Local and remote epileptogenicity in focal cortical dysplasias and neurodevelopmental tumours

Sandrine Aubert,1,2 Fabrice Wendling,3,4 Jean Regis,5 Aileen McGonigal,1,2 Dominique Figarella-Branger,6 Jean-Claude Peragut,5 Nadine Girard,7 Patrick Chauvel1,2,8 and Fabrice Bartolomei1,2,8

1 CHU Timone, Service de Neurophysiologie Clinique, Marseille, F-13000, France
2 Université de la Méditerranée, LNN, Marseille, F-13000, France
3 INSERM, U642, Rennes, F-35000, France
4 Université de Rennes 1, LTSI, Rennes, F-35000, France
5 CHU Timone, Service de Neurochirurgie Fonctionnelle, Marseille, F-13000, France
6 CHU Timone, Service d’Anatomopathologie, Marseille, F-13000, France
7 CHU Timone, Service de Neuro-Radiologie, Marseille, F-13000, France
8 INSERM, U751, Marseille, F-13000, France

Correspondence to: Pr Fabrice Bartolomei, MD, PhD, Service de Neurophysiologie Clinique, CHU Timone, 264 Rue St Pierre, 13005-Marseille, France
E-mail: fabrice.bartolomei@ap-hm.fr

During the pre-surgical evaluation of drug-resistant epilepsy, the assessment of the extent of the epileptogenic zone and its organization is a crucial objective. Indeed, the epileptogenic zone may be organized as a simple focal lesional site or as a more complex network (often referred to as the ‘epileptogenic network’) extending beyond the lesion. This distinction is particularly relevant in developmental lesions such as focal cortical dysplasias or dysembryoplastic neuroepithelial tumours and may determine both the surgical strategy and the prognosis. In this study, we have quantified the epileptogenic characteristic of brain structures explored by depth electrodes in 36 patients investigated by stereoelectroencephalography and suffering from focal drug-resistant epilepsy associated with focal cortical dysplasias or dysembryoplastic neuroepithelial tumours. This quantification was performed using the ‘Epileptogenicity Index’ method that accounts for both the propensity of a brain area to generate rapid discharges and the time for this area to get involved in the seizure. Epileptogenicity Index values range from 0 (no epileptogenicity) to 1 (maximal epileptogenicity). We determined Epileptogenicity Index from signals recorded in distinct brain structures including the lesional site. We studied the type of epileptogenic zone organization (focal versus network) and looked for a correlation with clinical data and post-surgical outcome. Mean Epileptogenicity Index in lesional regions was 0.87 (±0.25), and 0.29 (±0.30) in ‘non-lesional’ structures. The number of highly epileptogenic structures (defined by Epileptogenicity Index value > 0.4) was 3.14 (±1.87) in the whole population. We found that 31% of patients had only one epileptogenic structure (N_{E>0.4} = 1), therefore disclosing a strictly focal epileptogenic zone organization while 25 patients had more than one epileptogenic region, disclosing a network (61%) or bilateral (8%) epileptogenic zone organization. We observed a trend for a difference in seizure outcome according to the type of epileptogenic zone organization. Indeed, 57% of patients with network organization and 87% with focal organization were seizure-free while none of those with bilateral organization became seizure-free. The determination of Epileptogenicity Index computed from electrophysiological signals recorded according to the stereoelectroencephalography technique is a novel tool. Results suggest that it can help in the delineation of the epileptogenic zone associated with brain lesions and that it could be used in the definition of the subsequent surgical resection.
Introduction

Despite the large number of available antiepileptic drugs, the proportion of patients with focal epilepsy with uncontrolled seizures remains constant at around 20–30% (French, 2007). In focal drug-resistant epilepsy, surgery can lead to the suppression of seizures in some patients (Engel, 1998; Prayson, 2000; Wiebe et al., 2001). Pre-surgical evaluation of patients candidate to surgery consists of several steps (Bartolomei et al., 2002) that aim at determining the epileptogenic zone, historically defined as the brain region(s) that generate seizures (Talairach and Bancaud, 1966). The objective of epilepsy surgery is indeed to suppress seizures by removing the epileptogenic zone.

