Epilepsia, 52(6):1092–1099, 2011
doi: 10.1111/j.1528-1167.2011.03045.x

FULL-LENGTH ORIGINAL RESEARCH

Diffusion and volumetry abnormalities in subcortical nuclei of patients with absence seizures

***Cheng Luo, *Yang Xia, †‡Qifu Li, *Kaiqing Xue, *Yongxiu Lai, §Qiyong Gong, †Dong Zhou, and *Dezhong Yao**

***Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China; †Department of Neurology, West China Hospital of Sichuan University, Chengdu, China; ‡Department of Neurology, The Affiliated Hospital of Hainan Medical College, Haikou, China; and §Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, China**

Summary

Purpose: The thalamus and basal ganglia play an important role in the propagation and modulation of generalized spike and slow-wave discharges (SWDs) in absence epilepsy. Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique sensitive to microstructural abnormalities of cerebral tissue by quantification of diffusion parameter. The purpose of this study is to investigate the diffusion and volume changes in the basal ganglia and thalamus of patients with absence seizures.

Methods: In 11 patients with absence seizures and 11 controls, the thalamus, caudate nucleus, putamen, and pallidum were segmented using an automated atlas-based method on the DTI and three-dimensional (3D) anatomic T_1-weighted images. Then the fractional anisotropy (FA), mean diffusivity (MD), and volume were extracted and quantified.

Key Findings: Compared with controls, patients reveal increased MD values bilaterally in thalamus, putamen, and left caudate nucleus; increased FA value in bilateral caudate nuclei; and loss of volume in bilateral thalamus, putamen, and pallidum. Significant correlations were observed between age of onset and diffusion parameter alterations in caudate nucleus or putamen.

Significance: These findings provide preliminary evidence demonstrating that microstructural changes of subcortical structures are related to the chronic abnormal epileptic activity, and add further evidence for the involvement of thalamus and basal ganglia in propagation and modulation of SWDs in absence epilepsy. These results also indicate that DTI is more sensitive for detection of abnormal structure than the conventional MRI, and it may be adopted as a noninvasive means to understand the pathophysiologic evolution of absence seizures.

KEY WORDS: Thalamus, Basal ganglia, Diffusion tensor imaging, Magnetic resonance imaging, Absence epilepsy.

Absence seizures are nonconvulsive generalized seizures characterized clinically by impaired consciousness and bilateral, synchronous, 2.5–4 Hz generalized spike and slow-wave discharges (SWDs) on electroencephalography (EEG) (Crunelli & Leresche, 2002). In general, SWDs are postulated to be a consequence of abnormally synchronized epileptiform activity, which is propagated through thalamocortical circuits (Gloor et al., 1990; Crunelli & Leresche, 2002). Meanwhile, the basal ganglia may play an important role in modulation of absence seizures (Deransart et al., 1998). In previous simultaneous EEG and functional MRI (EEG–fMRI), the activity related to the SWD was found in thalamus and basal ganglia (Moeller et al., 2008; Li et al., 2009). On the other hand, the quantitative neuroimaging studies of childhood absence epilepsy have shown neuroanatomic abnormalities in thalamus, which include both thalamic atrophy in adolescent and young adult patients (Chan et al., 2006) and thalamic hypertrophy (increased thalamic volume) in adult patients (Betting et al., 2006). Seeck et al. (2005) found reduced volume in putamen and caudate nucleus in idiopathic generalized epilepsy.

Diffusion tensor imaging (DTI) is a neuroimaging technique that can detect the magnitude and directionality of water diffusion in vivo noninvasively (Basser & Pierpaoli, 1996). This technique provides three-dimensional (3D) information about tissue water diffusion in each voxel, and can quantify the magnitude of water diffusivity [mean diffusivity (MD)] and diffusion directionality [fractional

Accepted January 25, 2011; Early View publication March 31, 2011.
Address correspondence to Dezhong Yao, Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, China. E-mail: dyao@uestc.edu.cn
Dong Zhou, Department of Neurology, West China Hospital, Sichuan University, 610041, Chengdu, China. E-mail: zhoudong66@yahoo.de

anisotropy (FA)]. Several reports referred to the role of DTI in locating epileptogenic zone in different types of epilepsy (Eriksson et al., 2001; Rugg-Gunn et al., 2001; Arfanakis et al., 2002; Assaf et al., 2003; Dumas de la Roque et al., 2005; Chen et al., 2008). A DTI study in rat absence epilepsy models showed DTI abnormalities in white matter pathways (Chahboune et al., 2009). Altered diffusion parameters in thalamus have been revealed in some DTI studies in temporal lobe epilepsy (Kimiwada et al., 2006; Gong et al., 2008). These variations of diffusion parameters implicate structural disorganization and an expansion of extracellular space, resulting from neuronal loss, reduction of dendritic branching, and microstructural changes associated with epileptogenesis (Hugg et al., 1999; Yoo et al., 2002; Assaf et al., 2003; Yogarajah & Duncan, 2008). Although the origin of generalized absence epilepsy is still unclear (Meeren et al., 2005), thalamus and basal ganglia are involved in the process of absence seizures. Pathologic alterations may exist in these subcortical structures. In addition, because of the early age of onset in absence epilepsy, the seizures may interfere with the maturational processes of subcortical structures. Based on the predominant detection of DTI for microstructure changes in vivo, we hypothesize that DTI may provide a potential noninvasive means to understand the pathophysiologic evolution of absence seizures in subcortical structure.

