Interictal diffusion MRI in partial epilepsies explored with intracerebral electrodes

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Patients with refractory partial seizures may benefit from epilepsy surgery. However, invasive investigations are often needed to define the precise location and limits of the epileptogenic zone (EZ). In this study, we asked whether diffusion tensor imaging (DTI) might provide a non-invasive alternative to locate the EZ or at least provide insights to help place intracerebral electrodes for stereo-electroencephalography (SEEG). Whole brain DTI and voxel-based analysis (SPM99) was used to assess diffusion properties objectively in 16 epilepsy patients investigated with SEEG. Epilepsy was symptomatic in two patients and cryptogenic in the 14 remaining patients. The suspected onset of seizures was temporal in 10 patients, frontal in 2 and occipital in 4. Individual maps of apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were calculated and compared to a database of 40 healthy volunteers. Thirteen of 16 patients exhibited diffusion abnormalities. ADC abnormalities were better correlated with SEEG data than FA abnormalities which were usually located at a distance or in the white matter. A significant increase in ADC (P < 0.01) was found in 11 patients and was located in the regions explored with depth electrodes in 7 of them. Surgery outcome was available in 3 of these 7 patients (2 were seizure free and 1 not). DTI specificity was better in extratemporal lobe epilepsy (83%) than in temporal lobe epilepsy (20%). When abnormalities concurred with the SEEG data, the concordance was optimal between the localization of the diffusion abnormalities and the irritative zone defined by SEEG. These encouraging, preliminary results, suggest that DTI examinations may provide accurate spatial data on the location and extent of the epileptogenic network in extratemporal lobe epilepsies.

Keywords: partial epilepsies; diffusion tensor imaging; stereo-electroencephalography; irritative zone

Abbreviations: ADC = apparent diffusion coefficient; DTI = diffusion tensor imaging; EZ = epileptogenic zone; FA = fractional anisotropy; IZ = irritative zone; OZ = onset zone; SZ = spreading zone; SEEG = stereo-electroencephalography; SPECT = single photon emission computed tomography

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Introduction

About one-third of the patients suffering from focal epilepsy are refractory to antiepileptic drugs (Kwan and Brodie, 2000). Half of these patients can benefit from epilepsy surgery which appears to be successful in 60% of the cases (Engel, 1993).

Pre-surgical evaluation aims to determine the location and limits of the epileptogenic zone (EZ), defined as the area of cortex indispensable for the generation of epileptic seizures (Rosenow and Luders, 2001). Non-invasive EEG-video monitoring together with structural and functional imaging tools including morphological MRI, ictal single photon emission computed tomography (SPECT) and [18F]fluoro-2-deoxy-D-glucose PET (18FDG-PET) can often localize the EZ sufficiently accurately for surgery (Engel et al., 1990; Duncan, 1997). However, in >25% of the patients with refractory seizures (Spencer et al., 1998), these examinations do not localize the EZ sufficiently accurately and invasive investigations must be undertaken. Two types of invasive investigations are commonly used. Electrocorticographic
recordings are made using electrodes arranged in strips or grids and intracerebral electrodes are implanted stereotactically for stereo-electroencephalographic (SEEG) recordings. The precision with which SEEG data can localize the EZ depends evidently on the size of regions from which electrodes record and on their placement. In this study, we asked whether interictal diffusion tensor imaging (DTI) could be a useful adjunct technique to help delineate the EZ or at least to guide the placement of intracerebral electrodes when SEEG is required. DTI studies have proven accurate in epilepsy to show abnormalities in concordance with the localization of interictal and ictal EEG abnormalities (Sundgren et al., 2004). The localizing value of interictal DTI was first suggested by Rugg-Gunn et al. (Rugg-Gunn et al., 2001) in individual patients with partial cryptogenic epilepsy. They found that diffusion abnormalities concurred with the site of the epileptiform interictal EEG abnormalities in 7 out of 30 patients. They hypothesized that these DTI abnormalities might correspond either to occult epileptogenic lesions or to structural modifications caused by epilepsy. Intracranial EEG performed on one of their patient sample showed a rigorous spatial correlation between the DTI abnormalities and the onset zone (OZ) (Rugg-Gunn et al., 2002). Histopathological examination of the surgical specimen showed at this site a diffuse gliosis. In other patients the significance of the diffusion abnormalities was not further explored. In this study, we used whole brain DTI and voxel-based analysis (SPM99) to objectively assess diffusion differences between epilepsy patients investigated with SEEG and a database of healthy volunteers. We attempted to determine the accuracy (sensitivity and specificity) with which interictal DTI imaging can localize the EZ, and to examine its value in the specification of the EZ, and to examine its value in the specification of the EZ.