Invasive EEG recordings may be required to accurately determine the epileptogenic zone. In most cases, this type of electrophysiological investigation reveals that the seizure onset is characterized by the occurrence of high frequency, low amplitude rapid discharges in the beta/gamma range (Bancaud et al., 1965; Allen et al., 1992; Worrell et al., 2002, 2004; Wendling et al., 2003; Bartolomei et al., 2004, 2008). From these recordings, the definition of the epileptogenic zone is thus classically based on two criteria: the appearance of rapid discharges and the delay of involvement, in the ictal process, of explored brain structures. It has been shown that rapid discharges may be visible in several, anatomically separate structures during the period of seizure onset, raising the possibility of a network organization of the epileptogenic zone (Bancaud et al., 1970; Bartolomei et al., 2004, 2008). The definition of the epileptogenic zone is however problematic in these cases since no precise criteria exist to define the characteristics of the initial discharge in terms of its frequency and the delay of its appearance in a given structure. These aspects are indeed traditionally assessed simply by visual inspection of the stereoelectroencephalography (SEEG) recordings. Recently, we proposed a new method for quantifying the epileptogenicity of brain structures in patients explored with depth electrodes and SEEG. A first study was conducted in patients with medial temporal lobe epilepsy (MTLE) associated with hippocampal sclerosis or normal MRI (Bartolomei et al., 2008). It was based on the determination of the ‘Epileptogenicity Index’ (EI) that combines both spectral and temporal parameters related to the propensity of a brain area to generate rapid discharges and the time for this area to become involved in the seizure process (Bartolomei et al., 2008). This index ranging from 0 (no epileptogenicity) to 1 (maximal epileptogenicity) allowed us to quantify the epileptogenicity of each studied brain structure. This previous study showed that the epileptogenic zone in MTLE disclosed features of an epileptogenic network involving several distinct structures. The EI values also allowed us to estimate the extent of this network. Finally, it was concluded that the duration of epilepsy was correlated with the number of epileptogenic structures in MTLE. These results advocated for a gradual extension of brain epileptogenicity over time in these epilepsies.

In the present study, although we used a similar methodological approach based on the EI, the clinical context is different. We aimed at analysing the organization of the epileptogenic zone in partial epilepsies associated with neurodevelopmental tumours (NDT) or focal cortical dysplasia (FCD). These cortical malformations are frequently found in cases of pharmacoresistant epilepsy referred for surgical consideration (Wolf et al., 1993; Honavar et al., 1999; Pasquier et al., 2002). FCD accounts for 20–25% cases of patients with focal epilepsy (Kuzniecky et al., 1993; Tassi et al., 2002). Currently available high-resolution MRI techniques have improved detection of FCD compared to past decades, but small lesions are still quite difficult to detect (Duncan, 1997; Lee et al., 2001; McGonigal et al., 2007). NDT represent the second most frequent group of lesions found in focal pharmacoresistant epilepsy. These tumours correspond to dysembryoplastic neuro-epithelial tumours (DNET) and gangliogliomas. These are congenital lesions that probably develop during embryogenesis, and share some clinical, radiological and neuropathological features. For NDT, most series have found a prevalence between 15% and 30% of all operated patients with focal pharmacoresistant epilepsy (Daumas-Duport, 1993, 1999; Prayson et al., 1993).

Data from intracranial EEG including SEEG and electrocorticography (ECoG) in human patients have confirmed that FCDs are intrinsically epileptogenic (Palmini et al., 1995; Gambardella et al., 1996; Chassoux et al., 2000; Ferrier et al., 2001; Tassi et al., 2001). However, in many cases, it is established that the epileptogenic zone extends beyond the structural lesion seen on MRI (Chassoux et al., 2000; Colombo et al., 2003). Therefore, such cases provide an opportunity to study the relationship between focal brain lesions and the regions of seizure generation.

This study was performed to assess potential links between the epileptogenic zone organization (as characterized by EI values) and certain clinical, neuroradiological or histopathological parameters, and to determine, among these potential factors, those that may influence post-operative prognosis.