In the current study, we apply DTI in patients with absence seizures to determine whether the DTI parameters would be changed in bilateral thalamus, caudate nucleus, putamen, and pallidum. First the region of interest (ROI) was extracted using an automated atlas-based method. Second, the microstructure abnormality of thalamus and basal ganglia in patients with absence epilepsy is assessed through these parameters of the ROIs. In addition, MRI volume, the other measure of brain structure, is also adopted to evaluate the macroscopic structural changes in these subcortical nuclei.

Methods

Subjects

A total of 11 patients with absence seizures were recruited from epilepsy clinics for the EEG–fMRI study at Neurology Department in the West China Hospital, Sichuan University. All patients underwent clinical brain structural MRI and 24-h video-EEG. No patient exhibited any radiologic abnormalities. Diagnosis was established according to the diagnostic scheme published by the International League Against Epilepsy (ILAE) in 2001 (Engel, 2001). Clinical epilepsy syndromes included childhood absence epilepsy in nine patients and juvenile absence epilepsy in two patients. The clinical details are shown in Table 1. A total of 11 right-handed, healthy subjects, age- and sex-matched, were selected for the control group. Informed consent for the study was obtained from each participant and/or his/her parents.

Image acquisition

All subjects were scanned in a 3T MRI scanner (EXCITE, GE, Milwaukee, WI, U.S.A.) with an eight-channel-phased array head coil. Anatomic T_1-weighted images were acquired using a 3D spoiled gradient recall (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 degrees, matrix = 512 × 512]. The DTI acquisition used a single-shot spin-echo planar imaging sequence. Fifty contiguously slices were acquired with 3-mm thickness and 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 × 24 cm. At each slice position, except for S0 (b = 0 s/mm^2), a single b-value (b = 1,000 s/mm^2) was applied to 15 non-collinear gradient directions.

Image preprocessing

For DTI images, head motion was removed by aligning 15 diffusion-weighted scans to the unweighted B0 image

Table 1. Demographic data of 11 patients with absence seizures

Patient no.	Sex	Age	Age at seizure onset	Seizure type frequency	Antiepileptic drugs	History/family history	Frequency of SWDs (Hz)
1	M	10	5	AS 2–3/d	None	–	2.5–3.5
2	M	17	4	AS 40/d; two GTCS	VPA CZP	–	3–3.5
3	M	18	9	AS 7–8/d	None	–	3
4	M	6	5	AS several/d	None	–	3
5	F	8	6	AS 20–30/d	None	–	3
6	M	8	7	AS 40/d	None	–	3
7	F	14	9	AS several/d	TCM VPA	–	2–3
8	M	18	16	AS several/d	None	–	2.5–3.5
9	F	5	4	AS several/d	None	Hypoxia history at birth	3
10	M	18	16	AS several/d	None	–	2.5–3
11	F	11	9	AS 2–5/d	VPA	–	3.5

AS, Absence seizure; GTCS, generalized tonic–clonic seizure; d, day; VPA, valproic acid; CZP, clonazepam; TCM, traditional Chinese medicine.

(b = 0 s/mm^2) using the SPM8 software package (statistical parametric mapping http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Eddy current distortions were corrected by affine registration to the reference B0 image. The Diffusion Toolkit 0.6 (http://trackvis.org/dtk/) was used to yield three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and eigenvectors for each subject. The maps of MD and FA were obtained from the eigenvalues. Further assistant to FA and MD analysis, the parallel diffusivity ($\lambda_{\|}$), and perpendicular diffusivity ($\lambda_{\perp}$) were derived on a pixel-by pixel basis. They were defined by the following equation:

$$\lambda_{\|} = \lambda_1$$

$$\lambda_{\perp} = (\lambda_2 + \lambda_3)/2$$

$\lambda_{\|}$ was the primary eigenvalue (λ_1), indicating a preferred direction of diffusion. $\lambda_{\perp}$ was perpendicular to the preferred direction, which reflects the diffusion of shorter axis of the diffusion ellipsoid.