Materials and methods

Patients and controls

The study population included 16 consecutive patients who underwent pre-surgical evaluation at the epilepsy unit of the Salpêtrière hospital between February 2003 and November 2004. All patients underwent medical and neurological examinations, interictal EEG, video-EEG monitoring and SEEG. All 16 patients underwent an 18FDG-PET and 13 of them, an ictal/interictal SPECT.

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Clinical data including age, sex, the presence of an early event, age at the onset of epilepsy, mean duration of epilepsy, conventional MRI findings, surface ictal EEG features, ictal SPECT results, FDG-PET results and post-operative outcome are reported in Table 1.

Abnormalities were detected by conventional MRI in 2 patients, one with a gyration abnormality and the other with a hippocampal sclerosis. The suspected site of onset of seizures was temporal in 10 patients, frontal in 2 and occipital in 4.

The control group included 40 healthy volunteers (15 women, 25 men, mean age: 33.4 years ± 9.8, range 18–59) with no history of neurological disorders and a normal standard MRI. Structural T1-weighted images (IR-FSPGR) were systematically reviewed to exclude potential abnormalities in control subjects.

Informed written consent to participate in the study was obtained from all patients and healthy volunteers in concordance with the Declaration of Helsinki. The study was approved by the local ethics committee.

SEEG protocol

The modality of implantation, type and number of intracranial electrodes differed among patients, according to the hypotheses on the EZ and the region studied. These hypotheses were derived from the analysis of conjunct clinical, electrophysiological and imaging data. Between 4 and 9 electrodes were used. Depth electrodes were used in all cases, supplemented with subdural electrodes in 5 patients. Electrodes were positioned under stereotactic conditions using a gadolinium-enhanced 3D anatomical MRI and MR angiography (3D MOTSA). After implantation, the anatomical location of each site was precisely identified on a 3D reconstruction of the anatomical MRI.

We determined the location of the ictal OZ, the spreading zone (SZ), the irritative zone (IZ) and the EZ for each patient. The OZ was defined as the region which produced initial ictal activity. This activity usually consisted of fast low-voltage rhythmic discharges which propagated to other brain regions. We defined this region as the SZ and attempted to correlate it with ictal clinical symptoms. In some cases this was not possible due to an adverse electrode placement. The IZ was defined classically as regions exhibiting interictal epileptic spikes. Finally, the EZ was defined from both non-invasive and invasive data as the cerebral region to be excised.

Imaging protocol

Conventional MRI and DTI data were acquired during an interictal period before the SEEG procedure on a 1.5 T scanner (GE, Milwaukee, USA). Diffusion-weighted echoplanar images (EPI) were acquired with a standard head coil for signal reception. Twenty axial slices were obtained using the following parameters: TR: 6500 ms, TE: 85 ms, flip angle 90°, acquisition matrix 128 × 128, reconstruction matrix 256 × 256, FOV 32 × 32 cm², in plane resolution 1.25 × 1.25 mm² and slice thickness of 5 mm with no gap.

Diffusion weighting was performed along 23 optimized non-collinear directions with two excitations resulting in 480 images acquired in less than 6 min. A single b-value of 700 s/mm² was applied. In addition, a reference image with no diffusion weighting was also obtained (b₀ image).

Raw diffusion-weighted data were corrected for geometric distortion secondary to eddy currents using a registration technique based upon the geometric model of distortions (Haselgrove and Moore, 1996), as described by Lehericy et al. (2004). Maps of apparent diffusion coefficient (ADC) [corresponding to the mean diffusivity = trace (D)/3]] and fractional anisotropy (FA) were calculated from diffusion-weighted images.

