Diffusion tensor imaging of cryptogenic and acquired partial epilepsies

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Summary
Current optimal MRI identifies a relevant structural abnormality in up to 80% of patients with refractory partial seizures. Identification of a structural lesion is fundamental to pre-surgical evaluation. We used diffusion tensor imaging (DTI) and statistical parametric mapping (SPM) to examine objectively the diffusion properties, and hence structural organization, of cerebral tissue in 10 patients with partial seizures and acquired lesions and 30 patients with partial seizures and normal MRI. Fractional anisotropy and mean diffusivity maps were calculated and, using SPM, individual patients were compared with a group of 30 control subjects. Diffusion tensor imaging and voxel-by-voxel statistical comparisons identified significant increases in diffusivity and significant reductions of anisotropy in all patients with acquired non-progressive cerebral lesions and partial seizures. In all of these patients, the areas of increased diffusivity, and in nine patients the areas of decreased anisotropy, concurred with abnormalities identified on visual inspection of conventional MRI. In addition, there were 10 areas which were normal on conventional imaging which exhibited abnormal anisotropy or diffusivity. Individual analyses of the 30 patients with partial seizures and normal optimal MRI identified a significant increase in diffusivity in eight of the subjects. In six of these, the areas of increased diffusivity concurred with the localization of epileptiform EEG abnormality. Analysis of anisotropy in the MRI-negative patients revealed significant differences in two patients, one of which concurred with electroclinical seizure localization. Group analysis of nine patients with normal conventional MRI and electroclinical seizure onset localizing to the left temporal region revealed a significant increase in diffusivity and a significant reduction in anisotropy within the white matter of the left temporal lobe. DTI analysed using SPM was sensitive in patients with acquired cerebral damage. Significant differences in the diffusion indices in individual MRI negative patients and the group effect in patients with left temporal lobe epilepsy suggest that minor structural disorganization exists in occult epileptogenic cerebral lesions. These techniques are promising, non-invasive imaging methods for identifying the cause of partial seizures, and can contribute to pre-surgical evaluation.

Keywords: localization-related epilepsy; anisotropy; mean diffusivity; diffusion tensor imaging; cryptogenic

Abbreviations: DTI = diffusion tensor imaging; ROI = region of interest; SPM = statistical parametric mapping; TLE = temporal lobe epilepsy

Introduction
Current optimal MRI reveals an identifiable abnormality in up to 80% of patients with refractory partial epilepsy, allowing surgical management to be considered for many such patients (Duncan, 1997). Surgical treatment of patients without an abnormality on preoperative imaging is often associated with a poor outcome and, therefore, the identification of a cerebral lesion is an important goal in the management of patients with partial epilepsy (Cascino et al., 1992).

Patients with partial epilepsy and normal conventional MRI (‘MRI-negative patients’) have been studied previously with [11C]flumazenil-PET which revealed regional cortical abnormalities of central benzodiazepine receptors in 72% of patients (Richardson et al., 1998). Proton magnetic resonance spectroscopy in MRI-negative patients with temporal lobe epilepsy revealed abnormalities that concurred with other lateralizing data in 27% of patients (Woermann et al., 1999).

Chronic non-progressive acquired cerebral lesions are an important cause of partial seizures, and investigation of these patients with diffusion imaging has been limited to case reports or small series studies (Hajnal et al., 1991; Wieshmann et al., 1999a, b). In addition, studying this group of patients in detail, and interpreting diffusion abnormalities in the light
of cerebral lesions evident on routine MRI, may aid the analysis of the results of the MRI-negative patients. The scope of diffusion tensor imaging (DTI) of the brain is discussed in the accompanying manuscript (Eriksson et al., 2001).

The aim of this study was to test the hypothesis that DTI would identify areas of altered anisotropy and diffusivity in patients with epileptogenic acquired lesions, and would identify focal abnormalities in MRI-negative patients.