ROI extraction using an automated atlas-based method

Manual delineation of the thalamus and the nuclei of basal ganglia is difficult on T_1-weighted structural image because the boundaries between them and adjacent tissues are ambiguous. Here, an automated atlas-based scheme mentioned by Gong et al. (2008) was performed. First, each subject's high-resolution T_1-weighted images were linearly coregistered and resliced to unweighted B0 images (b = 0 s/mm^2) using a linear transformation. The coregistered T_1 image was then normalized to T_1 template in Montreal Neurological Institute (MNI). The resulting image was segmented and thresholded at a probability of 80%. The masks of white matter, gray matter, and cerebrospinal fluid were acquired for each subject. Second, the WFU_pickAtlas (http://www.fmri.wfubmc.edu/) was adopted to mask out the coarse volume of bilateral thalamus, caudate nucleus, putamen, and pallidum, respectively, in the normalized MNI space. Third, the inverse transformation of normalization was applied to acquire the masks of the native space of DTI for the eight subcortical ROIs, gray matter, white matter, and cerebrospinal fluid (Gong et al., 2008). The subject's whole brain mask without the cerebrospinal fluid was carried out by integration between the masks of white matter and gray matter. Fourth, because the MD map offers a good contrast between ventricle and subcortical structure (thalamus and caudate nucleus), and the FA map offers a dramatic contrast in subcortical structure (thalamus, caudate nucleus, putamen, and pallidum) and white matter (internal capsule and external capsule), we further polished the eight ROIs by removing the voxels if FA value >0.5 (to remove the voxel in the white matter) or MD value >1.3*10^{-3} mm^2/s (to ignore voxel in the ventricle) (Gong et al., 2008). Finally, the quality of the extraction of the ROIs was manually checked and confirmed for all subjects. Figure 1 is a processed result of a subject.

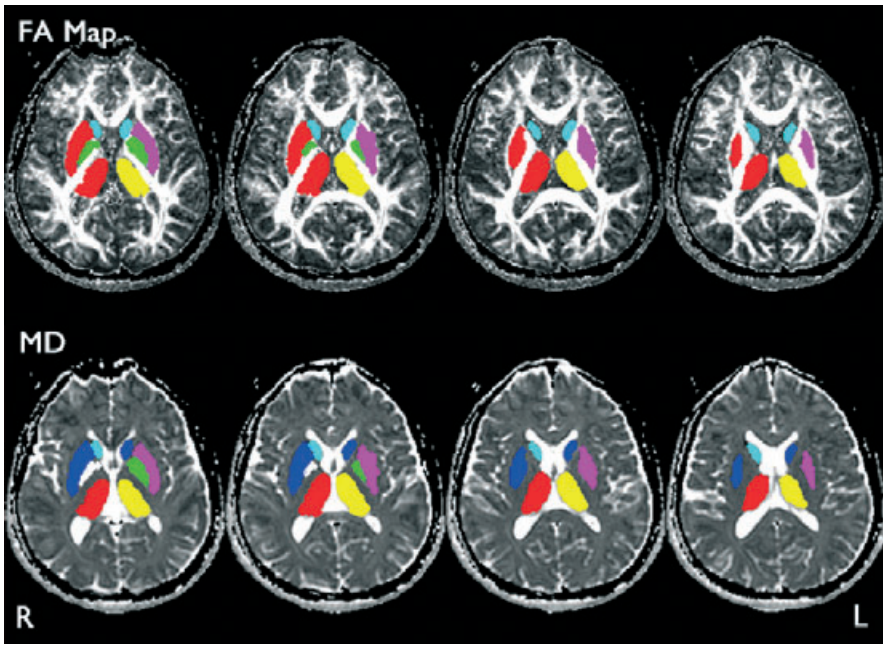

Figure 1.
Demonstration of eight ROIs segmentation for a health subject. All ROIs were overlaid in FA map and MD map in four sequent slices. The different color represents the variable ROI.

Statistical analysis

For each subject, the mean FA or MD value was calculated in eight ROIs. The volumes of these structures were normalized to the whole brain volume without cerebrospinal fluid. Subsequently, using independent-samples *t*-test, FA value, MD value, and volume in the patient group were compared to those in the control group for eight ROIs, respectively. The statistical significance level was set to $p < 0.05$.

To investigate the underlying relation between the significantly altered diffusion parameters or volume of subcortical structures and either age, duration of epilepsy, or age at onset, Pearson correlation analysis was performed.

Results

Diffusion parameter difference

The quantitative analysis of diffusion parameters revealed that the patients with absence seizures had significantly higher FA value than controls in bilateral caudate nuclei (Table 2). Compared with the control group, the increased MD value was found in bilateral thalamus, bilateral putamen, and left caudate nucleus in the patient group (Table 3). It is an interesting finding that the MD value and FA value in left caudate nucleus showed a significant increase simultaneously in the patient group; then the same comparison was processed for the two parameters ($\lambda_{\parallel}$ and $\lambda_{\perp}$) in eight ROIs, and the results were shown in Tables S1 and S2. In bilateral caudate nuclei, the $\lambda_{\parallel}$ value increased significantly in patients; however, the $\lambda_{\perp}$ value had no significant difference between groups. In this way, the enhancive $\lambda_{\parallel}$ value may contribute to the increase of both MD and FA in caudate nucleus. In bilateral thalamus and putamen, the two parameters ($\lambda_{\parallel}$ and $\lambda_{\perp}$) all increased in patients relative to controls. These facts may account for the results in Tables 2 and 3, showing that the changes in FA are not significant and that MD has a significant increase in bilateral thalamus and putamen.

