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Diffusion tensor imaging of partial intractable epilepsy

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Abstract Our aim was to assess the value of diffusion tensor imaging (DTI) in patients with partial intractable epilepsy. We used DTI (25 non-collinear directions) in 15 patients with a cortical lesion on conventional MRI. Fractional anisotropy (FA) was measured in the internal capsule, and in the normal-appearing white matter (WM), *adjacent to* the lesion, and *away from* the lesion, at a set distance of 2–3 cm. In each patient, increased or decreased FA measurements were those that varied from mirror values using an arbitrary 10% threshold. Over the whole population, ipsi- and contralateral FA measurements were also compared using a Wilcoxon test ($p<0.05$). Over the whole population, FA was significantly reduced in the WM *adjacent to* and *away from* the lesion, whilst being normal in the internal capsule. FA was reduced by more than 10% in the WM *adjacent to* and *distant from* the lesion in 13 and 12 patients respectively. For nine of the ten patients for whom the surgical resection encompassed the limits of the lesion on conventional MRI, histological data showed WM alterations (gliosis, axonal loss, abnormal cells). DTI often reveals WM abnormalities that are undetected on conventional MRI in patients with partial intractable epilepsy.

Keywords Diffusion tensor imaging · Epilepsy · White matter · Brain

Introduction

Diffusion of water within a tissue is governed by its molecular, microstructural and architectural properties. A tissue is said to be isotropic when diffusion is identical in all directions. Conversely, a tissue is considered to be anisotropic when water molecules move along a preferential direction. White matter (WM) is a highly anisotropic structure, presumably due to the fact that water molecules move along the long axis of myelinated fibers. A disruption of this microstructural environment will lead to a less ordered arrangement of nerve fibers and subsequent change in anisotropy [1]. Diffusion tensor imaging (DTI) can be used to assess non invasively the microstructure of the cerebral tissue [2–5]. Using anisotropic indices such as fractional anisotropy (FA), several disease conditions [6–8], including cerebral ischemia [9], acute stroke [10], multiple sclerosis [11], schizophrenia [12], traumatic brain injury [13], brain tumors [14, 15], and Alzheimer's disease [16] have been explored. For patients who suffer from epilepsy, MR techniques are becoming increasingly important in localizing the seizure focus and for the management of the patients [17]. Only a few studies have addressed the usefulness of DTI in epilepsy and have

demonstrated areas of increased diffusivity and reduced anisotropy in cerebral areas corresponding to the electric focus [18–22]. Our aim was to test the hypothesis that subtle abnormalities encompassing the lesion seen on conventional MRI could be detected in normal appearing WM using DTI.

Materials and methods

Subjects

Among patients admitted to our institution between January 2002 and January 2003, we retrospectively selected those who fulfilled the following criteria: (1) patients referred for presurgical work-up because of refractory partial seizures; (2) conventional MRI showing a cortical abnormality; and (3) MRI including a diffusion tensor pulse sequence. Fifteen patients fulfilled these criteria and constituted our study group. There were six men and nine women, with a median age of 27 years (range 12–54 years). The average duration of epilepsy was 17 years (range 2–47 years), and the mean age at onset was 10 years (range 6 months–41 years). On clinical and electroencephalographic data (including intracranial EEG recording in four patients), ten patients had temporal lobe epilepsy, three had frontal lobe epilepsy, one had parietal lobe epilepsy, and one had occipito-temporal lobe epilepsy. All patients had been clinically seizure free for at least 24 hours before MRI. On conventional MRI, epilepsy was presumed to be related to a low-grade tumor in five cases, hippocampal sclerosis in four cases, and cortical malformations in six cases.

At the time of the study, all but two patients had undergone surgical resection. The presurgical diagnosis of tumor in five cases was confirmed (two dysembryoplastic neuroepithelial tumors, two ganglioglioma, one low-grade oligodendroglioma). The four presumed cases of hippocampal sclerosis were surgically confirmed, with associated cortical dysgenetic changes in two patients. Of the six patients with presumed cortical malformation on conventional MRI, four underwent surgery, with a final diagnosis of Taylor dysplasia in three cases and dysgenesia with microgyria in one patient. For ten out of the 13 patients who underwent surgery, the resection encompassed the limits of the visible lesion on conventional MRI. For these ten patients, one pathologist searched for WM histological changes in areas surrounding the lesion seen on conventional MRI. This analysis was conducted by reading simultaneously axial histological sections and MR images, acquired or reformatted in the axial plane.

