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Cerebral white matter integrity in children with active versus remitted epilepsy 5 years after diagnosis

Ishmael Amarreh, PhD, MPA^{1,*}, Kevin Dabbs, MS², Daren C. Jackson, PhD², Jana E. Jones, PhD², Mary E. Meyerand, PhD¹, Carl E. Stafstrom, MD, PhD², David A Hsu, PhD, MD², Michael Seidenberg, PhD³, and Bruce P. Hermann, PhD²

¹Department of Medical Physics, University of Wisconsin School of Medicine and Public Health, Madison WI

²Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison WI

³Department of Psychology, Rosalind Franklin School of Medicine and Science, North Chicago IL

Abstract

Introduction—Diffusion Tensor Imaging (DTI) studies have reported white matter abnormalities in childhood-onset epilepsy, but the mechanisms and timing underlying these abnormalities, and their resolution, are not well understood. This study examined white matter integrity in children with active versus remitted epilepsy.

Methods—Tract-Based Spatial Statistics (TBSS) was used to examine whole-brain DTI indices of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) in 20 children with epilepsy 5–6 years after diagnosis, compared to 29 healthy controls. To determine the status of white matter following cessation of seizures, participants with epilepsy were classified as active versus remitted and comparisons included: (1) controls vs. all children with epilepsy, (2) controls vs. children with remitted seizures, (3) controls vs. children with active seizures, and (4) children with active vs. remitted epilepsy.

Results—In the active compared to remitted epilepsy group, significantly higher FA and lower MD, AD and RD values were dispersed in the internal capsule, cingulum, body of the corpus callosum, superior corona radiata and superior fronto-occipital fasciculus. Similar differences were found between the active epilepsy and the control group. There were no significant differences between the remitted epilepsy and control groups.

Conclusion—Children with active epilepsy differed in white matter integrity compared to children with remitted epilepsy and healthy controls. It remains to be determined whether these findings represent the outcomes of seizure remission versus an initial biomarker for those children who will ultimately have intractable epilepsy.

Keywords

DTI; childhood epilepsy; Tract based spatial statistics; epilepsy remission

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Corresponding author amarreh@wisc.edu, University of Wisconsin, Department of Medical Physics, 1111 Highland Avenue RM 1005, Madison, WI 53705 USA, Tel: (614-404-1008), Fax: (608-262-2413), Madison, WI 53792 USA.

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INTRODUCTION

Diffusion tensor imaging (DTI) is a sensitive tool for assessing cerebral white matter. Frequently utilized DTI-based indices include *fractional anisotropy* (FA), a measure of the preferred directionality of diffusion within a voxel ranging between 0 (isotropic diffusion) and 1 (unidirectional diffusion), radial diffusivity (RD) a measure of perpendicular diffusion of water, axial diffusivity (AD) a measure of diffusion along the largest Eigen vector of diffusion and mean diffusivity (MD), a measure of the average diffusion property within a voxel (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996).

Recent DTI studies indicate abnormalities in the microstructural integrity of cerebral white matter in both adults (Duncan, 2008; Yogarajah & Duncan, 2008) and children with epilepsy (Nilsson et al., 2008). Extensive research has characterized the patterns of abnormalities in adults with chronic established epilepsy, especially temporal lobe epilepsy (Otte et al., 2012), as well as adults with other epilepsy syndromes (Salmenpera, Symms, Boulby, Barker, & Duncan, 2006). These white matter (WM) abnormalities are evident in regions both proximal and distal to the primary epileptic zone (Arfanakis et al., 2002; Concha, Beaulieu, Collins, & Gross, 2009; Diehl et al., 2008; Knake et al., 2009; Rodrigo et al., 2007; Thivard et al., 2005). These findings are believed to reflect structural disorganization and expansion of extra cellular space, which is thought to reflect the underlying physiological changes in white matter associated with epilepsy, which may extend beyond the seizure focus.