Table 2. Fractional anisotropy values in eight subcortical structures

	Patient group		Control group			
	Mean	SD	Mean	SD	t	p-Value
L-thalamus	0.3108	0.0185	0.3072	0.0138	0.521	0.6081
R-thalamus	0.3046	0.0258	0.3198	0.0202	−1.5296	0.1418
L-caudate	0.2401	0.0255	0.211	0.0185	3.0636	0.0061**
R-caudate	0.2426	0.0223	0.2135	0.0165	3.4785	0.0024**
L-putamen	0.2658	0.026	0.2619	0.0184	0.4106	0.6858
R-putamen	0.2986	0.0207	0.3004	0.0116	−0.2569	0.7999
L-pallidus	0.3071	0.0273	0.3111	0.0201	−0.3938	0.6979
R-pallidus	0.2486	0.025	0.2526	0.0175	−0.4362	0.6674

*p < 0.05, **p < 0.01.

The Pearson correlation analysis revealed the presence of a significant relationship between FA value in the left caudate nucleus and age at onset ($R = -0.758$, $p = 0.007$) (Fig. 2). In addition, the MD values in the left putamen also had a significantly negative correlation with age at onset ($R = -0.638$, $p = 0.034$) (Fig. 3). Conversely, no significant relationship was found between the diffusion parameters and the age or epilepsy duration.

Volume difference

Significant volume decreases were found in bilateral thalamus, putamen, and pallidum in patients as contrasted against controls (Table 4). Marginally significant volume difference were found for bilateral caudate nuclei (Table 4). We also evaluated group difference in whole brain volume without cerebrospinal fluid. The result showed that there was no significant difference between patients and controls in whole brain volume (independent-samples *t*-test, $t = -1.81$, $p = 0.085$). For six subcortical structures with significant volume change in patient group (Table 4), no

Table 3. Mean diffusivity ($\times 10^{-4}$mm^2/s) in eight subcortical structures

	Patient group		Control group			
	Mean	SD	Mean	SD	t	p-Value
L-thalamus	7.9874	0.4254	7.5848	0.2699	2.6506	0.0153*
R-thalamus	7.9039	0.4782	7.475	0.2059	2.7324	0.0128*
L-caudate	8.2559	0.4507	7.7962	0.3436	2.6907	0.0141*
R-caudate	7.8139	0.6587	7.4538	0.277	1.6714	0.1102
L-putamen	7.4321	0.4511	6.9145	0.1761	3.5456	0.002**
R-putamen	7.5875	0.5143	7.1697	0.3181	2.2913	0.0329*
L-pallidus	7.5276	0.4914	7.2143	0.3614	1.703	0.1041
R-pallidus	7.31	0.6235	7.2041	0.3127	0.5034	0.6202

*p < 0.05, **p < 0.01.

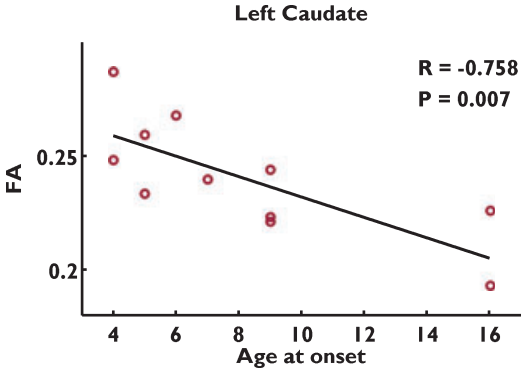

Figure 2.
Correlation between the FA value in left caudate nucleus and the age at onset of patients.
Epilepsia © ILAE

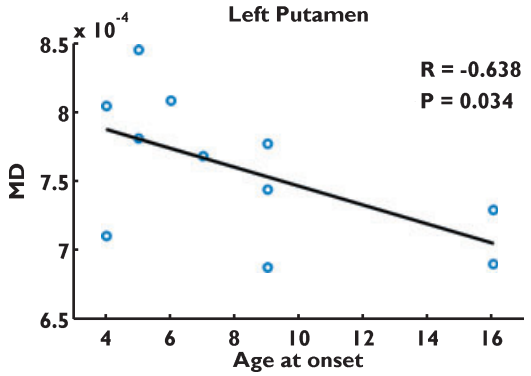

Figure 3.
Correlation between the MD value in left putamen and the age at onset of patients.
Epilepsia © ILAE

Table 4. Volumes of eight subcortical structures, normalized to the whole brain volume

	Patient group		Control group			
	Mean	SD	Mean	SD	t	p-Value
L-thalamus	0.0053	0.0006	0.0062	0.0005	−3.7107	0.0014**
R-thalamus	0.0054	0.0007	0.0067	0.0008	−4.0046	0.0007**
L-caudate	0.0021	0.0004	0.0024	0.0003	−1.9894	0.0605
R-caudate	0.0023	0.0005	0.0026	0.0003	−1.8954	0.0726
L-putamen	0.0059	0.0009	0.0069	0.0008	−2.8102	0.0108*
R-putamen	0.0068	0.0007	0.0083	0.0008	−4.5748	0.0002**
L-pallidus	0.0016	0.0002	0.002	0.0003	−3.5151	0.0022**
R-pallidus	0.0018	0.0001	0.0024	0.0004	−4.8741	0.0001**

*$p < 0.05$, **$p < 0.01$.

correlation was found between their volumes and the age, epilepsy duration, or age at onset, respectively.