Materials and methods

Patient selection and SEEG recordings

Among 138 consecutive patients who underwent SEEG in our centre between 2000 and 2007, 36 patients with focal pharmacoresistant epilepsy and neuroradiological findings suggestive of FCD or neurodevelopmental tumour (dysembryoplastic neuroepithelial tumour, ganglioglioma) were selected. We also included patients with non-lesional MRI in whom the surgical specimen pathological examination led to the diagnosis of FCD (Table 1).
Table 1 Clinical, neuroradiological and surgical outcome in the studied population

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at epilepsy onset (years)</th>
<th>Epilepsy duration (years)</th>
<th>Lesion on MRI (side)</th>
<th>Lesion type/localization</th>
<th>Surgery</th>
<th>Complete removal</th>
<th>Epileptogenic zone organization</th>
<th>Final diagnosis (*confirmed by histopathology)</th>
<th>Follow-up (years)</th>
<th>Engel class</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>4</td>
<td>18</td>
<td>Y</td>
<td>FCD/R precentral region</td>
<td>No (surgery contra-indicated)</td>
<td>–</td>
<td>NTW</td>
<td>FCD</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1.5</td>
<td>5</td>
<td>Y</td>
<td>FCD/R temporopolar region</td>
<td>No (not yet operated on)</td>
<td>–</td>
<td>NTW</td>
<td>FCD</td>
<td>–</td>
<td>5.5</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>3</td>
<td>12</td>
<td>Y</td>
<td>FCD/R central region</td>
<td>GK</td>
<td>–</td>
<td>NTW</td>
<td>FCD</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
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<td>27</td>
<td>Y</td>
<td>FCD/R parieto-occipital region</td>
<td>GK</td>
<td>–</td>
<td>B</td>
<td>FCD</td>
<td>6</td>
<td>IV</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
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<td>Y</td>
<td>FCD/L precentral region</td>
<td>GK</td>
<td>–</td>
<td>FCD</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>Y</td>
<td>NTW</td>
<td>FCD (gliosis*)</td>
<td>1.5</td>
<td>la</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>12</td>
<td>22</td>
<td>Y</td>
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<td>R parietal corticectomy</td>
<td>Y</td>
<td>F</td>
<td>FCD (gliosis*)</td>
<td>2</td>
<td>la</td>
</tr>
<tr>
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<td>F</td>
<td>5</td>
<td>20</td>
<td>Y</td>
<td>FCD/R superior temporal gyrus</td>
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<td>Y</td>
<td>F</td>
<td>FCD la (*)</td>
<td>6.5</td>
<td>la</td>
</tr>
<tr>
<td>9</td>
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<td>32</td>
<td>Y</td>
<td>FCD/R hippocampus</td>
<td>R temporal lobectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD la (*)</td>
<td>4</td>
<td>la</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>10</td>
<td>26</td>
<td>Y</td>
<td>FCD/R parieto-occipital region</td>
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<td>Y</td>
<td>NTW</td>
<td>FCD ib (*)</td>
<td>1</td>
<td>la</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>2</td>
<td>45</td>
<td>N</td>
<td>–</td>
<td>R frontal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD ib (*)</td>
<td>6.5</td>
<td>la</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>5</td>
<td>12</td>
<td>N</td>
<td>–</td>
<td>L prefrontal corticectomy</td>
<td>N</td>
<td>NTW</td>
<td>FCD ib (*)</td>
<td>4</td>
<td>III</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>5</td>
<td>3</td>
<td>Y</td>
<td>FCD/R temporopolar region and insula</td>
<td>R temporal lobectomy</td>
<td>N</td>
<td>NTW</td>
<td>FCD ib (*)</td>
<td>2</td>
<td>IV</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>12</td>
<td>27</td>
<td>Y</td>
<td>FCD/R prefrontal region</td>
<td>R prefrontal corticectomy</td>
<td>NA</td>
<td>NTW</td>
<td>FCD ib (*)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>12</td>
<td>23</td>
<td>N</td>
<td>–</td>
<td>L prefrontal and orbitofrontal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD IIa (*)</td>
<td>1</td>
<td>la</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>5</td>
<td>21</td>
<td>Y</td>
<td>HS/R hippocampus</td>
<td>R temporal lobectomy</td>
<td>Y</td>
<td>F</td>
<td>FCD IIa (*)</td>
<td>2</td>
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<tr>