MRI technique

All MRI examinations were performed on a 1.5-Tesla Signa MR Unit (General Electric Medical Systems, Milwaukee, WI) including at least a 3D T1-weighted spoiled gradient recovery (TR/TE/TI=9.2/4.2/450 ms, matrix 256×256, bandwidth 31.2 KHz, field of view 24×24 cm^2, slice thickness 1.2 mm, one excitation), and/or 2D fluid attenuated inversion recovery (FLAIR) sequences (TR/TE/TI=10,000/147/2,200 ms, matrix 192×256, bandwidth 15.6 KHz, field of view 24×24 cm^2, slice thickness 5 mm, no gap, one excitation). All patients had a DTI pulse sequence using single shot diffusion-weighted echo planar imaging

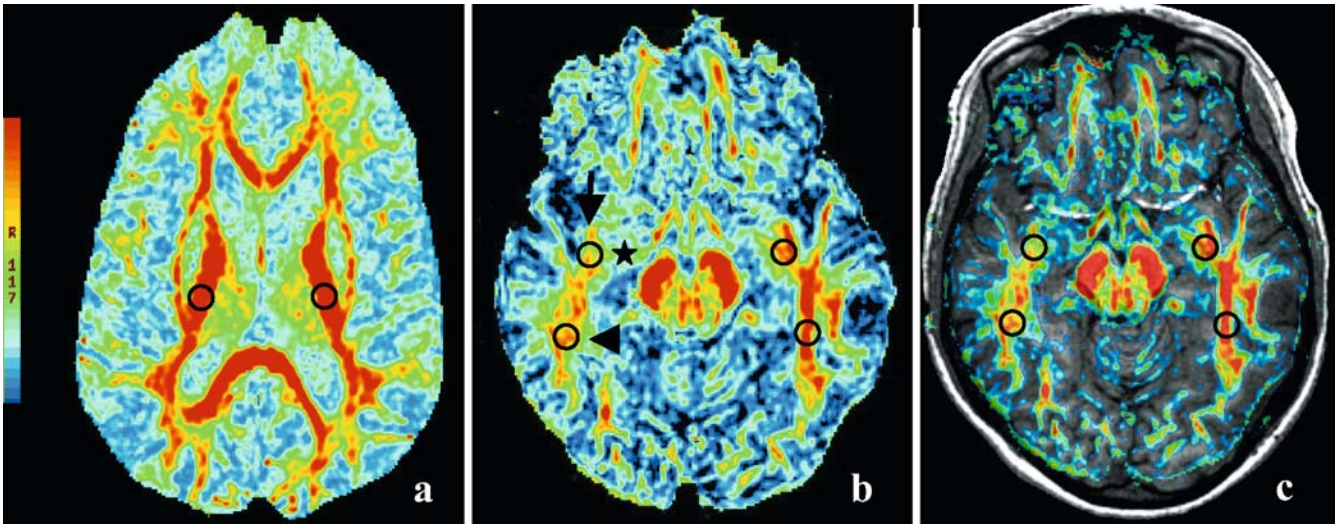

Fig. 1 **a**–**c** Example of positioning of regions of interest (ROIs) in an 18-year-old woman with right hippocampal sclerosis. **a** ROIs placed in the ipsi- and contralateral internal capsule. **b** Fractional anisotropy (FA) map showing reduced FA in the WM *adjacent to* (*arrow*) and *away from* (*arrowhead*) the lesion (*star*) when compared to the contralateral mirror region. **c** FA map (using a color scale) projected on T1-weighted images

(TR/TE=6,860/102 ms, matrix 128×128, bandwidth 95 KHz, field of view 24×24 cm^2), with two *b* values (0, 700 s/mm^2) applied sequentially in 25 non-collinear directions, at 15 axial slice positions (5-mm thickness, no gap, two excitations, 6 min 40 s duration) centered on the lesion seen on conventional MRI.