SPM data analysis

For voxel-by-voxel statistical comparisons, EPI images (T₁-weighted images obtained for b = 0) were spatially normalized to a customized template. This template was created by normalizing both patients and control’s EPI images to the standard EPI template provided in SPM99 using an affine transformation with 12 degrees of freedom. The 56 EPI images were then averaged and smoothed with an 8 mm Gaussian kernel to create a study-specific template. Diffusion maps were then normalized with a 4 × 5 × 4 non-linear warp
The origin for normalization was set manually to the anterior commissure. Normalized FA maps and ADC maps were smoothed with a 10 mm isotropic Gaussian kernel.

**Statistical analysis**

Each patient was compared to the control group using ANCOVA with age and sex as confounding variables. A statistical threshold of $P < 0.01$ was first applied (height threshold). Then, clusters were considered significant when they matched one of the following two criteria depending on their location: (i) in the regions with no a priori hypothesis concerning the location of the EZ, i.e. not explored with SEEG, an extent threshold of $P < 0.05$ corrected for multiple comparisons was applied at the cluster level; (ii) in the regions hypothesised as the EZ, a volume correction of 50 voxels was applied. The anatomical localization of DTI abnormalities in relation to each contact of the electrodes was precisely determined by co-registering the statistical parametric mapping with the anatomical MRI performed in each patient one day after implantation and normalized using the same normalization parameters as for DTI images.

**Results**

**Description of the frequency and type of diffusion abnormalities (Table 2)**

**Sensitivity**

Fourteen of 16 patients exhibited diffusion abnormalities. Two of these abnormalities were located outside the brain parenchyma in the ventricles. In one patient, this was the sole abnormality. These abnormalities were not analysed further (Table 2). Seven of the 13 remaining cases had both ADC and FA abnormalities, 4 had ADC alone and 2 had FA alone.

An increase of diffusion was detected in all 11 patients with ADC abnormalities and a mixed increase and decrease in 2 patients. FA abnormalities consisted of a decrease of diffusion in 6 patients, an increase in 2 and were mixed in 1.

**Specificity**

**ADC abnormalities.** In 7 patients, circumscribed diffusion abnormalities were found in the regions explored with depth electrodes (Fig. 1).

In 3 other patients (1, 2 and 8), all suffering from temporal lobe epilepsy (TLE), the abnormalities were located at a distance from the EZ. In Patient 1, ADC increase was located in the both hemispheres, involving the frontal, temporal, parietal and occipital regions. Patient 2 exhibited an abnormality located in the left corpus callosum and thalamus. Patient 8 exhibited a frontal abnormality ipsilateral to the EZ.

Lastly, Patient 3 exhibited a widespread ADC increase involving a large part of the left hemisphere. In this patient, diffusion abnormalities concurred together with OZ, IZ and SZ at the level of the temporal and frontal lobes. As diffusion abnormalities involved the whole left hemisphere, they were of weak interest in terms of localization and this patient was not included in the congruent patients group.
FA abnormalities. FA abnormalities were relatively small and located in the white matter, either abutting the ADC abnormalities (Patients 1, 3, 5, 13 and 15) or at a distance in another lobe (Patient 4). In two subjects (Patients 8 and 16), the FA abnormalities were isolated and located in the same lobe as the EZ but at a distance from it.

FA abnormalities were located either in non-explored white matter region beneath ADC abnormalities or at a distance from the EZ. Since the information content of FA changes seemed to be less than for ADC abnormalities, we restricted correlations to those between ADC and SEEG data.

Correlation between ADC abnormalities and SEEG data (Table 3, Fig. 2)

Patients with a medial temporal focus

Patient 5 had a right hippocampal sclerosis. The EZ was suspected to be in the right temporal lobe with a potential involvement of the right frontal lobe.