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<td>5</td>
<td>15</td>
<td>Y</td>
<td>FCD/L SMA</td>
<td>R frontostriatal cortex</td>
<td>Y</td>
<td>F</td>
<td>FCD IIb (*)</td>
<td>5.5</td>
<td>la</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>3</td>
<td>14</td>
<td>N</td>
<td>–</td>
<td>L prefrontal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>2.5</td>
<td>la</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
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<td>7</td>
<td>Y</td>
<td>FCD/R superior frontal sulcus</td>
<td>R prefrontal corticectomy</td>
<td>Y</td>
<td>F</td>
<td>FCD IIb (*)</td>
<td>4</td>
<td>la</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>16</td>
<td>11</td>
<td>Y</td>
<td>FCD/L anterior cingulate gyrus</td>
<td>IL prefrontal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>7</td>
<td>la</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>16</td>
<td>17</td>
<td>N</td>
<td>–</td>
<td>R frontal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>5.5</td>
<td>la</td>
</tr>
<tr>
<td>22</td>
<td>F</td>
<td>17</td>
<td>11</td>
<td>N</td>
<td>–</td>
<td>R prefrontal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>1.5</td>
<td>la</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>8</td>
<td>9</td>
<td>Y</td>
<td>FCD/R occipito-temporal region</td>
<td>R occipito-temporal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>4</td>
<td>II</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>4</td>
<td>25</td>
<td>Y</td>
<td>FCD/L anterior frontal region</td>
<td>L prefrontal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>5</td>
<td>II</td>
</tr>
<tr>
<td>25</td>
<td>F</td>
<td>7</td>
<td>16</td>
<td>N</td>
<td>–</td>
<td>R lateral occipito-temporal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>6.5</td>
<td>II</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>6</td>
<td>25</td>
<td>N</td>
<td>–</td>
<td>R temporoparietal corticectomy</td>
<td>Y</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>7</td>
<td>II</td>
</tr>
<tr>
<td>27</td>
<td>M</td>
<td>2</td>
<td>27</td>
<td>Y</td>
<td>FCD/R occipital region</td>
<td>R temporoparietal corticectomy</td>
<td>N</td>
<td>B</td>
<td>FCD IIb (*)</td>
<td>5</td>
<td>II</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>5</td>
<td>20</td>
<td>Y</td>
<td>FCD/L premotor cortex</td>
<td>L frontal corticectomy</td>
<td>N</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>3</td>
<td>III</td>
</tr>
<tr>
<td>29</td>
<td>F</td>
<td>3.5</td>
<td>12</td>
<td>Y</td>
<td>FCD/L mesial parietal region</td>
<td>L prefrontal and cingular corticectomy</td>
<td>N</td>
<td>NTW</td>
<td>FCD IIb (*)</td>
<td>7</td>
<td>IV</td>
</tr>
<tr>
<td>30</td>
<td>M</td>
<td>7</td>
<td>31</td>
<td>Y</td>
<td>FCD/L tempo-parieto-occipital region</td>
<td>L occipito-temporal corticectomy</td>
<td>NA</td>
<td>F</td>
<td>FCD IIb (*)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>31</td>
<td>F</td>
<td>14</td>
<td>2</td>
<td>Y</td>
<td>DNET/R middle temporal gyrus</td>
<td>No (surgery proposed to the patient but refused)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>32</td>
<td>M</td>
<td>1.5</td>
<td>22</td>
<td>Y</td>
<td>FCD/L temporo-mesial region</td>
<td>L temporal lobectomy</td>
<td>N</td>
<td>NTW</td>
<td>NDT (ganglioglioma*)</td>
<td>5.5</td>
<td>II</td>
</tr>
<tr>
<td>33</td>
<td>M</td>
<td>12</td>
<td>11</td>
<td>Y</td>
<td>DNET/R superior temporal gyrus</td>
<td>R temporal lobectomy</td>
<td>Y</td>
<td>F</td>
<td>NDT (DNET*)</td>
<td>3.5</td>
<td>la</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>6</td>
<td>10</td>
<td>Y</td>
<td>Ganglioglioma/L temporo-mesial region</td>
<td>L temporal lobectomy</td>
<td>Y</td>
<td>NTW</td>
<td>NDT (DNET*)</td>
<td>6</td>
<td>la</td>
</tr>
<tr>
<td>35</td>
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<td>2.5</td>
<td>38</td>
<td>Y</td>
<td>FCD/L mesial occipital region</td>
<td>L occipito-temporal corticectomy</td>
<td>Y</td>
<td>B</td>
<td>NDT (DNET*)</td>
<td>1</td>
<td>IV</td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>3.5</td>
<td>12</td>
<td>Y</td>
<td>FCD/L parietal operculum</td>
<td>Lesionectomy</td>
<td>N</td>
<td>F</td>
<td>NDT (ANET*)</td>
<td>2</td>
<td>IV</td>
</tr>
</tbody>
</table>