The echo planar distortions induced by eddy currents were corrected using an algorithm that determines the optimum affine transformation to be applied to each diffusion-weighted image, and uses a mutual information similarity test and Powell minimization scheme, using a commercially available software application (Functool Performance, GEMS, Buc, France). FA maps were generated using the same software. For each patient, small circular regions of interest (ROIs) of 40 mm^2 (45 pixels) were placed on T2-echo planar base line images (b=0 s/mm^2) in the normal appearing WM. ROIs were positioned as follows: (1) *adjacent to* the lesion, i.e. in contact to the lesion; and (2) *away from* the lesion, i.e. at a set distance of 2–3 cm. Mirror ROIs were positioned symmetrically in the contralateral areas, after checking for the lack of signal changes on T2-echo planar images. An additional ROI was placed in the posterior limb of the internal capsule, bilaterally, to verify the absence of ipsilateral and contralateral difference in FA values. An illustrative case of ROI positioning is presented in Fig. 1. Increased or decreased anisotropic measurements were those that varied by more than 10% from mirror reference values. Ipsi- and contralateral FA measurements were compared using a paired non parametric Wilcoxon test ($p<0.05$). We also used a correlation test to compare FA measurements with the following three parameters: age of patient, age at onset, and duration of epilepsy.

Results

There were no significant differences in FA values between the ipsi- and contralateral internal capsule (p=0.8). Over the whole study population, FA was significantly reduced in the WM *adjacent to* (p=0.0006) and *away from* the lesion (p=0.006), compared to the contralateral mirror regions. In the WM *adjacent to* the lesion, FA was reduced in 13 patients (Figs. 2, 3) and within the normal range in the remaining two patients. In the WM *away from* the lesion, FA was reduced in 12 patients, within the normal range in two and increased in the remaining patient. FA measurements were not significantly correlated with the three clinical parameters (age of patients, age at onset, and duration of epilepsy). Summary data for FA measurements in the study group are presented in Table 1.

For ten out of the 13 patients who underwent surgery, the resection encompassed the limits of the visible lesion on conventional MRI. For nine of these ten patients, in areas *adjacent to* the lesion that lacked signal changes on MRI but showed decreased FA values, histological data showed WM alterations (Figs. 2, 4): gliosis, axonal loss, and enlargement of the Virchow–Robin spaces. In addition, for five of these nine patients, abnormal cells (namely ectopic or abnormal neurons, balloon cells, or infiltrative tumor cells) were also observed. In the remaining patient, gliosis and ectopic neurons were observed on the basis of pathological data in the area surrounding the lesion seen on conventional MRI, despite the lack of significant anisotropic changes.