Methods

Subjects

Thirty healthy volunteers (20 women and 10 men, median age 30 years, range 20–50 years) with no history of neurological disease (same control subjects as in Eriksson et al., 2001) and 40 patients with partial seizures recruited from the clinics of The National Hospital for Neurology and Neurosurgery and The National Society for Epilepsy were scanned with conventional MRI and DTI. The patient group comprised 10 patients (nine men and one woman, median age 36 years, range 20–53 years) with clear history and imaging findings of past acute and non-progressive cerebral injury. These included three ischaemic lesions, five head injuries, one perinatal injury and one patient with a history of focal leuocencephalitis. The clinical and EEG findings of the acquired lesion group are presented in Table 1. Thirty patients (17 men and 13 women, median age 36 years, range 18–55 years) with normal conventional MRI were also studied (Table 2). Following video and EEG telemetry, nine were diagnosed with left temporal lobe epilepsy; six with right temporal lobe epilepsy; six with frontal lobe epilepsy; two with occipital lobe epilepsy; and seven had electroclinical evidence of less well-defined, more widespread abnormalities. The average duration of epilepsy was 21 years (range 2–48 years). Only one patient experienced a seizure in the 24 h preceding the scan (Patient 38, simple partial seizure).

Written informed consent from each subject and approval by the local ethical committee of the National Hospital for Neurology and Neurosurgery were obtained.

Conventional MRI scanning protocol

All controls and patients had conventional MRI (see Eriksson et al., 2001) These were reviewed by experienced neuroradiologists who detected no abnormalities in either the control or MRI-negative subjects. The abnormalities in the acquired-lesion group are described in Table 1.

DTI and image analysis

DTI imaging was performed on a 1.5 T Horizon Echospeed scanner (GE, Milwaukee, Wisc., USA) using single-shot CSF-suppressed diffusion-weighted echoplanar imaging. Two b-values (0 and 703 s/mm²) were applied in seven non-collinear directions (x, y, z, xy, xz, yz and xyz) at 26 slice positions. Maps of mean diffusivity and fractional anisotropy were calculated from the diffusion-weighted images using the method proposed by Basser and Pierpaoli (Pierpaoli and Basser, 1996; Pierpaoli et al., 1996). The diffusion maps were normalized to a standard template and the patients were compared individually with the 30 control subjects on a voxel-by-voxel basis using statistical parametric mapping (SPM) (Friston et al., 1995a, b). Significant differences in diffusivity or anisotropy were detected at a threshold of P < 0.001 (corrected for multiple comparisons with P < 0.05). Additionally, each control was statistically compared with the remainder of the control group. (For additional information, see Eriksson et al., 2001.) Group comparisons were also performed. All MRI-negative patients with distinct clinical and EEG evidence of left or right temporal lobe epilepsy (TLE) following video and EEG telemetry were grouped and statistically compared with the control group.

Results

Control group

Comparing each control subject with the remaining 29 control subjects using identical parameters and statistical thresholds as the comparison between patients and controls, three subjects had areas of significantly abnormal diffusion. At a statistical threshold of P < 0.05 and 60 examinations (30 subjects with two contrasts each, i.e. an increase and a decrease), up to three abnormal areas may have been anticipated by chance for each diffusion parameter. (For additional information, see Eriksson et al., 2001.)

Acquired lesions

Individual SPM analyses

In all 10 patients with acquired lesions, SPM detected areas of significantly reduced anisotropy and increased diffusivity (Table 1). In nine patients, the areas of reduced anisotropy and, in all patients, the areas of increased diffusivity corresponded to the abnormalities identified on visual inspection of the conventional MRIs. In three patients, areas of significantly reduced anisotropy and, in a further three patients, areas of significantly increased diffusivity were detected in regions previously reported as normal.

Analysis of Patients 1, 2 and 3 also demonstrated significant increases in anisotropy. In Patient 2, this was within an area of visualized damage whereas in Patients 1 and 3, the areas of increased anisotropy were within normal-appearing cerebral tissue, most commonly immediately adjacent to the areas of visualized damage.