F = female; M = male; N = no; Y = yes; DNET = dysembryoplastic neuroepithelial tumour; FCD = focal cortical dysplasia; HS = hippocampal sclerosis; L = left; R = right; GK = gamma-knife; B = bilateral epileptogenic zone organization; F = focal epileptogenic zone organization; NTW = network epileptogenic zone organization; NA = not applicable; SO = surgical outcome (Engel’s class); *final pathological diagnosis confirmed by histopathology.
Neuro-radiological findings suggestive of FCD were defined as follows: local thickening of a part of the cortex, blurring of the grey matter to white matter interface, and increased signal (in Fluid Attenuated Inversion Recovery and T2-weighted sequences) in the underlying white matter (Barkovich et al., 1988; Sisodiya, 2000; Lee et al., 2001; Urbach et al., 2002; Colombo et al., 2003; Widdess-Walsh et al., 2005), sometimes in a wedge-shaped tail extending radially to the ventricle (‘transmantle dysplasia’) (see example in Fig. 2b). A lesion being located in extra-temporal areas was a supplementary argument in favour of this diagnosis (Palmini et al., 1991, 1994; Hirabayashi et al., 1993; Chassoux et al., 2000).

Diagnosis of NDT could be evoked if particular features were present: a well-demarcated, cortical (rarely both cortical and subcortical), cystic lesion, sometimes heterogeneous, enhanced or not by contrast injection, showing calcifications or adjacent bone erosion (Daumas-Duport, 1993; Raymond et al., 1995; Ostertun et al., 1996; Chassoux et al., 2000; Stanescu Cosson et al., 2001); most of the time, NDT are located in the temporal lobe (Kirkpatrick et al., 1993; Raymond et al., 1995; Degen et al., 2002; Shin et al., 2002; Kral et al., 2003) (see example in Figs 1b and 3b).

All patients had a comprehensive evaluation including detailed history and neurological examination, neuropsychological testing, routine MRI, surface electroencephalography (EEG) and stereoelectroencephalography (SEEG, depth electrodes). SEEG exploration was carried out during long-term video-EEG monitoring, as part of patients’ normal clinical care. Recordings were performed using intracerebral multiple contact electrodes (10–15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) placed intracerebrally according to Talairach’s stereotactic method (Talairach et al., 1992).

In this study, all patients required invasive recordings after the non-invasive phase. In these cases (including patients with temporal lobe lesions), SEEG was indicated when the epileptogenic zone was observed during the non-invasive phase.

