A preliminary study of epilepsy in children using diffusional kurtosis imaging

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Purpose

Epilepsy is the second commonest neurological disease worldwide across all ages. The preferred diagnostic test is electroencephalography (EEG). Idiopathic epilepsy is the most frequent type in children, and constitutes those who do not demonstrate significant structural changes on conventional magnetic resonance image (MRI).

Diffusion weighted MRI is a powerful tool for assessing tissue microstructure. Diffusion tensor imaging (DTI), measure the diffusion properties of water molecules, with the assumption that diffusion occurs in an unrestricted environment with a Gaussian probability distribution. In biological tissues, the cellular microarchitecture restricts water movement, causing the diffusion displacement probability distribution to deviate substantially from a Gaussian form. Diffusional kurtosis imaging (DKI) has been proposed as a new technique for characterizing non-Gaussian diffusion components, in addition to Gaussian components, and is increasingly used in human brain studies. Recent research has demonstrated that DKI is a more comprehensive model than DTI in terms of describing the complex properties of water diffusion in vivo (1-3).

To our knowledge, only a few studies have reported on the use of DKI in children with idiopathic epilepsy. Given the sensitivity of diffusion kurtosis to changes in tissue microstructure and possibly edema, replacement of axons with glial cells and astrocyte proliferation may all be associated with damage caused by seizure activity. We hypothesize that DKI may play an important role in detecting a significant difference in non-Gaussian water diffusion in grey matter and white matter changes in epilepsy. To test this hypothesis, we investigated the value of diffusional kurtosis by studying diffusion abnormalities in children with epilepsy and comparing the results to those of normal controls (NC). We performed whole-brain voxel-based analyses, as all fifteen cases of epilepsy had abnormal EEG signals.
Methods and Materials

Participants

The study was approved by the Research Ethics Board in our hospital, and consent forms were signed by all children custodians. The criteria of the case group for recruitment of children with epilepsy were: (1) clinically diagnosed epilepsy; (2) epileptiform activity localized to both sides of the hemispheres on EEG examination; (3) no other neurological disorders; and (4) no febrile seizures. Eighteen age- and sex-matched children were recruited as normal controls. Additional inclusion criteria for the NC group were: (1) no record of a neurological disorder or brain injury; (2) normal hearing, vision and movement; and (3) normal conventional MRI findings.

MRI acquisition

Children who cannot fall asleep naturally were given 10% chloralhydrate 0.5ml/kg, oral administration for sedation before MRI scan.

The MRI acquisitions were performed on a 3.0-T MRI scanner (Signa, General Electric Medical Systems, Milwaukee, WI). Both DWI images with three b-values (0, 1250, and 2500 sec/mm²) and diffusion encoding vectors along 25 non-parallel directions for each nonzero b-value were acquired. The spin-echo echo-planar imaging sequence was used to acquire DWI images with the following parameters: TR/TE, 14000/76.9 ms; number of averages, 1; slice thickness, 2.5 mm; field of view (FOV) 24×16.8 cm²; data matrix, 96×96; imaging time, 12 minutes and 8 seconds. Whole-brain T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) images were acquired with: TI of 450 ms, TR/TE of 713/2.2 ms, flip angle 15°, one NEX, FOV of 24×24 cm², slice thickness, 1 mm, 320×256 matrix, in a total time of approximately 3 minutes and 50 seconds. In addition, T2-weighted images were acquired for all children using a FLAIR sequence with the following parameters: TR/TE, 8002/153.9 ms, one NEX, slice thickness, 5 mm; 18 slices; FOV 24×24 cm²; 320×192 matrix; imaging time of approximately 1 minute and 40 seconds. Sagittal fast spin echo (FSE) images were acquired with: TR/TE of 2560/116.6 ms, two NEX, FOV of 24×24 cm², slice thickness, 3 mm, 384×224 matrix, in a total time of approximately 1 minute and 15 seconds.

Data analysis

Preprocessing

For all DWI images, we first corrected raw DWI data distortion induced by eddy-current using the "eddy correct" tool in FSL, and removed non-brain tissue using the BET tool.
(FSL). The apparent diffusion coefficient (ADC) and the apparent kurtosis coefficient (AKC) along each gradient direction were estimated using the DWI data. Both MD and MK were subsequently calculated by averaging the ADC and the AKC along these directions. A diffusion tensor was then reconstructed at each voxel, and a fractional anisotropy (FA) map was estimated for each dataset. All estimations of DKI parameters were implemented using software developed in-house.

