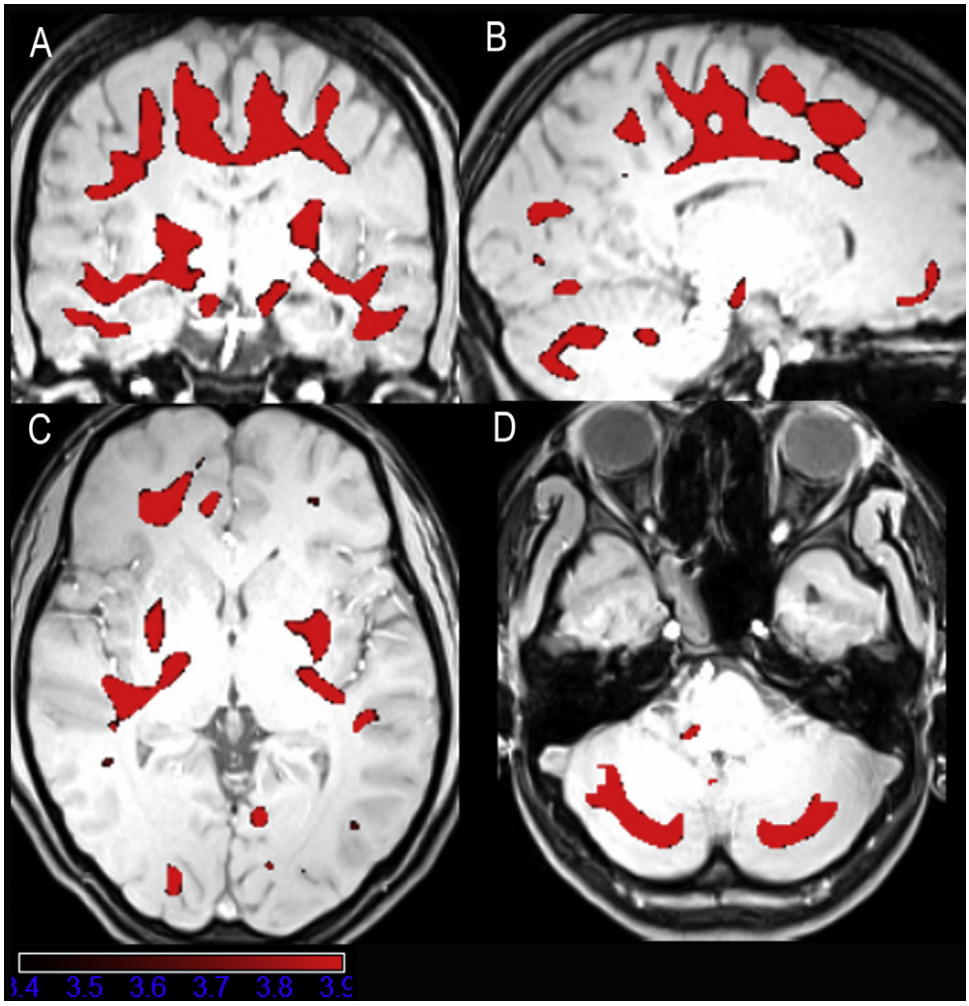

Figure 2 MD value changes in untreated CAE patients compared to healthy controls. The red voxels indicate brain regions where the MD value was significantly increased compared to controls. The statistical significance level was set to $P < 0.05$ (FDR corrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

as demonstrated in animal models of absence epilepsy (Deransart et al., 1998, 1999) and in IGE patients (Moeller et al., 2008; Li et al., 2009; Berman et al., 2010). For example, IGE patients have smaller putamen compared to healthy group (Seeck et al., 2005). In addition, a recent study reported increased MD values bilaterally in the putamen and the left caudate nucleus, along with increased FA values in bilateral caudate nuclei in patients with mixed absence seizures (Luo et al., 2011). In our study, we found that MD values were significantly increased in the bilateral putamen and that increased MD and decreased FA values were found in bilateral posterior limbs of the internal capsule in drug-naïve CAE patients. These results indicate that microstructural changes of the basal ganglia may be involved in the propagation and modulation of GSWDs in CAE.

A previous DTI study found structural abnormalities in the cerebellum of IGE patients GTCS only (Li et al., 2010). In contrast to that report, our study with another subgroup of IGE patients-CAE showed increased MD values in bilateral cerebellar hemispheres, mainly in the posterior lobe. The cerebellum shows activation in response to epileptic discharges, as shown by EEG recordings during the fMRI (Gotman et al., 2005; Liu et al., 2008). Intense involvement of the cerebellum during spike-and-wave discharges has also been observed in an experimental model (Kandel and Buzsaki, 1993). A single photon emission computed tomography (SPECT) study found interictal regional cerebral blood flow was reduced in the cerebellum of drug naïve IGE patients (Joo et al., 2008). These results suggest that there was damage to the white matter integrity of the cerebellum, which may be related to seizure symptoms in CAE.

A significant correlation between age at onset and the diffusion parameters in the caudate nucleus or putamen has been previously reported in patients with absence seizures (Luo et al., 2011). In our current study, no significant correlations were found between diffusion parameters of the ROIs and either the duration of the disease or the age of onset. The discrepancy between the results from these two studies may be explained by the medication and mixed patient groups in the Luo' research.

However, it is important to note that our regression analysis was based on a relatively small sample size and significant correlations may be detected with larger samples. It is not known whether the DTI changes were caused by seizures

or by some other developmental changes (Hermann et al., 2010). However, white matter abnormalities in CAE may contribute to some of the psychosocial problems observed in this form of epilepsy (Caplan et al., 2008; Thomason and Thompson, 2011). Finally, we acknowledge that the present study has methodological limitations. For example, the voxel-based analysis (VBA) was used instead of manual measurement of ROI due to the uncertainty of ROI positioning in patients without lesions visible on the MRI. The spatial normalization process in VBA and the process of comparing one subject with a control group may then give rise to false positive clusters. However, as mentioned in our previous study (Chen et al., 2008), we tried to limit the possibility of obtaining a false positive cluster by using a relatively strict restriction of $P < 0.001$ (FDR corrected with $P < 0.05$).

In conclusion, the present investigation demonstrated white matter integrity impairments in the basal ganglia-thalamocortical circuit in drug-naïve CAE patients. These abnormalities may be related to increased cortical excitability and cause deficits both during and between seizures. We hope our study further elucidates the neuropathophysiological mechanisms of chronic neurological deficits in children suffering from CAE and supports the development of new therapies for this disorder.

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