Discussion

The principal finding of the current study is abnormal water diffusion in the thalamus and caudate nucleus and putamen in patients with absence seizures. The patient group had less volume in all eight ROIs, six of them significant and two of them (bilateral caudate nuclei) marginally significant. These results were consistent with our hypotheses. In addition, the FA value in the left caudate nucleus and the MD values in left putamen were associated with the age at onset. These findings suggest that the epileptic activity in absence epilepsy may result in microstructural changes in the subcortical structures, which play a key role in propagation and modulation of SWDs in epilepsy.

Previous DTI studies of patients with epilepsy have focused mainly on partial epilepsy, and found increased average MD values in thalamus (Kimiwada et al., 2006) and epileptogenic areas (Rugg-Gunn et al., 2001, 2002; Chen et al., 2008). To the best of our knowledge, this is the first study to evaluate the diffusion abnormalities in subcortical nuclei in patients with absence epilepsy. Righini et al. (1994) have proposed the dynamic profile of seizure-associated change in diffusion parameters, which was a pattern of early postictal depression and then transient or chronic elevation of the MD value. The increased MD in bilateral thalamus, putamen, and left caudate nucleus during interictal duration observed in our study was concordant with the previous findings in interictal studies in partial epilepsy (Rugg-Gunn et al., 2001; Thivard et al., 2005; Chen et al., 2008). In our previous study, we found that MD presented a higher sensitivity than FA in detecting the diffusion abnormalities in refractory partial epilepsy (Chen et al., 2008). Consistent with that, the change in FA was found only in bilateral caudate nuclei in this work. This indicated that MD is a more sensitive marker than FA in patients with epilepsy. This fact was also noted in other epilepsy studies (Rugg-Gunn et al., 2001; Thivard et al., 2005). On the other hand, the abnormalities of diffusion parameters in subcortical nuclei, which were normal on conventional MRI, suggest that DTI might reflect the microstructure changes related to accumulated epileptic discharges, and that DTI might be more sensitive for detection of abnormal structure than conventional MRI in epilepsy.

The thalamus is important for the propagation of SWDs in epilepsy (Gloor et al., 1990), and is considered to have a crucial role in the pathophysiology of absence seizures in electrophysiologic studies (Williams, 1953; Danober et al., 1998) and EEG–fMRI studies (Laufs et al., 2006; Moeller et al., 2008; Li et al., 2009). The diffusion parameter abnormality of the thalamus in this work provides new evidence to support the importance of the thalamus in absence epilepsy. In addition, the increased MD in thalamus was consistent with the findings observed in temporal lobe epilepsy (Kimiwada et al., 2006; Gong et al., 2008). Kimiwada et al. found a trend for increased MD in the thalamus ipsilateral to the epileptic focus in temporal lobe epilepsy, and Gong et al. found a significantly increased MD value in thalamus in temporal lobe epilepsy with mesial temporal sclerosis. The possible interpretation for this observation was structural disorganization and the expansion of extracellular space in thalamus, resulting from the chronic effects of epileptic discharge. For example, the excitotoxic mechanisms caused by seizures may lead to cell lysis and death (Wasterlain et al., 1993; Pitkänen et al., 2002; Yogarajah & Duncan, 2008), as the latter result in an increase in extracellular space and increasing diffusion. These mechanisms also provide an explanation for the volume decrease of thalamus in absence epilepsy, consistent with the thalamic atrophy in childhood absence epilepsy found by Chan et al. (2006).

Accumulating evidence suggest that the basal ganglia play a major role in the modulation of absence seizures [reviewed by (Deransart et al., 1998)]. Electrophysiologic studies demonstrated a severe functional imbalance

between striatonigral and subthalamonigral pathways during SWD propagating in basal ganglia circuits, that is, the subthalamonigral pathway showed rhythmic bursting, whereas striatal output neurons were silenced during SWDs (Slaght et al., 2004; Paz et al., 2005). Additional evidence came from experiments involving neuropharmacology (Danober et al., 1998; Deransart et al., 1998) and deep brain stimulation in epilepsy. It was also confirmed that basal ganglia was involved in modulating epileptic discharge and seizure activity (Loddenkemper et al., 2001). With structural MRI, volume decrease in basal ganglia was also observed in a previous study (Seeck et al., 2005). In this work, the diffusion abnormalities in putamen and caudate nucleus as well as the reduced volumes in putamen and pallidum were observed, which may reflect the chronic effects of epileptic discharge. Such effects may increase the extracellular space and cause structure reorganization, each of which may induce diffusion-related microstructural changes.