Normalization

As suggested by Wilke et al. (4), attention needs to be paid to the spatial normalization of data from children, due to differences in size, composition and shape between pediatric and adult brains. Thus, a pediatric template should be used instead of a conventional template in order to minimize the amount of deformation that can occur during spatial normalization and any possible errors. We created a subject-specific template using baseline DWI data (S0). The procedure consisted of three steps: 1) The creation of a template, matched for age, of GM, WM and cerebrospinal fluid (CSF) using the Template-O-Matic (TOM) toolbox (http://dbm.neuro.uni-jena.de/software/tom/) The toolbox was developed from an NIH study of normal brain development (6), which arose from the structural data of 404 participants aged between 4.75 and 18.58 years, and it can generate high quality templates of T1-weighted data and tissue probability density for ages between 5 and 18; 2) Normalization of the S0 images of all controls to the initial template using the unified segment method (SPM), which provides a probabilistic framework to combine image registration, tissue classification, and bias correction into a generative model (7); and 3) Averaging the normalized S0 images, smoothing the average with an 8-mm (full width at half maximum (FWHM)) Gaussian kernel, and thus obtaining our subject specific S0 template.

The S0 images of all participants were then nonlinearly registered to this template, using the normalizing tool in SPM, and the resulting deformation fields were applied to their corresponding FA, MD, MK maps. Finally, all normalized parameter maps were smoothed with an 8-mm FWHM Gaussian kernel.

Statistical analysis

We performed a voxel-based analysis for the entire brain on normalized and smoothed FA, MD and MK maps. We applied a 2-sample t-test for group analysis between the fifteen patients and the eighteen NCs. Contiguous voxels with a p-value < 0.001 (uncorrected) and cluster size >100 were adopted to retain significant differences between the patient and NC groups.
Results

The data included fifteen patients (eight girls and seven boys) in the case group, and eighteen healthy children in the NC group, matched for age and sex. All subjects in both groups were consecutively recruited between September 2009 and August 2011. Characteristics of the fifteen children with interictal epileptiform discharges (IED) located in bilateral hemispheres (No.2-4, 6-8, 10, and No.13, n = 8), bilateral frontal lobes (No.5 and No.11, n = 2), bilateral temporal lobes (No.1 and No.9, n = 2), bilateral occipital lobes (No.14, n = 1), bilateral frontal-occipital areas (No.12 and No.15, n = 2). There was no significant difference in average age between the cases group (6.81 ± 3.23 years) and the NC group (6.41 ± 1.41 years), p = 0.6595.

MRI findings in axial MPRAGE, T2W FLAIR and sagittal FSE sequences included a small lacunar focus in the left frontal lobe in patients No.6, No.11, No.12, and in the frontal lobes bilaterally in patient No.5. The other cases had normal conventional MRI findings.

Differences in FA regions between the two groups occurred mainly in the left cerebrum, WM and GM of the frontal and temporal lobes, the rectus, the frontal superior inferior orbital area, the caudate, the frontal gyrus and the subcallosal gyrus. These differences can be seen in Figure 1-3. Figure 1-3 indicated coronal, axial and sagittal images of FA maps. Yellow regions indicated significant differences of FA between epilepsy and NC groups.

Differences in MD regions between the two groups occurred primarily in the cerebrum bilaterally, WM and GM of the limbic lobes, the uncus, the left frontal lobe, the rectus, the right temporal lobe, the parahippocampal area and the rectus. These differences can be seen in Figure 4-6. Figure 4-6 indicated coronal, axial and sagittal images of MD maps. Yellow regions indicated significant differences of MD between epilepsy and NC groups.

Differences in MK regions between the two groups occurred mainly in both cerebral hemispheres, and several WM and GM regions of the frontal and parietal lobes. These differences can be seen in Figure 7-9. Figure 7-9 indicated coronal, axial and sagittal images of MK maps. Yellow regions indicated significant differences of MK between epilepsy and NC groups.
Images for this section:

**Fig. 1:** Figure 1: Coronal images of FA maps. Yellow regions indicate significant differences between epilepsy and NC groups.

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**Fig. 2:** Figure 2: Axial images of FA maps. Yellow regions indicate significant differences between epilepsy and NC groups.

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**Fig. 3:** Figure 3: Sagittal images of FA maps. Yellow regions indicate significant differences between epilepsy and NC groups.

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**Fig. 4:** Figure 4: Coronal images of MD maps. Yellow regions indicate significant differences between epilepsy and NC groups.

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**Fig. 5:** Figure 5: Axial images of MD maps. Yellow regions indicate significant differences between epilepsy and NC groups.

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**Fig. 6:** Figure 6: Sagittal images of MD maps. Yellow regions indicate significant differences between epilepsy and NC groups.