Two clusters of increased ADC were detected, one in the right temporal lobe extending from the hippocampus to the lateral part of the lobe and the other, extensive, located in the frontal lobes extending from the anterior/lateral part to the posterior/medial part.
The OZ was located in the anterior part of the right hippocampus with an SZ extending laterally in the temporal lobe and in the right orbito-frontal region, involving two electrodes.

The IZ was found in the medial and lateral temporal lobe and along two electrodes in the right orbito-frontal region.

In this patient, diffusion abnormalities included the OZ and also correlated largely with the SZ and IZ.

Patient 6 had an EZ thought to be located in the left medial temporal lobe with no visible lesion on MRI.

A circumscribed increase in ADC was found in the posterior part of the left medial temporal lobe, corresponding to a region investigated with a hippocampal electrode. An ipsilateral parietal increase in ADC was also detected.

The OZ was found in the posterior part of the hippocampus. The SZ was found in the anterior hippocampus, amygdala and temporo-polar region. The IZ involved the posterior hippocampus and the temporo-polar region.

In this patient, diffusion abnormalities were close to the contacts of the hippocampal electrode exhibiting OZ and IZ.

Patients with an occipital focus

Patient 11 had an EZ thought to be in the left occipital lobe. No lesion was visible on MRI.

A circumscribed increase in ADC was located in the left occipital lobe, near the temporo-occipital junction. Several OZs were detected along three electrodes located in the medial part of the occipital lobe, in the calcine sulcus and in the temporo-occipital junction. The SZ was found in the calcine sulcus and the occipital pole. The IZ was found in the occipital pole and in the temporo-occipital junction.

In this patient, diffusion abnormalities were located very close to one of the OZ and correlated well with one of the IZ. There was no correlation with the SZ.

Patient 12 had a gyration abnormality located in the upper medial and posterior part of the right occipital lobe. A large cluster of increased ADC was apparent in the right occipital lobe at the inferior part of the lesion (peak of abnormality) and under it. Thus, diffusion abnormalities extend beyond the visible lesion and also did not include it completely. The OZ was located in the middle part of the lesion (plot 4). The SZ

<table>
<thead>
<tr>
<th>Patient</th>
<th>Structural MRI</th>
<th>SEEG defined EZ</th>
<th>ADC increase</th>
<th>ADC decrease</th>
<th>FA increase</th>
<th>FA decrease</th>
</tr>
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<tbody>
<tr>
<td>Temporal medial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 n</td>
<td>R medial and basal temporal</td>
<td>Bilateral fronto-temporal, R occipito-parietal</td>
<td>None</td>
<td>None</td>
<td>L occipito-parietal</td>
<td></td>
</tr>
<tr>
<td>2 n</td>
<td>Bitemporal medial</td>
<td>R &gt; L</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>3 n</td>
<td>L medial and basal temporal</td>
<td>L occipito-parieto-temporal, bilateral frontal</td>
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<td>None</td>
<td>L temporal</td>
<td></td>
</tr>
<tr>
<td>4 n</td>
<td>Bitemporal medial</td>
<td>R &gt; L</td>
<td>None</td>
<td>None</td>
<td>L occipital</td>
<td></td>
</tr>
<tr>
<td>5 R HS</td>
<td>R medial temporal</td>
<td>R temporal, bilateral frontal</td>
<td>L temporal, bilateral frontal</td>
<td>R frontal</td>
<td>L parietal, bilateral frontal</td>
<td></td>
</tr>
<tr>
<td>6 n</td>
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<td>L parietal and temporal</td>
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<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>7 n</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 n</td>
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<td>R frontal</td>
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<td>None</td>
<td>R temporal</td>
<td></td>
</tr>
<tr>
<td>9 n</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>10 n</td>
<td>R lateral temporal</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 n</td>
<td>L occipital</td>
<td>Occipito-temporal, inferior part of the visible lesion and above it</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>12 R occ MCD</td>
<td>MCD (inferior part)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>13 n</td>
<td>L occipital</td>
<td>L occipital</td>
<td>None</td>
<td>None</td>
<td>L temporo-occipital</td>
<td></td>
</tr>
<tr>
<td>14 n</td>
<td>L occipital</td>
<td>L occipito-temporal</td>
<td>R frontal and parietal</td>
<td>None</td>
<td>Bilateral frontal and parietal</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 n</td>
<td>L frontal (MFG)</td>
<td>L frontal (MFG)</td>
<td>None</td>
<td>None</td>
<td>L frontal</td>
<td></td>
</tr>
<tr>
<td>16 n</td>
<td>R frontal</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>R frontal</td>
<td></td>
</tr>
</tbody>
</table>