In this work, we found that the change in FA of caudate nucleus was different from that of the other subcortical structures, that is, significantly elevated FA value was revealed in bilateral caudate nuclei. In the analysis for two additional diffusion parameters ($\lambda_\perp$ and $\lambda_\parallel$), only $\lambda_\parallel$ increased in caudate nucleus, whereas both $\lambda_\perp$ and $\lambda_\parallel$ increased in the thalamus and putamen. The increased FA and $\lambda_\parallel$ reflected a prolate diffusion within a voxel. This change indicates a more ordered tissue containing larger numbers of similarly aligned neurons (Mukherjee et al., 2008). Hence, the finding might indicate an increased cellular density with increased fiber barriers in caudate nucleus in patients with absence seizures. Although no histopathologic evidence confirmed this hypothesis, no significant difference of volumes in caudate nucleus between groups meant at least no distinct cell lost. Recently, many EEG–fMRI studies for patients with absence seizures found deactivation in caudate nucleus, but no deactivation absence in putamen (Salek-Haddadi et al., 2003; Moeller et al., 2008; Li et al., 2009). Furthermore, Moeller et al. (2008) speculated that the change in the caudate nucleus might be a consequence of changes in activity at the thalamocortical level and might reflect a reduced corticostriatal drive during SWDs. The differences between the caudate nucleus and putamen demonstrated in this work might hint at inconsistency of diffusion in them. In addition, the anatomic connection between the cerebral cortex and the caudate nucleus or putamen is also different. Frontoparietal associative cortex mainly connected with the caudate nucleus, and sensorimotor cortex with putamen (Selemon & Goldman-Rakic, 1985; Parent & Hazrati, 1995). Because the disruption of frontoparietal associative network may result in impaired consciousness in epilepsy (Cavanna & Monaco, 2009; Liao et al., 2010), this finding in the caudate nucleus may have implicit association with the unconsciousness during absence seizures.

In addition, significant correlation between age at onset and the diffusion parameters in caudate nucleus or putamen was found in patients with absence seizures. Previously, Gong et al. (2008) found the FA value in ipsilateral thalamus was related significantly to the age at onset in temporal lobe epilepsy with mesial temporal sclerosis. They suggested that patients with early onset temporal lobe epilepsy have more severe pathology. Although no significant correlation was observed between the thalamic diffusion parameters and age at onset in this work, we did find similar correlation in basal ganglia. This might also reflect that the subcortical nuclei microstructure change was more severe in early onset patients than the late-onset ones. Furthermore, previous DTI studies focused on normal human brain maturation have observed age-dependent decrease of water diffusion in the basal ganglia throughout the course of brain development (Mukherjee et al., 2001, 2002; Mukherjee & McKinstry, 2006). The findings in this work imply that the absence seizures starting in childhood or adolescence might interfere with this maturational process, resulting in persistent diffusion alteration, as the diffusion abnormality in patients was more serious with early age of onset than with late age of onset.

There are several limitations in this study. The sample size of patients is small. Some changes reported in previous studies were not observed in our current study, for example., the FA in thalamus. Therefore, these findings should be considered as a preliminary and need to be validated and extended with a larger population. The segmentation of subcortical structures should be considered. Due to specific differences between the gray matter and white matter or cerebrospinal fluid in the FA and MD map, the profile of caudate nucleus and thalamus could be circumscribed satisfactorily. However, the boundary between the putamen and the pallidum is unclear in T1 image and diffusion image (including FA map and MD map). Although we tried to correct for this through careful review by two radiologists, some error may remain there to affect the measurement of volume for the structures. However, the lentiform nucleus, comprising putamen and pallidum, can be delineated because it was encircled by white matter (internal capsule and external capsule). The volume of the lentiform nucleus bilaterally was also reduced in patients in contrast with controls (right: $p = 0.0001$, left: $p = 0.0004$). In this study, we focused only on the diffusion property of subcortical structures in absence epilepsy. The DTI abnormalities in white matter have been reported in rat absence models (Chahboune et al., 2009). In future studies, the white matter diffusion and tractography should be investigated in patients with absence seizures.

In summary, the current study revealed diffusion and volumetry abnormalities in subcortical structures in patients with absence epilepsy. The results provide preliminary evidence for microstructural changes of subcortical structures

related to the chronic abnormal epileptic activity. Moreover, the alterations were more serious in patients with early age of onset than those with later age of onset. Our findings also added evidence for the involvement of basal ganglia and thalamus in propagation and modulation of SWDs in patients with absence seizures. Furthermore, DTI is more sensitive for detection of abnormal structure than conventional MRI in absence epilepsy, and it can provide a noninvasive means to understand the pathophysiologic evolution of absence seizures.