In pediatric studies, temporal epilepsy has been shown to be associated with reduced FA in the anterior and posterior limbs of the of the internal capsule, splenium of the corpus callosum, as well as higher MD, RD and AD in the same structures (Meng et al., 2010). Additional DTI results from pediatric temporal lobe epilepsy studies include significantly reduced FA in the hippocampus contralateral as well as ipsilateral to side of seizure onset (Kimiwada et al., 2006), along with decreased anisotropy in white matter tracts (uncinate, arcuate, and inferior longitudinal fasciculus as well as corticospinal tract) both contralateral and ipsilateral to the side of seizure onset (Govindan, Makki, Sundaram, Juhász, & Chugani, 2008).

Abnormalities in white matter integrity are not confined to children with established and chronic epilepsy, as reduced FA and increased RD in the posterior corpus callosum and cingulum have been reported in children with new onset idiopathic epilepsies (Hutchinson et al., 2010). Recently, newly diagnosed and untreated children with childhood absence epilepsy (CAE) were found to have significantly lower FA values in prefrontal white matter, anterior cingulate, and increased MD in parietal lobe white matter, prefrontal white matter, and posterior cerebellar hemispheres, in addition to subcortical structures including bilateral putamen and posterior limbs of the internal capsule (Yang et al., 2012). A recent report of new-onset mixed syndrome groups revealed significantly reduced FA in left postcentral, elevated RD in left posterior cingulum and right external capsule, and elevated AD in left middle temporal WM and left thalamus, in children with epilepsy relative to controls (Widjaja et al., 2012). Together, the findings from adult and childhood epilepsy suggest that DTI is a sensitive tool in detecting WM abnormalities that may be due to etiological factors or acquired damage.

To date, the causative mechanisms of the reported diffusion abnormalities and their course over time remain largely unknown (Hutchinson, et al., 2010). Furthermore, the relationship between seizure remission and white matter integrity has not been examined in pediatric epilepsy. This study investigates, for the first time, whether these abnormalities persist 5–6

years after epilepsy diagnosis and to what degree epilepsy remission status (active vs. remitted) is associated with variations in white matter integrity. In this study we used the TBSS pipeline within FSL, which addresses the main shortfalls of conventional voxel-wise approaches.

METHODS AND MATERIALS

Subject Groups

Participants were 20 children and adolescents with epilepsy age 8–18 at the onset of epilepsy (9 female, 11 male) and 29 normally developing participants (current average age $\pm$ SD = 18.34 $\pm$ 2.91 years; 13 female, 16 male). The epilepsy participants, and controls, were seen five years after their baseline evaluations. The epilepsy participants were selected based on a diagnosis of idiopathic epilepsy with no other developmental disabilities or neurological disorders and normal brain MRI scans. The epilepsy group contained 9 with active epilepsy (current average age $\pm$ SD = 18.61 $\pm$ 3.57 years; 5 female, 4 males), and 11 with remitted epilepsy (current average age $\pm$ SD = 18.52 $\pm$ 2.76 years; 4 female, 7 males). Each child's epilepsy syndrome was defined in a research consensus meeting by the pediatric epileptologist who reviewed all available clinical data (e.g., seizure description and phenomenology, EEG, clinical imaging, neurodevelopmental history) while blinded to all research cognitive, behavioral, and neuroimaging data. Two levels of syndromic classification were undertaken including a broad band classification (i.e., Idiopathic Generalized Epilepsies [IGE] and Localization Related Epilepsies [LRE]) as well as narrow band diagnostic classifications within the IGE (Juvenile Myoclonic Epilepsy, Childhood Absence, Juvenile Absence, and IGE NOS) and LRE groups (Benign Epilepsy with Centrottemporal Spikes, Temporal Lobe Epilepsy, Frontal Lobe Epilepsy, Focal NOS).