Region-of-interest (ROI) analyses

In order to demonstrate the magnitude of the effect, quantitative ROI analyses were made in two patients whose
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Aetiology of epilepsy</th>
<th>Duration of epilepsy (years)</th>
<th>EEG features</th>
<th>Conventional MRI findings</th>
<th>DTI findings</th>
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</tbody>
</table>
| 1       | 44          | M      | Head injury           | 33                          | R. temp. i.e.a. | R. temp. par. occ. multicyclic damage | R. temp. par. occ. 
\(P < 0.001\) + R. frontopar. 
\(P < 0.001\) + L. par. 
\(P < 0.001\) |
| 2       | 33          | M      | Head injury           | 13                          | Bil. temp. i.e.a. | R. temp. par. + minor L. front damage | R. temp. 
\(P = 0.008\) + R. front. 
\(P = 0.018\) |
| 3       | 38          | M      | Head injury           | 3                           | R. temp. i.e.a. | R. temp. par. temp. par. occ. R. frontopar. 
\(P < 0.001\) + R. front. 
\(P < 0.001\) + L. par. 
\(P < 0.001\) |
| 4       | 27          | M      | Head injury           | 6                           | Bil. frontotemp. i.e.a. | Bifront. + R. temp. + corpus callosum damage | L. front. 
\(P = 0.046\) + bil. temp. 
\(P = 0.003\) |
| 5       | 51          | M      | Head injury           | 47                          | L. temporopar. i.e.a. | Superficial atrophy of L. hemisphere, sparing temp. | L. mesial temp. 
\(P = 0.007\) |
| 6       | 35          | M      | Infarction            | 27                          | R. front + L. temp. i.e.a. | Post. L. middle cerebral artery territory damage | L. par. occ. 
\(P = 0.013\) |
| 7       | 38          | M      | Infarction            | 36                          | R. front. temp. par. i.e.a. | R. temp. par. occ. ischaemic damage | R. temp. par. occ. 
\(P = 0.008\) + R. par. 
\(P = 0.024\) |
| 8       | 20          | F      | Infarction            | 12                          | R. frontotemp. i.e.a. | R. lat. front. cortical scar | R. med. 
\(P = 0.003\) + lat. front. 
\(P = 0.036\) |
| 9       | 23          | M      | Focal leucoencephalitis | 7                           | R. frontotemp. i.e.a. | R. front. scarring, CSF-filled cortical cavity | R. frontopar. 
\(P < 0.001\) |
| 10      | 53          | M      | Perinatal injury      | 48                          | R. temp. i.e.a. | Diffuse signal change in bil. post. WM | L. occ. WM 
\(P = 0.018\) |

R. = Right; L. = Left; bil. = bilateral; post. = posterior; med. = medial; lat. = lateral; front. = frontal; par. = parietal; temp. = temporal; occ. = occipital; WM = white matter; i.e.a. = interictal epileptiform activity; Sig. = significant; M = male; F = female.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Aetiology of epilepsy</th>
<th>Duration of epilepsy (years)</th>
<th>Seizure types</th>
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<td>CPS, 2° gen.</td>
<td>L. temp.</td>
<td>L. temp.</td>
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<td>Sig. decreases in anisotropy (P-value) = 0.005</td>
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<td>R. &gt; &gt; L. temp.</td>
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<td>L. front.</td>
<td>L. &gt; R. frontotemp.</td>
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<tr>
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<td>F</td>
<td>Cryptogenic</td>
<td>35</td>
<td>CPS, 2° gen.</td>
<td>R. &gt; L. front.</td>
<td>R. &gt; L. front.</td>
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<tr>
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<td>L. temp.</td>
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<td>55</td>
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<tr>
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<td>CPS, 2° gen.</td>
<td>L. hemisphere</td>
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<tr>
<td>40</td>
<td>52</td>
<td>F</td>
<td>Cryptogenic</td>
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<td>CPS, 2° gen.</td>
<td>L. hemisphere</td>
<td>L. temp.</td>
<td>None</td>
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</table>