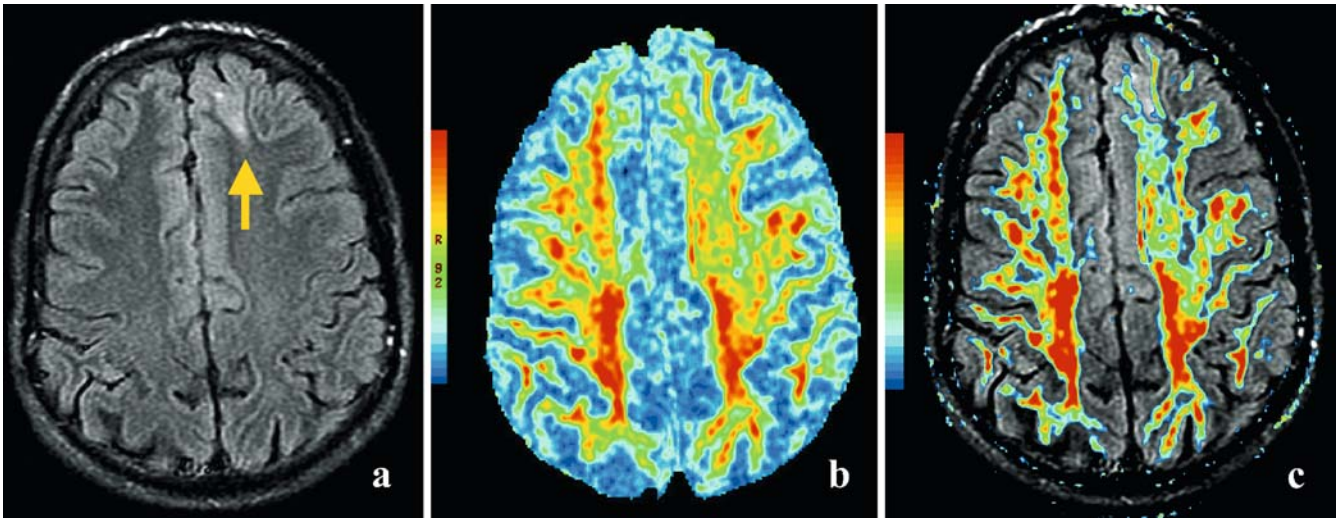

Fig. 2 **a**–**c** Frontal lobe dysplasia in a 31-year-old patient. **a** FLAIR sequences showing subtle hyperintensity of the left frontal lobe (*arrow*). **b** Fractional anisotropy (FA) map. Area of decreased FA of the left frontal lobe, more extensive than the area of FLAIR signal abnormality. **c** Superposition of FA (using a color scale) and FLAIR images

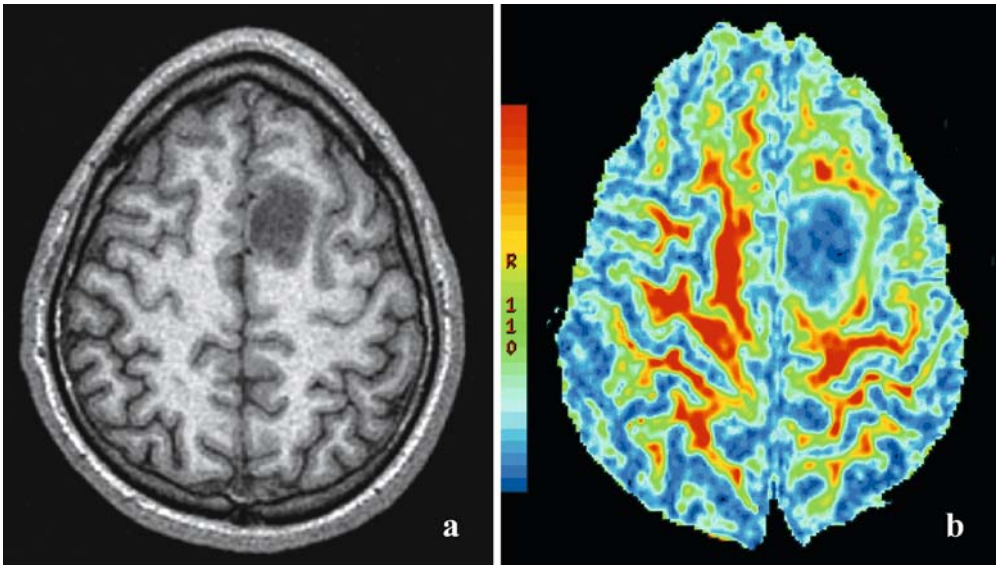

Fig. 3 **a**,**b** Frontal low-grade oligodendroglioma in a 22-year-old patient. **a** 3D T1-weighted sequence showing a left frontal hyposignal corresponding to the tumor. **b** Fractional anisotropy (FA) map. Reduced FA in the WM seen beyond the edge of the lesion seen on the 3D T1-weighted image

Discussion

Our data indicate that most patients (13 out of 15 patients in our study) have decreased anisotropy in normal appearing WM surrounding the lesion seen on conventional MRI, and that distant anisotropic changes can also be observed, as was the case in 12 of the 15 studied patients. This reinforces the previous findings, suggesting that decreased anisotropy may encompass the lesion seen on conventional MRI [18–20]. None of the previous studies simultaneously studied the FA values in WM *adjacent to* and *away from* the lesion. The proportion of patients with anisotropic changes reported here is higher than that previously published in patients with intractable seizures. In normal appearing WM *adjacent to* the lesion, Rugg-Gunn et al. [18] reported reduced FA in 30% of patients with partial seizures and acquired lesions using a whole brain voxel-based analysis. This group also reported reduced FA in 27% of patients with malformation of cortical development in areas surrounding the lesion [19]. There are at least three plausible explanation for the higher proportion of patients with reduced FA in the area surrounding the lesion in our study: first, it may be due to the 10% threshold we arbitrarily chose for abnormal anisotropic values; second, while most authors have used DTI pulse sequence with gradients applied in six [21], seven [18, 19, 22] or 23 directions [20], we measured anisotropy with gradients applied in 25 directions. This potentially improves the angular resolution by providing a better estimate of the diffusion tensor. Third, we chose to analyze mean values using an ROI-based approach, while others have proposed an histogram based approach [23], or a voxel-based statistical approach. The latter method may limit the sensitivity of anisotropic measurements. Because a smoothing step and a normalization scheme are usually performed, abnormalities have to be sufficiently great to remain significant with the stringent statistical approach used [19].