Epilepsy remission was defined as remaining seizure free for 12 months and no longer taking anti-epileptic drugs (AEDs). Of the 11 participants with epilepsy remission, 8 were on medications at the time of their baseline assessment and the average duration of AED treatment for this group was 30 months. The remitted participants by definition were all withdrawn from AEDs at the time of assessment. Children with localization-related ($n = 6$) and generalized epilepsy ($n = 5$) were equally represented in the remitted group. The 29 control participants were first-degree cousins of the children with epilepsy who were comparable in age, gender and handedness to the epilepsy group (Table 1). The control group had no history of seizures and no other developmental or neurological disease. The full details on the selection criteria are available elsewhere (Hermann et al., 2006). The results presented involve DTI scans taken at the third visit—5–6 years after their baseline evaluation. A total of 84 DTI scans were collected, but due to a scanner malfunction, 32 scans contained image artifacts and were not included in this analysis, leaving a final sample size of 23 epilepsy participants and 29 controls. Three epilepsy subjects could not be confidently classified as active or remitted and thus were not included in the analysis. This study was reviewed and approved by the Institutional Review Boards of both institutions. On the day of study participation families and children gave informed consent and assent and all procedures were consistent with the Declaration of Helsinki (1991).

Image Acquisition

T1, T2, and DWI MRI scans were acquired for each participant. All MRI scans were collected on a clinical 1.5T GE Signa LX MRI scanner (General Electric Corporation, Milwaukee, WI). T1-weighted, three-dimensional, spoiled gradient recalled echo (SPGR) scans were collected with TR/TE = 24/5 ms, flip angle = 40°, coronal acquisition with a reconstructed matrix size of 256x256, field of view (FOV) = 200mm, slice thickness 1.5 mm and contiguous spacing. DTI scan parameters were as follows: one reference scan with $b=0$

s/mm² and 25 diffusion weighted scans with b=1000 s/mm² each with a unique set of gradient directions optimized for DTI axial acquisition with reconstructed matrix size of 256x256, FOV = 240 mm, and slice thickness = 3mm.

DTI Preprocessing

Images were transferred to an offline workstation for processing. After initial conversion to the NIFTI format, processing was performed with the FMRIB Software Tools (FSL) software package unless otherwise indicated (Woolrich et al., 2009). The FSL eddy current correction toolbox was used to correct for eddy-current artifacts. Calculation of the diffusion tensor was performed in Hispeed, an in-house software package (Koay, Chang, Carew, Pierpaoli, & Basser, 2006). Hispeed utilizes a nonlinear least squares technique to compute the tensor. The diffusion tensor was decomposed into its eigenvalues and maps created for FA, MD, RD and AD. These maps were then used in the voxel-wise analyses to disambiguate differences in specific structures of brain white matter. To address the structural differences in white matter we conducted a voxel-wise analysis using Tract-based spatial statistics (TBSS) on FA, MD, RD and AD.

TBSS Processing

The TBSS pipeline within FSL addresses the main limitations associated with a conventional voxel-wise approach. Namely, TBSS is less vulnerable to registration mismatches in group comparisons and does not require an arbitrarily determined amount of spatial smoothing (Smith et al., 2006).

All the FA images undergo voxel-wise nonlinear registration to a target image provided by FSL (FMRIB_1mm). An intermediate degree of freedom registration (DoF) was chosen for TBSS to avoid poor alignment (insufficient DoF) and “broken topology” (excess DoF). This process involved carrying out only one registration per participant and gave sufficient alignment results. All images were transformed to the MNI152 coordinate system where all subsequent processing were done. Next, the mean of all FA images was created, and then fed into the FA skeletonization algorithm to generate a “reference skeleton”. This white matter skeleton is a pseudo-anatomical representation intended to represent the average of the centers of white matter tracts. The reference skeleton was then thresholded at an FA value of 0.2, which eliminates skeletal remnants at the outer white matter tissue where higher inter-subject variability likely causes poor alignment.

The thresholded reference skeleton was then projected onto the individual, registered FA images. A TBSS algorithm was used to search orthogonally outward from the skeleton until the corresponding WM tract center for that participant was determined. The skeletons of all participants are merged into a single 4D file. Cross-subject voxelwise statistical analysis was performed on the skeletons to determine voxels of significant difference.