S/CPS = simple/complex partial seizure; 2° gen = generalized seizure; R. = right; L. = left; bil. = bilateral; front. = frontal; par. = parietal; temp. = temporal; occ. = occipital; N/A = not available; Sig. = significant; M = male; F = female.
Diffusion tensor imaging in epilepsy

Fig. 1 Patient 8, mature cortical infarct in right frontal lobe. (A–C) Normalized axial anisotropy maps at the same slice position for the averaged 30 control subjects (A) and the patient (B) and (C). (E–G) Normalized axial diffusivity maps at the same slice position for the averaged 30 control subjects (E) and the patient (F) and (G). The difference in signal-to-noise ratios between the maps is due to averaging of the 30 control subjects. The region of significantly decreased anisotropy is superimposed on map C and the region of significantly increased diffusivity is superimposed on map G. These regions coincide with the localization of the abnormality identified on conventional MRI. (D and H) The equivalent slice of the patient’s T1-weighted image. The regions in C and G were used for quantitative ROI analyses of anisotropy and diffusivity values, respectively. Note that right on the images is the patient’s right.

Two areas of reduced anisotropy were seen in Patient 8 (cerebral infarction). The lateral frontal area (Fig. 1) was associated with an increased T2 signal on standard imaging, whereas the medial frontal region appeared normal. The mean anisotropy in these two frontal regions was 0.28 and 0.29, respectively. These were both 51% of the mean anisotropy within the corresponding areas in the control group (0.56 and 0.57). The average diffusivity within the lateral frontal region in Patient 8 was 902 × 10⁻⁶ mm²/s (128% of the control group’s average of 704 × 10⁻⁶ mm²/s) (Fig. 1).

MRI-negative patients

Individual SPM analyses: anisotropy

SPM analyses of the 30 individual patients in the MRI-negative group revealed two patients with statistically significant differences in anisotropy compared with the control group (Table 2). One (Patient 23) had an area of increased anisotropy in the right temporal lobe that was concordant with both seizure semiology and interictal EEG appearances on conventional imaging were considered typical for each aetiology. In Patient 1 (head injury), the average anisotropy within the identified right parietal region was 0.24. This was 41% of the mean anisotropy within the corresponding regions in the control subjects (mean anisotropy of 0.59). The average diffusivity within the identified right parietal region was 1038 × 10⁻⁶ mm²/s. This was 146% of the average diffusivity within the corresponding regions in the control subjects (average diffusivity of 710 × 10⁻⁶ mm²/s). The mean anisotropy within the region of increased anisotropy in Patient 1, anterior to the identified region of cerebral damage, was 0.64 (159% of the control group’s mean anisotropy of 0.40). The average diffusivity within the area of normal-appearing cerebral tissue in the right frontal region, immediately anterior to the conspicuous cerebral damage (but separate from the area of increased anisotropy), was 843 × 10⁻⁶ mm²/s (117% of the control group’s average of 722 × 10⁻⁶ mm²/s).

MRI-negative patients

Individual SPM analyses: anisotropy

SPM analyses of the 30 individual patients in the MRI-negative group revealed two patients with statistically significant differences in anisotropy compared with the control group (Table 2). One (Patient 23) had an area of increased anisotropy in the right temporal lobe that was concordant with both seizure semiology and interictal EEG
Fig. 2 Patient 27, right frontal lobe epilepsy with normal conventional MRI. A–C, normalized axial diffusivity maps at the same slice position for the averaged 30 control subjects (A) and the patient (B) and (C). The region of significantly increased diffusivity is superimposed on map C. The region of increased diffusivity is localized to the normal-appearing cerebral tissue of the right frontal lobe. (D) The equivalent slice of the patient’s T1-weighted image. The region in C was used for quantitative ROI analysis of diffusivity values. Note that right on the images is the patient’s right.

recordings (ictal EEG data not available). The other (Patient 15) demonstrated significant decreases in anisotropy in both left occipital and right occipitoparietal regions, with clinical and ictal EEG recordings suggesting left temporal lobe seizure onset.