Acknowledgments

This project was funded by grants from the National Nature Science Foundation of China (30870655, 81071222, 60736029), the 863 Program (2009AA02Z301), and the 973 project 2011CB707803. This study was also sponsored by the program of International Cooperation and Exchange of National Natural Science Foundation of China (No. 30811120424).

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Arfanakis K, Hermann BP, Rogers BP, Carew JD, Seidenberg M, Meyerand ME. (2002) Diffusion tensor MRI in temporal lobe epilepsy. *Magn Reson Imaging* 20:511–519.

Assaf BA, Mohamed FB, Abou-Khaled KJ, Williams JM, Yazeji MS, Haselgrove J, Faro SH. (2003) Diffusion tensor imaging of the hippocampal formation in temporal lobe epilepsy. *AJNR Am J Neuroradiol* 24:1857.

Basser PJ, Pierpaoli C. (1996) Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 111:209–219.

Betting LE, Mory SB, Lopes-Cendes Í, Li LM, Guerreiro MM, Guerreiro CAM, Cendes F. (2006) MRI volumetry shows increased anterior thalamic volumes in patients with absence seizures. *Epilepsy Behav* 8:575–580.

Cavanna AE, Monaco F. (2009) Brain mechanisms of altered conscious states during epileptic seizures. *Nat Rev Neurol* 5:267–276.

Chahboune H, Mishra AM, DeSalvo MN, Staib LH, Purcaro M, Scheinost D, Papademetris X, Fyson SJ, Lorincz ML. (2009) DTI abnormalities in anterior corpus callosum of rats with spike-wave epilepsy. *Neuroimage* 47:459–466.

Chan CHP, Briellmann RS, Pell GS, Scheffer IE, Abbott DF, Jackson GD. (2006) Thalamic atrophy in childhood absence epilepsy. *Epilepsia* 47:399–405.

Chen Q, Lui S, Li CX, Jiang LJ, Ou-Yang L, Tang HH, Shang HF, Huang XQ, Gong QY, Zhou D. (2008) MRI-negative refractory partial epilepsy: role for diffusion tensor imaging in high field MRI. *Epilepsy Res* 80:83–89.

Crunelli V, Leresche N. (2002) Childhood absence epilepsy: genes, channels, neurons and networks. *Nat Rev Neurosci* 3:371–382.

Danober L, Deransart C, Depaulis A, Vergnes M, Marescaux C. (1998) Pathophysiological mechanisms of genetic absence epilepsy in the rat. *Prog Neurobiol* 55:27–57.

Deransart C, Vercueil L, Marescaux C, Depaulis A. (1998) The role of basal ganglia in the control of generalized absence seizures. *Epilepsy Res* 32:213–223.

Dumas de la Roque A, Oppenheim C, Chassoux F, Rodrigo S, Beuvon F, Daumas-Duport C, Devaux B, Meder JF. (2005) Diffusion tensor imaging of partial intractable epilepsy. *Eur Radiol* 15:279–285.

Engel J. (2001) A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 42:796–803.

Eriksson SH, Rugg-Gunn FJ, Symms MR, Barker GJ, Duncan JS. (2001) Diffusion tensor imaging in patients with epilepsy and malformations of cortical development. *Brain* 124:617.

Gloor P, Avoli M, Kostopoulos G. (1990) Thalamo-cortical relationships in generalized epilepsy with bilaterally synchronous spike-and-wave discharge. In Avoli M, Gloor P, Kostopoulos G, Naquet R (Eds) *Generalized epilepsy: neurobiological approaches*. Birkhauser, Boston, pp. 190–212.

Gong G, Concha L, Beaulieu C, Gross DW. (2008) Thalamic diffusion and volumetry in temporal lobe epilepsy with and without mesial temporal sclerosis. *Epilepsy Res* 80:184–193.

Hugg JW, Butterworth EJ, Kuzniecky RI. (1999) Diffusion mapping applied to mesial temporal lobe epilepsy: preliminary observations. *Neurology* 53:173.

Kimiwada T, Juhász C, Makki M, Muzik O, Chugani DC, Asano E, Chugani HT. (2006) Hippocampal and thalamic diffusion abnormalities in children with temporal lobe epilepsy. *Epilepsia* 47:167–175.

Laufs H, Lengler U, Hamandi K, Kleinschmidt A, Krakow K. (2006) Linking generalized spike-and-wave discharges and resting state brain activity by using EEG/fMRI in a patient with absence seizures. *Epilepsia* 47:444–448.

Li Q, Luo C, Yang T, Yao Z, He L, Liu L, Xu H, Gong Q, Yao D, Zhou D. (2009) EEG–fMRI study on the interictal and ictal generalized spike-wave discharges in patients with childhood absence epilepsy. *Epilepsy Res* 87:160–168.

Liao W, Zhang Z, Pan Z, Mantini D, Ding J, Duan X, Luo C, Wang Z, Tan Q, Lu G. (2010) Default mode network abnormalities in mesial temporal lobe epilepsy: a study combining fMRI and DTI. *Hum Brain Mapp* (in press) doi: 10.1002/hbm.21076.