The statistical analysis included investigation of each voxel along the representative skeletons using masks of regions of interest. In voxel-wise analyses of brain imaging like TBSS, the results are corrected for multiple comparisons. While this is necessary to achieve statistically sound results, these corrections may also remove any underlying group differences that exist. To address this issue, we narrowed our analysis to specific regions of interest (ROI)(Figure 1). These ROI were selected based on a whole brain ROI analysis of the DTI indices. Analysis was performed on each of the 48 WM ROIs designated in the John Hopkins University White Matter Atlas (Mori & Crain, 2005). These ROIs were used as masks in the statistical analysis step of the TBSS pipeline. A two-sample t-test adjusted for age using two contrasts (Patients > Controls) and (Controls > Patients) was performed upon the diffusion map skeletons of FA, MD, AD, RD. Similar analyses were conducted for all

group comparisons. Using FSL's "randomize" function, the nonparametric test was executed with 5000 permutations. The Threshold-Free Cluster Enhancement (TFCE) method with the -T2 option was implemented to avoid an arbitrary cluster threshold (Smith & Nichols, 2009). The optimized parameters used were H=2 and E=0.5. All results were then corrected for multiple comparisons using a threshold of $p < 0.05$.

TBSS was also performed on the diffusion maps of other measures. Processing time was saved by using the predetermined centers of the WM tracts of the FA analysis. The corresponding values were then used to create skeletons of MD, RD and AD. Statistics were carried out in a similar manner to the FA skeleton detailed above.

RESULTS

Controls vs. all children with epilepsy

TBSS revealed significant group differences in FA, MD, RD and AD between children with epilepsy (n=20) and controls (n=29) in distributed regions across the brain ($p < 0.05$ corrected). The epilepsy group showed reduced FA in major white matter tracts that included the left hemisphere of internal capsule, right cingulum and the fornix (Table 2 and Figure 2). Additionally, there was an increase in MD in the fornix, bilateral superior coronal radiata, and right superior fronto-occipital fasciculus. While AD in the epilepsy group was increased in bilateral superior corona radiata, and bilateral superior fronto-occipital fasciculus, RD was increased only in the left internal capsule and fornix.

Controls vs. children with active and remitted epilepsy

When the epilepsy group was divided into active versus remitted groups, the active epilepsy group showed reduced FA in bilateral superior fronto-occipital fasciculus, right cingulum and fornix compared to controls ($p < 0.05$ corrected). This active epilepsy group also exhibited an increase in MD in bilateral superior fronto-occipital fasciculus and left superior coronal radiata. RD was increased in bilateral superior fronto-occipital fasciculus, and the left superior corona radiata was the only region in which an increase in AD was detected in this comparison (Table 3 and Figure 3). In contrast, there were no differences in any of the DTI indices between the remitted epilepsy group and controls.

Children with active vs. children with remitted epilepsy

Comparing the active (n=9) versus remitted (n=11) epilepsy groups, TBSS analysis revealed group differences in FA, MD, RD and AD distributed across several regions of the brain ($p < 0.05$ corrected) (Table 1). The active epilepsy group showed reduced FA in the bilateral internal capsule, right cingulum, right superior corona radiata, and the splenium of the corpus callosum compared to children with remitted epilepsy ($p < 0.05$ corrected) (Table 4) (Figure 4). The active epilepsy group also exhibited increased MD bilaterally in superior coronal radiata, and left superior frontooccipital fasciculus. The active epilepsy group also showed increased RD in the right internal capsule, right cingulum, bilateral superior corona radiata and the splenium of the corpus callosum compared to children with remitted epilepsy. The left internal capsule in the active group was the only region with an increase in AD compared to the remitted group ($p < 0.05$ corrected).