**Figure 1** Patient no 36. (A) Sketch of the SEEG exploring the left hemisphere. Each electrode contains 10–15 contacts. Electrode OF investigated the opercular frontal region (external contacts) and the anterior insula (internal contacts). Electrode L’ was placed in the parietal operculum exploring a probable NDT, visible on the MRI (B). The route of electrode L’ is shown on the MRI passing through the lesion. P: parietal electrode reached the posterior part of the cingulate gyrus. T recorded the superior temporal gyrus (lateral contacts) and the insular cortex (temporal part, internal contacts). A recorded the middle temporal gyrus (lateral contacts) and the amygdala (internal contacts). (B) MRI (Flair sequence) showing the lesion (NDT) in the left parietal operculum. (C) SEEG recordings from three regions: L’9–10: bipolar derivation from the lesional site (L’); T7–8: bipolar derivation from the superior temporal gyrus (STG), P7–8: bipolar derivation from the parietal region (P). Below are represented the increase in energy ratio ER[n] in the three SEEG signals from L, STG and P. The Page–Hinkley algorithm provides a detection time (orange marks) for each brain structure if involved in the generation of a rapid discharge. The first detection time is arbitrarily defined as the reference time N0 (L in this case). (D) EI values obtained in seven regions in this patient. Maximal values are observed in L and low values in other regions, corresponding to a very focal onset.
suspected to be larger than the lesion and/or when extratemporal regions were suspected to be involved in temporal lobe seizures (temporoperisylvian or temporal plus seizures) and/or when bilateral-ity was suspected. The placement of electrodes was established, in each patient, based upon available non-invasive information providing hypotheses about the localization of the epileptogenic zone (see examples in Figs 1A, 2A and 3A). Therefore, the number of electrodes and their location were defined for each individual case, including the need to place contralateral electrodes. Pre-planning of the implantation was performed on 3D T_{1} MRI images using dedicated software ('Brainvisa', http://brainvisa.info) for surface rendering calculation, cortical anatomy analysis and sulci labelling (Mangin et al., 2004). The final determination of each electrode trajectory was elaborated on a workstation allowing for stereotactic registration of a preoperative stereotactic MR and a preoperative stereotactic telemetric angiography. The implantation accuracy was controlled per-operatively by telemetric X-ray imaging. A post-operative computerized tomography (CT) scan was then used to verify the absence of bleeding and the position of electrodes. In each patient, video-EEG recording was prolonged as long as necessary to allow recording of several ‘habitual’ seizures. We also performed intracerebral electrical stimulations, thus helping to determine the epileptogenic zone determination and to localize the electrodes with accuracy. Intracerebral electrodes were then removed and an MRI was performed, permitting visualization of the trajectory of each electrode (3D T_{1}-weighted images and T_{2}-weighted coronal images).

**Figure 2** Patient no 23. (A) Sketch of the SEEG exploring the right hemisphere. Electrode CU explored the intraparietal sulcus (external contacts) and the occipital cuneiform gyrus (internal contacts); LI recorded the posterior part of the lateral occipital sulcus on its external contacts and the lingual gyrus on its internal contacts. L was placed in the lesion and reached lateral occipital area (external contacts) and the anterior calcaine fissure (internal contacts). The route of electrode L is shown on the MRI passing through the lesion. Electrode GC was situated in the supramarginalis gyrus and in the isthmus of the cingulate gyrus (on its external and internal contacts, respectively). TO investigated the inferior temporal gyrus (external contacts) and the fusiform gyrus, then the anterior calcaine fissure on its internal contacts. Electrodes B and C explored middle temporal gyrus (external contacts) and the anterior and posterior hippocampus, respectively. TB was placed in the temporobasal area (external contacts) and in the entorhinal cortex (internal contacts). (B) MRI (flair sequence) showing an FCD-like lesion in the right lateral temporo-occipital region. (C) SEEG recordings from three regions: the right entorhinal cortex (TB1-2), the lesion (L10-11), and the right internal occipital region (CU1-2). Below are represented the increase in energy ratio ER[n] in the three SEEG signals. In that case, the first detection time found by the Page–Hinkley algorithm was the one recorded in the lesion (L10–11). (D) EI values obtained in seven regions in this patient. Maximal values are observed in L but EI values >0.4 were also recorded in other structures (entorhinal cortex, internal occipital region, supramarginale gyrus and fusiform gyrus), corresponding to a network epileptogenic zone organization.
Siemens 1.5 T). Finally, CT scan/MRI data fusion was performed to accurately check the anatomical location of each contact along the electrode trajectory.

Signals were recorded on a 128 channel Deltamed™ system. They were sampled at 256 or 512 Hz and recorded on a hard disk (16 bits/sample) using no digital filter. Two hardware filters were present in the acquisition procedure. The first is a high-pass filter (cut-off frequency equal to 0.16 Hz at -3 dB) used to remove very slow variations that sometimes contaminate the baseline. The second is an anti-aliasing low-pass filter (cut-off frequency equal to 97 Hz at 256 Hz or 170 Hz at 512 Hz).