Histological changes, such as gliosis, axonal loss, or increased cell bodies (i.e., ectopic or abnormal neurons, balloon cells, or infiltrative tumor cells), were observed in the area surrounding the lesion seen on conventional MRI. In line with this, several histopathological epilepsy surgery and necropsy series [24–27] have found microdysgenesis and an increased number of neurons in WM of patients with epilepsy. This indicates that there may be an histological substrate to the loss of anisotropy in the normal appearing area surrounding the lesion. An increased number of cell bodies, namely neurons, balloon cells, or infiltrative tumor cells, in the WM, could disrupt the WM tracts and result in a reduction of anisotropy. Poor myelinization, gliosis, and axonal loss may also contribute to reduced WM anisotropy [28]. The diffuse and relatively homogenous distribution of these chronic histological

Table 1 Summary of fractional anisotropy (FA) measurements in the internal capsule, WM *adjacent to* and *away* from the lesion, in regions of interest placed in the ipsilateral hemisphere and the contralateral hemisphere

	Internal capsule		WM adjacent to lesion		WM away from lesion	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Min	0.49	0.47	0.25	0.31	0.25	0.31
Max	0.74	0.74	0.49	0.60	0.55	0.58
Mean	0.64	0.64	0.34	0.43	0.36	0.45
SD	0.07	0.08	0.06	0.09	0.09	0.09