DISCUSSION

The primary finding of this study is the differential integrity of cerebral white matter microstructure in children with active versus remitted epilepsy 5 years after diagnosis. Children with persisting active epilepsy exhibited reduced FA and increased MD, RD and AD compared to controls. Additionally, the active epilepsy group presented similar results

of reduced FA and increased MD, RD and AD when compared to the remitted epilepsy group. In contrast, children with remitted epilepsy showed no significant differences compared to the healthy control group. This is the first study to examine cerebral white matter structure as a function of remission status at a fixed time point post diagnosis (5–6 years after diagnosis).

DTI indices are highly sensitive in measuring microstructural differences across different tissues. Seizure associated changes have been observed in both animal and human studies, which generally show a pattern of early postictal depression, followed by normalization and then chronic elevation of mean diffusivity (Righini, Pierpaoli, Alger, & Di Chiro, 1994). In this study, children with active epilepsy showed reduced FA bilaterally in superior fronto-occipital fasciculus, right cingulum, and the fornix compared to controls. Comparing the active with the remitted group, reduced FA was observed in regions such as the internal capsule and splenium of the corpus callosum. The reduction in FA, which represents the ratio of anisotropic components of diffusion, suggests a reduction in axonal density (Luis Concha, Livy, Beaulieu, Wheatley, & Gross, 2010).

RD in the active group was elevated in bilateral superior fronto-occipital fasciculus compared to controls. The active epilepsy group also showed increased RD in the right internal capsule, right cingulum, bilateral superior corona radiata and the splenium of the corpus callosum compared to children with remitted epilepsy. This increase in perpendicular diffusivity measured by RD, which is the mean of the magnitude of diffusion or the eigenvalues of λ_{medium} and λ_{minor} , is consistent with myelin degradation (Beaulieu, 2002; Concha, Gross, Wheatley, & Beaulieu, 2006; Song et al., 2002; Song et al., 2003).

AD was increased in the left superior corona radiata in the active epilepsy group compared to controls. The left internal capsule in the active group was the only region with an increase in AD compared to the remitted group. While an increase in perpendicular diffusivity measured by RD, is consistent with myelin degradation (Beaulieu, 2002; Luis Concha, et al., 2006; Song, et al., 2002; Song, et al., 2003), decreased AD, which is λ_{major} and represents the magnitude of principle diffusivity, is considered to reflect axonal degeneration (Kim et al., 2007; Song, et al., 2003; Thomalla et al., 2004). Although, several studies relate AD to axonal degeneration, others view the nature of the underlying changes related to AD to be inconclusive. In the current study, the findings of elevated RD, AD and depressed FA suggests that axonal and myelin abnormalities are present in children with active epilepsy.

Using ROIs placed in the anterior and posterior corpus callosum, fornix, cingulum, internal and external capsule, diffusion differences were evaluated in the same population of children with epilepsy examined in here at baseline (Hutchinson et al., 2010). Children with new onset epilepsy were found to have reduced FA and increased RD in the posterior corpus callosum and cingulum. Here we found the same pattern in the posterior corpus callosum and right cingulum of children with active epilepsy.

The present findings are the first to reveal differential outcomes in white matter integrity as a function of seizure remission status 5–6 years after diagnosis. Whether there is *recovery* of DTI abnormalities reported in children with chronic and new onset epilepsy (Hutchinson et al. 2010; Widjaja et al. 2012) remains to be determined. While our findings suggest there may be recovery, our data are insufficient to document this point. Needed is a longitudinal investigation of children with DTI both at baseline and longitudinal follow-up where changes can be related to seizure outcome status—a research question we are pursuing at present.

There are several limitations to our study. First, the sample size was small, and investigation of a larger sample would be most helpful in determining the reliability of the present findings. The small sample size resulted in children with heterogeneous epilepsy syndromes being grouped together for the analysis in both the active and remission groups. There was no difference (tested by Chi Square) between the proportion of LRE and IGE subjects in the active versus remitted groups. However, given our small sample size, the differences in the number of LRE vs. IGE is a limitation of this study that we plan to address in future studies. We are currently recruiting a new and larger cohort that will have both baseline and follow-up DTI scans. Second, all nine participants in the active group remain on AEDs and the contributions of seizures/epilepsy syndromes versus medications cannot be isolated here.