n = no visible lesion; R = right; L = left; HS = hippocampal sclerosis; MCD = malformation of cortical development; occ = occipital; MFG = middle frontal gyrus.
was found in a region located inferiorly to the lesion. The IZ was located at the level of the OZ.

In this patient, diffusion abnormalities were extensive and located a few centimetres below the OZ and IZ. The SZ was located at the level of diffusion abnormality.

Patient 13 had a slight dilatation of the left occipital horn. The EZ was thought to be located in the left occipital lobe.

Two clusters of increased ADC were detected in the left occipital lobe posteriorly and laterally to the occipital horn. Another cluster was located in the left precuneus. A small cluster was also found in the left posterior cingulate gyrus. No OZ was determined in this patient. The SZ was relatively widespread predominantly at the level of the posterior occipital lobe and also involving the cuneus, the calcarine fissure, the isthmus and the occipito-temporal sulcus. The IZ was located in the same regions as the SZ with a tempo-basal electrode in addition.

In this patient, diffusion abnormalities were closely correlated with several sites of SZ and IZ.

Patient 14 had a suspected EZ in the left occipital lobe and no visible lesion on MRI (Fig. 3).
A circumscribed increase in ADC was found in the left temporo-occipital junction.

The OZ was found between two electrodes located near the left temporo-occipital junction, one named superior 2 and the second inferior 3. The SZ was located to the same electrodes, more anteriorly in the inferior 2. The IZ was found in a more anterior region at the level of electrodes superior 1 and inferior 1 and 2. In this patient, diffusion abnormalities correlated well with the IZ.

**Patient with a frontal focus**

Patient 15 had a suspected EZ in the left frontal lobe and no visible lesion on MRI.

A circumscribed increase in ADC was found in the left middle frontal gyrus, in a region located a few millimetres behind one of the electrodes.

The OZ was located in the superior frontal sulcus, in a region located anterior to diffusion abnormalities. No clear SZ was identified. The IZ was found at the same location as the OZ.

In this patient, diffusion abnormalities were found in a region not directly explored by the electrodes but located near the OZ and the IZ.

**Post-operative outcome (Table 1)**

To date, half of the patients \( n = 8 \) were operated with a mean post-operative interval of 7.5 months (3–18 months). Among these 8 patients, 5 belonged to Engel’s class Ia, one belonged to Engel’s class II and two patients belonged to Engel’s class III–IV (Engel, 1987).

Two of the patients who are seizure free (Patients 6 and 15) had diffusion abnormalities that were congruent with the SEEG data. Patient 12, who has not been improved by surgery (Engel’s class III–IV), also exhibited good correlations between diffusion abnormalities and SEEG data. However, in this patient, surgery was restricted 1 cm around the OZ defined