**Signal analysis: definition and computation of the EI**

The EI was first proposed in a recent study (Bartolomei et al., 2008), where a detailed description is provided. In this section, we provide a short summary of the main features of this index, along with the main methodological aspects. The EI is a normalized quantity (ranging from 0 to 1) computed from depth-EEG signals. This quantity accounts for both (i) the propensity of a given brain structure to generate a rapid discharge; and (ii) the delay of involvement of this structure with...
respect to seizure onset. Indeed, it is generally accepted that these two features (high frequency oscillations and delay of involvement) are relevant indicators of the epileptogenic nature of the recorded underlying neuronal systems. From a methodological viewpoint, the EI can be estimated using a two-stage procedure.

First, the signal energy ratio (ER) between high [β(12.4–24 Hz) and γ(24–90 Hz)] and low [θ(3.4–7.4 Hz) and α (7.4–12.4 Hz)] frequency bands of the EEG is computed, over a sliding window, from the signal spectral density $\Gamma(w)$ (squared modulus of its Fourier transform):

$$ER[n] = \frac{E_\beta + E_\gamma}{E_\delta + E_\alpha}$$

where

$$E_{\text{sub-band}} = \int_{\text{sub-band}} \Gamma(w) dw$$

where ‘sub-band’ denotes the θ, α, β and γ frequency sub-bands classically used to categorize rhythms reflected by EEG signals and where $n$ denotes the current position of the window, in time (Figs 1C, 2C and 3C).

Second, change-points are detected in the $ER[n]$ quantity which is sensitive to frequency changes in the signal. This detection is automatic. It makes use of an optimal algorithm (‘cumulative sum algorithm’ or ‘CUSUM’) (Hinkley, 1970, p. 1954) to determine the time instant when $ER[n]$ increases significantly, i.e. when θ–α activity (that is predominant in background SEEG signals) changes into β–γ activity (that is predominant in SEEG signals during rapid discharges) (Figs 1C, 2C and 3C).

These two steps allow for the computation of the EI, from the SEEG signal $s_i$ recorded from brain structure $S_i$:

$$EI_i = \frac{1}{N_0 - N_0 + \tau} \sum_{n=N_0}^{N_0+H} ER[n], \quad \tau > 0$$

where $N_0$ is the time instant corresponding to seizure onset (defined hereafter), $N_0$ is the detection time in signal $s_i$ recorded from structure $S_i$, and $H$ is the time interval over which $ER[n]$ is integrated. From this equation, it can be observed that the sooner structure $S_i$ gets involved in the seizure, the higher the index $EI_i$.

Parameter $\tau$ accounts for the particular where $S_i$ is the first structure that generates the fast activity ($N_0 = N_0$, seizure onset) and avoids division by zero. It was arbitrarily set to 1. Another particular case is when structure $S_i$ does not generate fast activity. In this case, $N_0$ is set to be equal to the time corresponding to seizure termination. This operation leads to a very low value of $EI_i$, as expected. Parameter $H$ was set to be equal to 5 s. This value corresponds to the average duration of rapid discharges. Finally, in order to obtain a normalized value ranging from 0 (no epileptogenicity) to 1 (maximal epileptogenicity) for considered structures $S_i$, EI values were divided by the maximal value obtained in each patient. In the sequel, normalized EI values are simply denoted by ‘EI values’.

Statistical analysis

Statistical analysis was performed (i) to assess potential links between the epileptogenic zone organization (as characterized by EI values) and some clinical, neuroradiological or histopathological parameters; and (ii) to determine, among these potential factors, the one(s) that could influence post-operative prognosis.

Due to the amount of data to be processed, only one seizure (considered as representative of the patient’s usual seizures) was analysed for EI determination. The epileptogenic zone organization was considered as being either focal, network or bilateral. Focal organization corresponded to a situation where seizures were generated by only one structure characterized by an EI value $>0.4$. Network organization was considered present in situations where seizures originated in at least two distant structures disclosing EI value $>0.4$. Finally, bilateral epileptogenic zone organization corresponded to seizures whose onset rapidly involved homotopic regions (disclosing EI $>0.4$). The localization of the lesions and the epileptogenic zone was defined as frontal, temporal or ‘posterior’ (grouping together parietal and occipital cases). In order to evaluate the relationship between epileptogenicity and distance between studied sites, we estimated the Euclidian distance between the recorded regions and compared with EI values.