In summary, this study provides the first examination of the relationship of cerebral white matter integrity and seizure remission in childhood epilepsy 5–6 years after the diagnosis of epilepsy. Abnormal cerebral white matter was detected in the active epilepsy group, but not in children with remitted seizures or controls. These findings have implications for the prediction of seizure outcomes and long-term treatment of children with new onset epilepsy.

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- Compared cerebral white matter in children with active epilepsy to children with remitted epilepsy and controls using DTI.
- Children with active epilepsy have abnormal cerebral white matter as measured by DTI
- No differences in cerebral white matter between Children with remitted epilepsy and controls.

Figure 1. The John Hopkins University Atlas (left) showing its 48 unique white matter ROIs. The atlas is superimposed (right) on a sample patient to demonstrate alignment post registration.

Figure 2.

Regions that were significantly abnormal in children with epilepsy (n=20) compared to controls (n=29) after multiple comparison corrections. Gray is the standard FA template; overlaid is the white matter skeleton (yellow). (A) The right cingulum with lower FA in children with epilepsy compared to controls (blue). (B-D) Left superior corona radiata, Fornix and the left superior fronto-occipital fasciculus with higher MD, RD and AD respectively in children with epilepsy (red).

Figure 3.

Regions that were significantly abnormal in children with active epilepsy (n=9) compared to controls (n=29) after multiple corrections. Gray is the standard FA template; overlaid is the white matter skeleton (yellow). (A) The right cingulum with lower FA in children with epilepsy compared to controls (blue). (B-D) Left superior corona radiata, right superior fronto-occipital fasciculus and the left superior coronal radiata with higher MD, RD and AD respectively in children with epilepsy (red).

Figure 4.

Regions that were significantly abnormal in children with active epilepsy (n=9) compared to children with remitted epilepsy (n=11) after multiple corrections. Gray is the standard FA template; overlaid is the white matter skeleton (yellow). (A) The right cingulum with lower FA in children with active epilepsy compared to in children with remitted epilepsy (blue). (B-D) Left superior corona radiata, right internal capsule and the left internal capsule with higher MD, RD and AD respectively in children with epilepsy (red).

Table 1

Demographic characteristics of the epilepsy and control groups

	Epilepsy (n = 20)		Control (n = 29)
	Remit (n = 11)	Active (n = 9)	
	Mean (SD)	Mean (SD)	Mean (SD)
Age (yrs)	18.52 (2.76)	18.61 (3.57)	18.34 (2.96)
Gender	7 M / 4 F	4 M / 5 F	16M / 13F
IQ Full Score[*]	120.27 (9.50) [*]	107.00 (8.12) ^{*^}	117.14 (10.63) [^]
Seizure Duration (yrs)	6.81 (0.72) [*]	5.90 (0.70) [*]	---
Age of Onset (yrs)	11.53 (3.20)	11.95 (3.52)	
Syndrome	6 ILRE / 5 IGE	7 ILRE / 2 IGE	
Antiepileptic Drugs			---
(polytherapy, monotherapy, none)	0 / 0 / 11 [*]	4 / 4 / 1 [*]	---

Superscript symbol pairs (“*”, “^”) denote significant differences; $p < 0.05$.

ILRE = Idiopathic localization-related epilepsy; IGE = Idiopathic generalized epilepsy

Table 2

Regions that were significantly abnormal in children with epilepsy (n=20) compared to controls (n=29) after correction for multiple comparisons.