### Table 3 Correlation between diffusion abnormalities and SEEG

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset zone (%)</th>
<th>Spreading zone (%)</th>
<th>Irritative zone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEEG</td>
<td>DTI</td>
<td>SEEG</td>
</tr>
<tr>
<td>Temporal medial</td>
<td>R temporal lobe (plot 1)</td>
<td>+++</td>
<td>R temporal lobe (plots 3–4)</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>R orbito-frontal (plot 2)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>L posterior hippocampus (plot 1)</td>
<td>++</td>
<td>L anterior hippocampus (plot 2–3)</td>
</tr>
<tr>
<td></td>
<td>L temporo-polar (plots 1–4)</td>
<td>0</td>
<td>L temporo-polar (plots 2–4)</td>
</tr>
<tr>
<td></td>
<td>L amygdala (plots 1–4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>L calcarine sulcus (plot 2)</td>
<td>0</td>
<td>L calcarine sulcus</td>
</tr>
<tr>
<td></td>
<td>L occipital pole (plots 1–5)</td>
<td>++</td>
<td>L occipital pole</td>
</tr>
<tr>
<td>6</td>
<td>L calcarine sulcus (plot 1)</td>
<td>++</td>
<td>L calcarine sulcus (plot 1–2)</td>
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<tr>
<td></td>
<td>L occipital pole</td>
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<td>L calcarine sulcus (plot 1)</td>
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<td></td>
<td>L isthmus (plots 1–2)</td>
<td>0</td>
<td>L isthmus (plot 1–2)</td>
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<tr>
<td></td>
<td>L basal temporal (plot 2)</td>
<td>0</td>
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</tr>
<tr>
<td></td>
<td>L occipital posterior</td>
<td>++</td>
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<tr>
<td></td>
<td>L occipito-temporal sulcus</td>
<td>++</td>
<td>L occipito-temporal sulcus</td>
</tr>
<tr>
<td></td>
<td>L cuneus (plot 1–4)</td>
<td>++</td>
<td>L cuneus (plot 1–4)</td>
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<td></td>
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<tr>
<td></td>
<td>L isthmus (plots 3–5)</td>
<td>++</td>
<td>L isthmus (plots 3–5)</td>
</tr>
<tr>
<td></td>
<td>L temporo-occipital</td>
<td>++</td>
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</tr>
<tr>
<td></td>
<td>L calcarine sulcus (plot 1)</td>
<td>++</td>
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<td>L cuneus (plot 1–2)</td>
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<td></td>
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</tr>
<tr>
<td>Frontal</td>
<td>L sup frontal sulcus (plot 5)</td>
<td>+</td>
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</tr>
</tbody>
</table>

SEEG = stereo-electroencephalography; DTI = diffusion tensor imaging; R = right; L = left; n = no visible lesion; MCD = malformation of cortical development; HS = hippocampal sclerosis; sup = superior; inf = inferior; Diffusion abnormalities: ++++, involves at least one plot; ++, involves an adjacent plot or an adjacent region; +, near but not adjacent; 0, at a distance. The name of the electrode did not always correspond to the exact anatomical region.
by SEEG because of expected functional consequences. The other patient belonging to Engel’s class III–IV (Patient 9), who did not anyway exhibit congruent data, had also a restricted resection because of a functional risk.

Patients 5 and 10 are waiting for surgery and a second SEEG exploration in the occipital region is planned for Patient 13.

Five patients were excluded from surgery because of either bilateral temporal lobe epilepsy (Patients 2, 4 and 7) or an OZ located partly into a functional region (Patients 11 and 14).

Discussion

We report here two major findings. First, the specificity of DTI is better in extratemporal lobe epilepsy than in temporal lobe epilepsy. Secondly, when diffusion abnormalities concurred with some part of the SEEG data, the IZ defined by SEEG was most optimally congruent with the diffusion abnormalities.

DTI specificity

Diffusion abnormalities were detected in 13 out of 16 patients and consisted mainly of an increase in ADC. FA abnormalities were present in 9 patients, but provided little further aid in localization beyond that given by ADC. While anisotropy and diffusivity values derived from diffusion imaging clearly provide complementary information, their links with an underlying physiopathology remain unclear.

In 7 patients, diffusion abnormalities concurred with part of the SEEG data and in 4 patients diffusion abnormalities were apparent at sites distant from the EZ. An interesting finding was that most of the concordant cases between DTI and SEEG findings were detected in extratemporal epilepsy patients: only 2 temporal lobe epilepsy patients (20%) exhibited congruent abnormalities whereas 5 extratemporal lobe epilepsy patients (4 occipital epilepsy patients, 1 frontal epilepsy patient) (83%) exhibited congruent abnormalities.