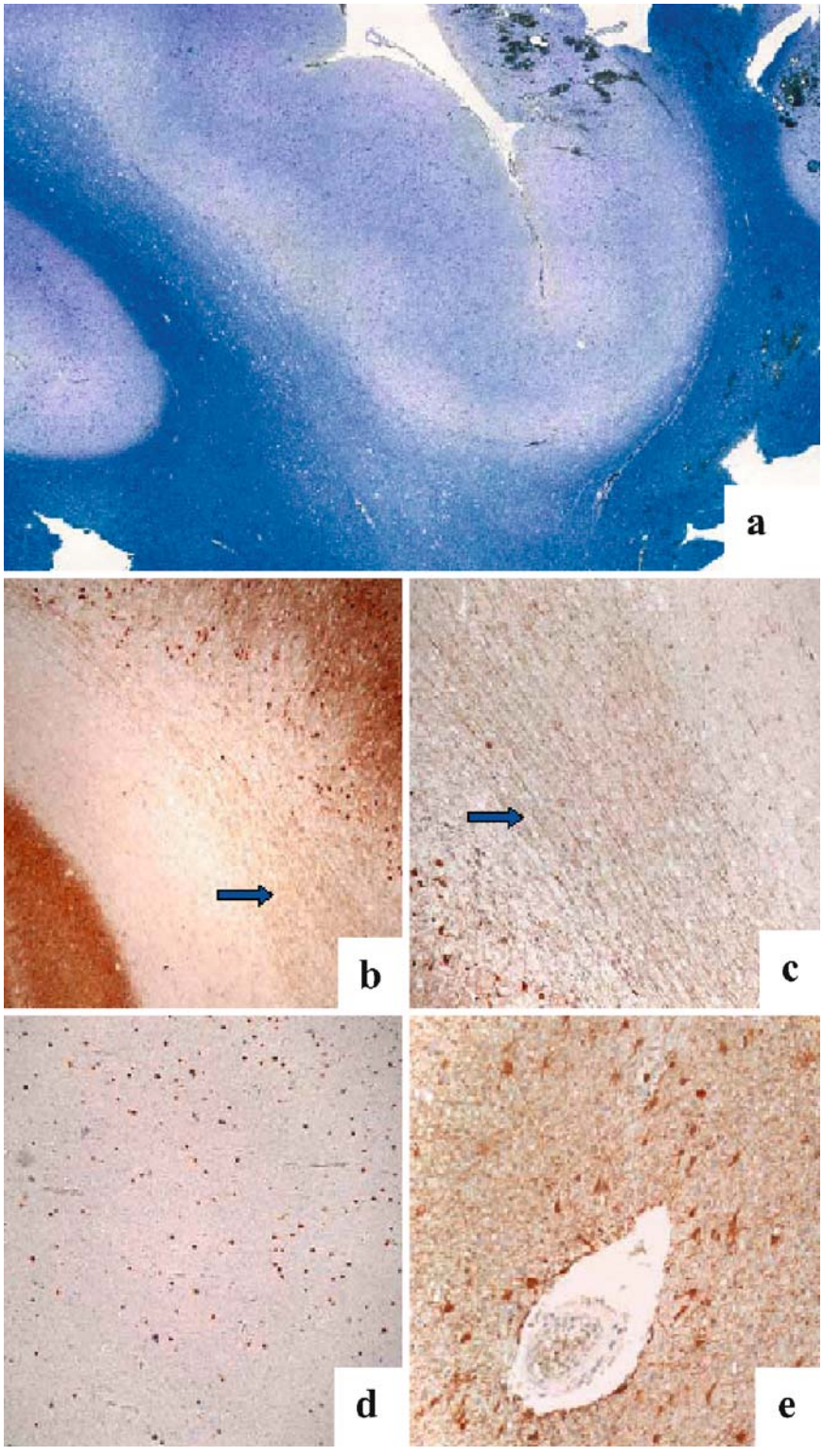

Fig. 4 **a**–**e** Histological sections corresponding to the patient with frontal lobe dysplasia presented in Fig. 2. **a** Widen cortex with blurred demarcation between the gray and white matter (Kluwer Barrera). **b**, **c** Bundles of irregular, swollen axons (*arrows*) in the normal appearing white matter surrounding the lesion seen on conventional MRI (MAP2 immunostaining ×40 and ×200). **d** Numerous ectopic neurons in normal appearing WM (NeuN immunostaining ×100). **e** Astrocytic gliosis and enlargement of the Virchow–Robin spaces in area that appeared normal on conventional MRI (GFAP immunostaining ×200)

changes may explain the lack of signal changes on T2-weighted sequences in corresponding areas [29].

Arfanakis et al. [20] investigated the diffusion characteristics of WM in patients with focal temporal lobe epilepsy, and showed that FA changes were not restricted to temporal lobes but might extend into other brain regions distant from the lesion. In light of these findings, we observed reduced anisotropy *away from* the lesion, in 12

of the studied patients. One can speculate that these distant WM anisotropic changes could be due to Wallerian degeneration of WM tracts [30] or gliosis resulting from chronic seizures. The increased FA in the WM *away from* the lesion found in a single patient with a temporal ganglioglioma, remains unexplained.

Our study has several limitations. First, we chose not to study patients with cryptogenic epilepsy because of the uncertainty in ROI positioning when there is no visible lesion on conventional MRI. In addition, cryptogenic epilepsy is likely to be associated with minor structural disorganization, which may not be disruptive enough to cause significant and measurable alterations in diffusion parameters. Previous authors have indeed failed to detect any significant modification of the diffusion parameters in most patients with cryptogenic seizures [18]. Second, we chose to focus our analysis on FA because a previous report using an ROI-based approach indicated a higher sensitivity of anisotropic measurements compared to diffusivity measurements in patients with intractable seizures [22]. Third, we chose to use the contralateral mirror region as a reference. One can argue that chronic seizures might induce diffuse WM changes, potentially resulting in abnormal FA in the contralateral hemisphere. We initially verified that no difference existed in FA measurements between the ipsi- and contralateral internal capsule. We also relied on the work of Assaf et al., who demonstrated that comparison with the contralateral hemisphere was more sensitive than comparison with a control group for anisotropic measurements in patients with intractable seizures [21]. Fourth, the lack of correlation between FA values and clinical data could reflect the limited number of patients in different age groups and the heterogeneous anatomical locations of the studied lesions. Finally, for technical reasons, DTI was acquired in the axial plane without whole brain coverage. The FA changes might have been better delineated using a coronal DTI acquisition [21], especially for lesions located in the temporal lobes.

Conclusion

Using an ROI approach and a set threshold of 10%, we found that most patients had decreased anisotropy in normal appearing WM surrounding the lesion seen on conventional MRI. Reduced anisotropy was also observed in tissue *away from* the lesion. Our study also suggests that there may be an histological substrate to the loss of anisotropy in the normal appearing area surrounding the lesion. Anisotropic changes found beyond the limits of the visually detected lesions suggest that abnormalities are often more extensive than can be seen on conventional MRI.

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