DTI parameters	MNI Coordinates x y z	Corresponding white matter cortical label (JHU-ICBM-DTI-81 white-matter labels atlas)	Significant contrast	P cor.
Reduced FA	x="1" y="-10" z="16"	Fornix (column and body of fornix)	C > E	< 0.05
	x="-27" y="-25" z="6"	Retrolenticular part of internal capsule L	C > E	< 0.05
	x="24" y="-25" z="-19"	Cingulum R	C > E	< 0.05
Increased MD	x="1" y="-10" z="16"	Fornix (column and body of fornix)	C < E	< 0.05
	x="27" y="-17" z="24"	Superior corona radiata R	C < E	< 0.05
	x="-28" y="-17" z="24"	Superior corona radiata L	C < E	< 0.05
	x="20" y="-5" z="21"	Superior fronto-occipital fasciculus R	C < E	< 0.05
Increased RD	x="1" y="-10" z="16"	Fornix (column and body of fornix)	C < E	< 0.05
	x="-27" y="-25" z="6"	Retrolenticular part of internal capsule L	C < E	< 0.05
Increased AD	x="27" y="-17" z="24"	Superior corona radiata R	C < E	< 0.05
	x="-28" y="-17" z="24"	Superior corona radiata L	C < E	< 0.05
	x="20" y="-5" z="21"	Superior fronto-occipital fasciculus R	C < E	< 0.05
	x="-20" y="-5" z="21"	Superior fronto-occipital fasciculus L	C < E	< 0.05

Table 3

Regions that were significantly abnormal in children with active epilepsy (n=9) compared to controls (n=29) after correction for multiple comparisons.

DTI parameters	MNI coordinates x y z	Corresponding white matter cortical label (JHU-ICBM-DTI-81 white-matter labels atlas)	Significant contrast	P cor.
Reduced FA	x="1" y="-10" z="16"	Fornix (column and body of fornix)	C > A	< 0.05
	x="24" y="-25" z="-19"	Cingulum R	C > A	< 0.05
	x="20" y="-5" z="21"	Superior fronto-occipital fasciculus R	C > A	< 0.05
	x="-20" y="-5" z="21"	Superior fronto-occipital fasciculus L	C > A	< 0.05
Increased MD	x="-28" y="-17" z="24"	Superior corona radiata L	C < A	< 0.05
	x="20" y="-5" z="21"	Superior fronto-occipital fasciculus R	C < A	< 0.05
	x="-20" y="-5" z="21"	Superior fronto-occipital fasciculus L	C < A	< 0.05
Increased RD	x="20" y="-5" z="21"	Superior fronto-occipital fasciculus R	C < A	< 0.05
	x="-20" y="-5" z="21"	Superior fronto-occipital fasciculus L	C < A	< 0.05
Increased AD	x="-28" y="-17" z="24"	Superior corona radiata L	C < A	< 0.05

Table 4

Regions that were significantly abnormal in children with active epilepsy (n=9) compared to children with remitted epilepsy (n=11) after correction for multiple comparisons.

DTI parameters	MNI Coordinates x y z	Corresponding white matter cortical label (JHU-ICBM-DTI-81 white-matter labels atlas)	Significant contrast	P cor.
Reduced FA	x="5" y="-37" z="16"	Splenium of corpus callosum	A < R	< 0.05
	x="-27" y="-25" z="6"	Retrolenticular part of internal capsule L	A < R	< 0.05
	x="29" y="-25" z="6"	Retrolenticular part of internal capsule R	A < R	< 0.05
	x="66" y="101" z="48"	Cingulum R	A < R	< 0.05
	x="27" y="-17" z="24"	Superior corona radiata R	A < R	< 0.05
Increased MD	x="27" y="-17" z="24"	Superior corona radiata R	A > R	< 0.05
	x="-28" y="-17" z="24"	Superior corona radiata L	A > R	< 0.05
	x="-20" y="-5" z="21"	Superior fronto-occipital fasciculus L	A > R	< 0.05
Increased RD	x="5" y="-37" z="16"	Splenium of corpus callosum	A > R	< 0.05
	x="24" y="-25" z="19"	Cingulum R	A > R	
	x="29" y="-25" z="6"	Retrolenticular part of internal capsule R	A > R	< 0.05
	x="-28" y="-17" z="24"	Superior corona radiata L	A > R	
	x="27" y="-17" z="24"	Superior corona radiata R	A > R	< 0.05
Increased AD	x="-27" y="-25" z="6"	Retrolenticular part of internal capsule L	A > R	< 0.05