**ROI analyses: anisotropy**
Quantitative ROI analyses within the right temporal lobe of Patient 23 revealed a mean anisotropy of 0.50, 167% of the mean anisotropy within the corresponding regions of the control subjects of 0.30. In Patient 15, the mean anisotropy within the left occipital region and right occipitoparietal region were both 0.45, i.e. 69 and 68%, respectively of the mean anisotropy within the identical areas in the control group of 0.65 and 0.66.

**Individual SPM analyses: mean diffusivity**
Eight patients had regions of significantly increased diffusivity. Six of these concurred with the location of interictal epileptiform activity, and four of these also agreed with ictal EEG recordings and clinical seizure semiology (Table 2). Two patients therefore had areas of significantly increased diffusivity in regions distinct from EEG abnormality and clinical seizure focus. Patient 15 demonstrated increased diffusivity in the right frontal and both occipital regions. Patient 38 had areas of increased diffusivity in the right temporal lobe and bi-parietally, but ictal EEG evidence suggested a left temporoparietal seizure focus.

**ROI analyses: mean diffusivity**
Quantitative ROI analyses within the right frontal lobe of Patient 27 (Fig. 2) revealed an average diffusivity of 907 × 10⁻⁶ mm²/s which was 117% of the average diffusivity within the corresponding regions of the control subjects of 772 × 10⁻⁶ mm²/s. In Patient 31, the average diffusivity within the left frontotemporal region was 846 × 10⁻⁶ mm²/s (118%), compared with 716 × 10⁻⁶ mm²/s for the control group.

**Group analyses: anisotropy and mean diffusivity**
Group analyses were performed on patients with EEG evidence of either left or right temporal lobe seizures. The left temporal lobe group consisted of nine patients (Patients 11–19) and the right temporal lobe group six (Patients 20–25). Compared with the 30 control subjects, the left temporal lobe group had a significant decrease in anisotropy and significant increase in diffusivity within the white matter of the left temporal region (Fig. 3). The ROI analysis of this area demonstrated a mean anisotropy in the patient group of 0.40 (80%), compared with a mean of 0.50 in the control subjects. The average diffusivity in this region in the patient group was 830 × 10⁻⁶ mm²/s (106%), compared with 780 × 10⁻⁶ mm²/s for the control group. A similar, but non-significant trend of reduced anisotropy was found in the right temporal lobe of the right temporal lobe patients (patient mean, 0.33; control mean, 0.41; P = 0.09).

**Discussion**
There were several major findings in this study. DTI and voxel-by-voxel statistical comparison identified significant increases in diffusivity and significant reductions of anisotropy in all patients with acquired non-progressive cerebral lesions and partial seizures. In all of these patients, the areas of increased diffusivity, and in nine patients the areas of decreased anisotropy, concurred with abnormalities
Diffusion tensor imaging in epilepsy

Fig. 3 Left temporal lobe epilepsy group with normal conventional MRI. (A and B) Normalized axial anisotropy maps at the same slice position for the averaged 30 control subjects (A) and the nine patients (B). (D and E) Normalized axial diffusivity maps at the same slice position for the averaged 30 control subjects (D) and the nine patients (E). The regions of decreased anisotropy and increased diffusivity are superimposed on normalized T1-weighted SPM templates at the same slice position—C and F, respectively. These regions are localized to the left temporal lobe. The regions in C and F were used for quantitative ROI analyses of anisotropy and diffusivity values. Note that right on the image is the patients’ right.

identified on visual inspection of conventional MRI. In addition, there were 10 areas which were normal on visual inspection of the conventional MRIs which exhibited significantly different anisotropy or diffusivity, indicating added sensitivity from the new method. Individual analyses of 30 patients with partial seizures and normal conventional MRI identified a significant increase in diffusivity in eight of the subjects. In six of these, the areas of increased diffusivity concurred with the localization of epileptiform EEG abnormality. Analysis of anisotropy in the MRI-negative patients revealed significant differences in two patients, one of which concurred with electroclinical seizure localization. Group analysis of nine patients with electroclinical seizure onset localizing to the left temporal region revealed a significant increase in diffusivity and a significant reduction in anisotropy within the white matter of the left temporal lobe.