Two factors might underlie a higher sensitivity and specificity of DTI in extratemporal lobe epilepsy: (i) the frequency of occult lesions and especially focal dysplastic lesions is higher in extratemporal lobe epilepsy and (ii) specific epileptogenesis in distinct cortical regions might involve different epileptic networks. Most of the studied patients exhibited cryptogenic epilepsy. Nevertheless, the two patients with a clear MRI abnormality [hippocampal sclerosis in one case and occipital malformation of cortical development (MCD) in the other case] had DTI abnormalities congruent with the SEEG data. Cortical dysgenesis is recognized as the second most common finding in patients with refractory focal extratemporal lobe epilepsies whereas hippocampal sclerosis is first in refractory temporal lobe epilepsy. Standard neuroimaging analysis may not recognize lesions of focal cortical dysplasia (FCD) in all patients. Such malformations may not always be recognized in visual examination of conventional MRI due to their subtlety and the complexity of the brain’s convolutions (Bernasconi, 2003). Recently, enhanced, automated imaging tools such as voxel-based morphometry (VBM) have been able to detect subtle MCD or dysplasia (Kassubek et al., 2002; Wilke et al., 2003) which were difficult

Fig. 3 View of a 3D representation of the brain of the Patient 14 (P < 0.01 corrected for cluster extent at 50 voxels). The region of increased ADC is in red, the two plots corresponding to the onset zone are in blue and the five plots corresponding to the irritative zone are in green.
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to detect on morphological MRI. Multiplanar reconstruction and curvilinear reformatting (Bastos et al., 1999) and texture analysis (Bernasconi et al., 2001) enhance both the diagnosis and localization of occult cortical dysplasia and the spatial extent with which the lesion can be defined (Montenegro et al., 2002). Ericksson et al. have shown that DTI can detect the anatomical correlates of such dysplastic lesions even when they occur in otherwise normal cortex (Ericksson et al., 2001), as shown in Patient 12. Possibly, the higher prevalence of diffusion abnormalities in extratemporal lobe epilepsies reflects occult dysplastic lesions often associated with these epilepsies.

A second explanation is that epileptic networks associated with temporal and extratemporal lobe epilepsies are different. The anatomical connections and cytoarchitecture differ as do pathways for propagation of ictal discharges. Differences may even extend to the molecular level. Animal studies have shown region-specific and seizure-dependent changes in expression of specific proteins involved in epileptogenesis (Matsushashi et al., 2003). The higher frequency of concordant DTI abnormalities in extratemporal lobe epilepsy could reflect such regional specificities.

Another finding of this study is that half of the patients had either no diffusion abnormalities or abnormalities unrelated to the SEEG data. As we have noted, these were largely cases of temporal lobe epilepsy. This discrepancy may be related to the fact that DTI and SEEG have different spatial resolutions. DTI examines the whole brain, but SEEG is restricted to a finite number of recording electrodes placed according to a priori hypotheses on the location of the EZ. Clearly, DTI may highlight distant components of a diffuse epileptic network that SEEG might miss. Anyway, in our study, extratemporal cases did not have a more extensive exploration than temporal cases. First, the number of electrodes was often similar for both. Secondly, in term of lobar exploration, temporal cases had often a better coverage than extratemporal cases. For example, in addition to temporal or bitemporal exploration, 1–4 additional frontal or occipital electrodes were present in 8 of 10 TLE patients. On the other side, 4 extratemporal cases were explored in 1 lobe only and 2 in more than 1 lobe. Furthermore, due to the size of the lobes and of anatomical constraints, it was easier to explore the whole temporal lobe than the parietal, frontal or occipital lobes in which only partial coverage was possible. Alternatively, distant diffusion abnormalities unrelated to the SEEG data may correspond to the widespread consequences of the repetitive epileptic discharges, including neuronal loss and gliosis (Vinters et al., 1993). Nevertheless, diffusion abnormalities detected in periventricular zones, or at the interface between the CSF and other tissues seem unlikely to play an active role in epileptogenesis. Such true false positive cases could emerge from methodological biases derived from statistical parametric mapping normalization and smoothing processes (Wilke et al., 2003). We could not in this study use the preferred ROI technique due to the diversity of EZ locations in different patients and we would tend to interpret imaging abnormalities always cautiously in light of the electroclinical data.