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**Fig. 7:** Figure 7: Coronal images of MK maps. Yellow regions indicate significant differences between epilepsy and NC groups.

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**Fig. 8:** Figure 8: Axial images of MK maps. Yellow regions indicate significant differences between epilepsy and NC groups.

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**Fig. 9:** Figure 9: Sagittal images of MK maps. Yellow regions indicate significant differences between epilepsy and NC groups.

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Conclusion

Studies have addressed the usefulness of DTI in epilepsy and have demonstrated increased diffusivity and reduced FA in areas corresponding to the electric focus (8-10). Increased diffusivity and reduced FA have been demonstrated with DTI in the hippocampus of patients with temporal lobe epilepsy (TLE) (11), in patients with malformations of cortical development, which is commonly associated with epilepsy (10), and in the hippocampus of patients with hippocampal sclerosis (12).

Although DTI is an important technique for investigating mechanisms of health and disease in brain WM, there are limitations, including a lack of specificity in terms of histological features (13). The simplified description of the diffusion process prevents DTI from being truly effective for the characterization of relatively isotropic tissue in GM structures, such as the cortex, the hippocampus and the basal ganglia, and the inability of DTI-based fiber tractography to resolve fiber crossings.

Diffusional kurtosis imaging has been proposed as a minimal extension of DTI, and as such has been recently developed to probe non-Gaussian diffusion properties (1,2,14). It is a more comprehensive model for describing the restricted diffusion process in vivo, and could lead to improved neural characterization with better sensitivity and directional specificity. Thus, DKI is a potentially valuable tool for probing pathological alterations in neural tissues. In order to study density changes in GM, voxel-based morphometry (VBM) is commonly used. Thus far, DKI has demonstrated promising results in several brain conditions, including attention deficit and hyperactivity disorder (15), Parkinson’s disease (16), Alzheimer’s disease (17), schizophrenia (18), traumatic brain injury (19,20), stroke (21), as well as in the staging of gliomas (22). In these studies, DKI has proven to be a more sensitive tool for the detection and characterization of subtle changes in both WM and GM. It has also been explored in terms of resolving the crossing of WM fibers, thereby potentially leading to more accurate tracking and characterization.

A typical DKI brain protocol acquires DWI images with a 6 b-value (maximum b-value at 2000-2500 s/mm$^2$) and along more than 15 different directions. Diffusion of water protons in tissue is typically characterized by MD, which measures the average distance a water molecule traverses within a given observation time. A further parameter that is frequently derived from DTI data is FA, which provides information on the degree of diffusion anisotropy that exists within a given voxel. The axial diffusivity (AD or MD$_{ax}$) and radial diffusivity (RD of MD$_{rd}$) provide further insights into the nature of the microstructural changes. The MK is a dimensionless index that quantifies the deviation of the water diffusion displacement profile from the Gaussian distribution, and measures the degree of diffusion hindrance or restriction (14,22,23). The average apparent kurtosis along all diffusion gradient encoding directions has been measured and shown to offer an improved sensitivity for the detection of developmental and pathological changes in neural tissues compared to conventional DTI. Studies of brain maturation have shown
that MK is sensitive to changes in GM, where MK increases with brain maturation, while DTI parameters, MD and FA, remain relatively unchanged. The increase in MK observed during maturation in GM and WM is likely to be due to consistent and continuing myelination, an overall increase in microstructural complexity and increased cell-packing density, particularly in GM (24).

Our results showed that in children with bilateral epilepsy, there was a significant reduction in FA in the left cerebrum of several WM and GM regions compared to NCs, such as the frontal and temporal lobes, the rectus, the frontal superior/inferior orbital, the caudate, the frontal gyrus and the subcallosal gyrus. In addition, it is clear from our data that this reduction was due to a significant increase in MD in several WM and GM regions of the cerebrum bilaterally, such as the limbic lobe, the uncus, the left frontal lobe, the rectus, the right temporal lobe, the parahippocampal region and the rectus. There was a significant reduction in MK in both cerebral hemispheres and several WM and GM regions of the frontal and parietal lobes, indicating that MK is sensitive to changes in tissue microstructure secondary to epilepsy. These regions of reduced FA, increased MD and reduced MK could reflect myelin deficiency, increased permeability in the axon membranes, or a less tightly packed neuronal network.

By quantifying FA, MD and MK, DKI may provide improved sensitivity and specificity for the characterization of micro-structural complexities of neural tissues. The DKI method could greatly advance basic and clinical brain investigations by providing unprecedented micro-anatomical information from studies of WM and GM, particularly in those with epilepsy and normal brain imaging on conventional MRI.
References


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