Pathophysiological and clinical implications
Diffusion of water within a tissue is governed by its molecular, microstructural and architectural properties. It has been suggested that the main determinants of anisotropy in densely packed unmyelinated fibres are axonal membranes and, in myelinated tracts, the multiple myelin laminae (Rutherford et al., 1991; Beaulieu and Allen, 1994a, b; Nomura et al., 1994; Wimberger et al., 1995). A disruption to this microstructural environment such as ischaemic injury, gliosis or cerebral dysgenesis will lead to a less ordered arrangement of nerve fibres and subsequent change in anisotropy and diffusivity.

Diffusivity is reduced in seizure foci during ictal events (Wieshmann et al., 1997; Lansberg et al., 1999) and induced status epilepticus (Zhong et al., 1993; Ebisu et al., 1996). This is thought to be the result of cellular swelling and reduction of extracellular space (Lux et al., 1986; Anderson et al., 1996). Anisotropy measurements are not available from these studies; however, it is likely that this would be reduced similarly. This is because the cells would be more tightly opposed and paths between them more tortuous and hindering to diffusing molecules (Van der Toorn et al., 1996; Duong et al., 1998). There was an acute reduction in diffusion during pilocarpine-induced status epilepticus and, in rats
which subsequently developed chronic seizures, a progressive increase in diffusion developed in both seizure foci and mesial temporal lobe structures (Lynch et al., 1996). The hypothesis was that chronic seizures lead to cellular loss and structural disruption in both these areas. This is the likely explanation for the decreased anisotropy in the mesial temporal lobe structures of Patient 5 in the acquired lesion group and also the group effect of reduced anisotropy and increased diffusivity found in the MRI-negative TLE patients.

Significant reductions of anisotropy were detected in all of the patients with acquired lesions and, in all but one patient (Patient 5), these were within areas previously identified as abnormal on conventional MRI. All areas of abnormality on conventional MRI were associated with significant increases in diffusivity. These results concur with findings from previous diffusion studies on patients with acquired non-progressive cerebral lesions (Hajnal et al., 1991; Werring et al., 1998; Wieshmann et al., 1999a).

In three patients with head injury (Patients 1–3), increases in anisotropy were identified. In Patients 1 and 3, these areas were commonly immediately adjacent to the major traumatic lesion, in cerebral tissue which appeared normal on conventional MRI. This may represent displacement of white matter tracts into regions of inherently low anisotropy or the compaction of fibre bundles into denser and more structured, hence more anisotropic, tracts. Four patients with head injuries (Patients 1, 3, 4 and 5) had reduced anisotropy or increased diffusivity in regions appearing normal on conventional MRI, suggesting loss of structural organization secondary to occult cerebral damage.

In chronic ischaemic lesions, increased diffusivity and reduced anisotropy have been noted previously, concordant with gliosis, expansion of the extracellular space and loss of discrete microstructural organization (Warach et al., 1995). In all three patients with partial seizures secondary to mature infarcts, DTI and SPM demonstrated reduced anisotropy and increased diffusivity within each lesion. In one patient (Patient 8), an additional area of reduced anisotropy was demonstrated within the same vascular territory. This was in normal-appearing cerebral tissue, suggesting that the ischaemic injury extended beyond the visible abnormality. Furthermore, another patient with a mature cerebral infarct (Patient 6) had an area of increased diffusivity in the contralateral hemisphere in normal-appearing tissue, again suggesting the presence of occult injury. Overall, six patients with head injury or ischaemic damage (Patients 1, 3, 4, 5, 6 and 8) had significantly altered diffusion indices within normal-appearing cerebral tissue. This finding would be of importance should surgical management of similar patients be considered.

Areas of significantly abnormal diffusion were detected in nine MRI-negative patients. In seven patients, these regions concurred with localization of epileptiform EEG abnormality and, in four of these, the regions also concurred with ictal EEG recordings and clinical seizure semiology. The areas of significantly increased diffusivity in the MRI-negative patients, and the significant reduction of anisotropy and increase in diffusivity in the TLE group are most likely to be caused by disruption in the microstructural environment due to aetiological factors, such as occult dysgenesis or acquired damage, or as a result of repeated seizures, e.g. atrophy, gliosis and expansion of the extracellular space. These patients are being evaluated for surgical treatment; pathological material is not yet available.