We are convinced that a DTI examination is useful in presurgical examinations for extratemporal epilepsy patients. Even with the present methodology, which can be further improved, the method has a good sensitivity and specificity. DTI may also help guide the choice of electrode placement in evaluating complex cases especially in extratemporal lobe epilepsy when functional imaging is insufficient.

Concordance with SEEG data

In the 7 patients where we observed a good concurrence between DTI and SEEG data, diffusion abnormalities agreed best with the EZ. In 7 patients, DTI abnormalities were near the OZ, which remained undetermined after the investigation in another case. Correlation with the SZ was present in only 4 patients.

There has been little work comparing the different techniques of functional neuroimaging, including PET, SPECT and spectroscopy MRI, with SEEG data. Merlet et al. have found that hypometabolism always included the dipolar sources of interictal spikes in 7 of 8 patients with non-lesional TLE. Nevertheless, within the hypometabolic zone, the decrease in glucose uptake was not more pronounced in regions containing dipoles (Merlet et al., 1996). Lucignani et al. compared FDG-PET and SEEG in 16 refractory lesional TLE patients and found no correlation between the site of the hypometabolism, the EZ, the IZ or the lesional zone as defined by SEEG (Lucignani et al., 1996). Vera et al. using interictal SPECT in frontal lobe epilepsy patients, also found no specific correlation between the interictal hypoperfusion, the EZ, the IZ and the lesional zone defined from SEEG explorations (Vera et al., 1995). Usually, the hypoperfusion occupied a zone larger or equal in volume to that defined from SEEG. In contrast, a good correlation between interictal hypoperfusion and interictal spiking was found in TLE patients explored with SEEG (Guillon et al., 1998).

Correlations of SEEG studies with neurochemistry are promising. Merlet et al. compared SEEG data with PET results on the distribution of 5-hydroxytryptamine-1A (5-HT$_{1A}$) receptors in patients suffering from refractory TLE (Merlet et al., 2004). Receptor binding was decreased in the epileptogenic temporal lobe with a significantly greater decrease in regions involved in the seizure onset than in those exhibiting either only interictal or no epileptic activity. The decrease in 5-HT$_{1A}$ binding appeared to be well correlated with epileptogenicity rather than just with pathological changes or neuronal loss in the focus.

Guye et al. found that MRI spectroscopic abnormalities were well correlated with the EZ and the IZ in TLE patients in which there was a clear overlap between these regions as defined by SEEG (Guye et al., 2002). Correlation between MRI spectroscopic abnormalities and interictal spiking has been described in TLE patients studied with MEG (Shih et al., 2004). Furthermore, Serles et al. showed that in temporal and
frontal epilepsy patients regions with pronounced neuronal metabolic dysfunction tended to generate higher interictal spike frequencies in surface EEG, suggesting perhaps that both variables were related to an underlying pathologic substrate (Serles et al., 1999).

Our major finding is an excellent concordance between the site of diffusion abnormalities and that of the interictal focus in patients with a good congruence between diffusion and SEEG data. A diffusion study performed in patients with tuberous sclerosis demonstrated a higher ADC in the epileptogenic tubers as compared to non-epileptogenic ones (Jansen et al., 2003). In this study epileptogenic tubers were identified by the presence of an interictal epileptiform activity (spikes) in MEG records.

Interictal discharges represent the extracelluar correlates of the synchronous discharges of a cortical neuronal ensemble (de Curtis and Avanzini, 2001). Interactions mediated via changes in the extracellular space have often been implicated in the epileptiform synchrony of cortical neurons (de Curtis and Avanzini, 2001). While neither morphological nor functional processes underlying diffusion abnormalities are fully understood (Sykova, 2004), Darquie et al. suggested that changes in cell volume are accompanied by changes in water diffusion (Darquie et al., 2001). Increases in ADC could result from increases in the extracellular space possibly due to cell shrinkage, reduced spine density or other changes in neuronal geometry. Thus, an increase in ADC due to changed cellular volume or geometry might explain the good spatial congruence with interictal spiking, even though this might not necessarily be a causal relationship and reflect instead other cerebral dysfunctions.

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