Loddenkemper T, Pan A, Neme S, Baker KB, Rezai AR, Dinner DS, Montgomery EB Jr, Lüders HO. (2001) Deep brain stimulation in epilepsy. *J Clin Neurophysiol* 18:514.

Meeren H, van Luijtelaar G, Lopes da Silva F, Coenen A. (2005) Evolving concepts on the pathophysiology of absence seizures: the cortical focus theory. *Arch Neurol* 62:371.

Moeller F, Siebner HR, Wolff S, Muhle H, Granert O, Jansen O, Stephani U, Siniatchkin M. (2008) Simultaneous EEG–fMRI in drug-naive children with newly diagnosed absence epilepsy. *Epilepsia* 49:1510–1519.

Mukherjee P, McKinstry RC. (2006) Diffusion tensor imaging and tractography of human brain development. *Neuroimaging Clin N Am* 16: 19–43.

Mukherjee P, Miller JH, Shimony JS, Conturo TE, Lee BCP, Almli CR, McKinstry RC. (2001) Normal brain maturation during childhood: developmental trends characterized with diffusion-tensor MR imaging. *Radiology* 221:349.

Mukherjee P, Miller JH, Shimony JS, Philip JV, Nehra D, Snyder AZ, Conturo TE, Neil JJ, McKinstry RC. (2002) Diffusion-tensor MR imaging of gray and white matter development during normal human brain maturation. *AJNR Am J Neuroradiol* 23:1445.

Mukherjee P, Berman JI, Chung SW, Hess CP, Henry RG. (2008) Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings. *AJNR Am J Neuroradiol* 29:632–641.

Parent A, Hazrati LN. (1995) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res Brain Res Rev* 20:91–127.

Paz JT, Deniau JM, Charpier S. (2005) Rhythmic bursting in the cortico-subthalamo-pallidal network during spontaneous genetically determined spike and wave discharges. *J Neurosci* 25:2092.

Pitkänen A, Nissinen J, Nairismägi J, Lukasiuk K, Gröhn OH, Miettinen R, Kauppinen R. (2002) Progression of neuronal damage after status epilepticus and during spontaneous seizures in a rat model of temporal lobe epilepsy. *Prog Brain Res* 135:67–83.

Righini A, Pierpaoli C, Alger JR, Di Chiro G. (1994) Brain parenchyma apparent diffusion coefficient alterations associated with experimental complex partial status epilepticus. *Magn Reson Imaging* 12:865–871.

Rugg-Gunn FJ, Eriksson SH, Symms MR, Barker GJ, Duncan JS. (2001) Diffusion tensor imaging of cryptogenic and acquired partial epilepsies. *Brain* 124:627.

Rugg-Gunn FJ, Eriksson SH, Symms MR, Barker GJ, Thom M, Harkness W, Duncan JS. (2002) Diffusion tensor imaging in refractory epilepsy. *Lancet* 359:1748–1751.

Salek-Haddadi A, Lemieux L, Merschhemke M, Friston KJ, Duncan JS, Fish DR. (2003) Functional magnetic resonance imaging of human absence seizures. *Ann Neurol* 53:663–667.

Seeck M, Dreifuss S, Lantz G, Jallon P, Foletti G, Despland PA, Delavelle J, Lazeyras F. (2005) Subcortical nuclei volumetry in idiopathic generalized epilepsy. *Epilepsia* 46:1642–1645.

Selemon LD, Goldman-Rakic PS. (1985) Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J Neurosci* 5:776.

Slaght SJ, Paz T, Chavez M, Deniau JM, Mahon S, Charpier S. (2004) On the activity of the corticostriatal networks during spike-and-wave discharges in a genetic model of absence epilepsy. *J Neurosci* 24:6816.

Thivard L, Lehéricy S, Krainik A, Adam C, Dormont D, Chiras J, Baulac M, Dupont S. (2005) Diffusion tensor imaging in medial temporal lobe epilepsy with hippocampal sclerosis. *Neuroimage* 28:682–690.

Wasterlain CG, Fujikawa DG, Penix LR, Sankar R. (1993) Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia* 34(suppl 1):S37–S53.

Williams D. (1953) A study of thalamic and cortical rhythms in petit mal. *Brain* 76:50–69.

Yogarajah M, Duncan JS. (2008) Diffusion-based magnetic resonance imaging and tractography in epilepsy. *Epilepsia* 49:189–200.

Yoo SY, Chang KH, Song IC, Han MH, Kwon BJ, Lee SH, Yu IK, Chun CK. (2002) Apparent diffusion coefficient value of the hippocampus in patients with hippocampal sclerosis and in healthy volunteers. *AJNR Am J Neuroradiol* 23:809.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Perpendicular diffusivity ($\times 10^{-4}$ mm^2/s) in eight subcortical structures.

Table S2. Parallel diffusivity ($\times 10^{-4}$ mm^2/s) in eight subcortical structures.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.