Our results suggest that diffusivity is a more sensitive diffusion index than anisotropy in identifying occult epileptogenic regions in MRI-negative patients. This implies that, although expansion of extracellular space has occurred, the major white matter tracts have mostly retained their structural organization and parallel fibre bundle arrangement.

Despite its sensitivity in patients with epilepsy and acquired lesions, the technique did not identify a clinically concordant abnormality in the majority of patients with normal conventional MRI. Histopathological studies of surgically resected epileptogenic areas which appeared normal on MRI have shown features of mild subpial or white matter gliosis, focal cortical dysplasia, clusters of neuronal aggregates in white matter, impaired cortical lamination and subcortical laminar heterotopia (Theodore et al., 1990; Palmini et al., 1991; Zentner et al., 1995). These occult epileptogenic regions, which are encountered most frequently in the grey matter or white–grey junction, are likely to be associated with only minor structural disorganization, perhaps at a microscopic level, and may not be disruptive enough to cause significant, measurable alterations in diffusion parameters. Further, anisotropy is greatest in the central, major white matter tracts and progressively reduces as the cortex is neared and fibres fan out or cross (Peled et al., 1998). Subtle lesions within these areas where anisotropy is naturally low might not result in a significant alteration in anisotropy compared with control subjects. It is likely that our positive findings represent the most structurally abnormal of all the MRI-negative patients and, with improvements in diffusion imaging, further occult epileptogenic regions may be identified.

One MRI-negative patient (Patient 23) had an electro-clinically concordant significant increase in anisotropy within the right temporal lobe when compared with the control subjects. As in the case of acquired lesions, this increased anisotropy may be associated with tract displacement or compression; without pathological material, however, the explanation is not clear.

Two MRI-negative patients had areas of altered diffusion in regions that were not implicated by EEGs. Patient 15 had regions of decreased anisotropy and increased diffusivity in the occipital regions bilaterally, in addition to an area of increased diffusivity in the right frontal region. This patient had suffered a perinatal hypoxic event. Patient 10 (acquired lesion group) sustained a similar injury and SPM analysis revealed comparable diffusion abnormalities; however, in this patient, conventional MRI revealed an increased signal on T2-weighted images in occipital regions bilaterally. Patient 38 had a region of increased diffusivity distinct from the
seizure focus. This patient had experienced a number of unprovoked episodes of status epilepticus. It is most likely that the regions of increased diffusivity in these patients were the consequence of the prior insults.

Although the significant group effect in MRI-negative patients with left temporal lobe epilepsy is not clinically useful in individual patients, it suggests that given greater sensitivity, an effect in individual patients might be demonstrated. Ongoing work of this group therefore is to develop a DTI sequence with improved resolution and signal-to-noise ratio, particularly in the region of the grey–white matter interface. Our aim is to characterize the nature of the occult lesions in MRI-negative patients further, and provide a means of accurately identifying focal abnormalities prior to more invasive diagnostic procedures and possible epilepsy surgery.

Conclusions

Voxel-by-voxel statistical analysis of anisotropy and diffusivity in patients with non-progressive acquired lesions identified areas of significantly altered diffusion in all patients, the majority within regions previously identified as abnormal on conventional MRI. In addition, these new methods conferred additional sensitivity by detecting abnormal diffusivity and anisotropy in normal-appearing cerebral tissue. Analysis of 30 patients with localization-related epilepsy and normal conventional MRI revealed seven patients with abnormalities of diffusion in regions which concurred with the localization of an epileptiform EEG abnormality. In addition, a significant group effect in patients with left temporal lobe epilepsy was detected. These findings imply that occult epileptogenic regions are associated with minor structural disruption and can be identified using voxel-based statistical analysis of diffusion tensor imaging.

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