Statistical analysis was performed in order to compare the data between different groups using a rank-analysis of variance (Kruskal–Wallis) for quantitative data. Bivariate analysis used the non-parametric Mann–Whitney test. Chi square (or Fisher’s exact test when appropriate) was used for qualitative data. An analysis with logistical regression was realized in order to determine factors potentially influencing the epileptogenic zone organization. A $P$-value smaller than or equal to 0.05 was considered to be statistically significant. Statistical tests were realized with the software statistical package for the social sciences (SPSS) for Windows, version 13.1 and Statview 5.0. for Windows.

Results

Clinical data

Clinical data are summarized in Table 1. Thirty-six patients were included in the study (15 males and 21 females). Mean age at epilepsy onset was 6.6 years (range 6 months–17 years; SD 4.7) and mean epilepsy duration was 19.2 years (range 2–45 years; SD 10). Among the 36 patients, 8 had a normal MRI despite repeated explorations. For the patients whose MRI was abnormal, several features could be found, suggestive of FCD (24 cases), or of DNET/ganglioglioma (four cases). Ten MRI-visible lesions were located in the frontal lobe (three in the precentral cortex), nine in the temporal lobe and nine in posterior cortices (parietal, occipital, or parieto-occipital region).

Following SEEG, 33/36 patients went on to have surgical or radio-surgical treatment. Surgery was contraindicated in one patient because of involvement of the language area (left temporo-basal FCD); one patient refused surgery and another is awaiting surgery. Among the 33 patients, radiosurgery was proposed in three cases, targeting the visible MRI lesion, also determined as the epileptogenic zone: two cases of probable dysplastic lesions of the primary motor cortex and one case of NDT located in the visual cortex (calcarine region). Poor outcome was observed in these three cases but low doses were used to avoid functional deficit (three are in class IV).

Thirty patients underwent surgical resection, the limits of which were accurately defined and tailored for each patient on the basis of SEEG. Most of them underwent cortectomy (23 cases); six patients had lobectomy (mainly temporal anterior lobectomy), one had lesionectomy with peri-operative ECoG. Mean follow-up was 4.1 years (min = 6 months to max = 7 years; SD 2.24). Two cases with a follow-up of less than 1 year were not included in the
Histopathological analysis. Thus surgical results involve 28 patients. Among 28, 16 patients were in class I (15 IA, 1 IB) (57.2%); 5 (17.8%) in class II and 7 (25%) in class III or IV. Age at epilepsy onset was lower in the non-seizure free (NSF) group [NSF 4.5 versus seizure free (SF) 8.5; \( P = 0.03 \), Mann–Whitney] but duration of epilepsy before surgery was not significantly different (\( P = 0.44 \), NSF 20.2 versus SF 19.2).

In 75% of all cases (21/28 patients with surgical treatment), resection of the lesion was considered as complete, based on peri-operative neurosurgical record and on post-operative MRI. In these cases, 76% (16/21) were in Engel class I whereas, if resection was incomplete, 84% (6/7) were in class III or IV. Thus, the complete resection of the lesion was significantly associated with a better seizure outcome (\( P = 0.0004 \)).

Histopathological features

Histopathological diagnosis was available in 30 patients (for three patients who underwent gamma-knife, histopathological study was not available). For the eight patients with normal MRI, analysis of the resection piece displayed features of FCD and 6/8 were Taylor-type FCD (FCD-II).

As shown in Table 1, the most common histopathological diagnosis after surgical resection was FCD in 23/30 patients (77%), and more frequently FCD II, representing 47% of our population (14 patients). FCD I was found in 23% of all cases (seven patients); five cases could be included as NDT, three DNET (10%), one ganglioglioma (3.3%) and one case with histopathologic diagnosis of angiocentric glioma, a newly described lesion (Louis et al., 2007) that corresponds to benign developmental lesions or low-grade tumours, with long-standing epilepsy and low proliferation indices on histopathology, without malignant evolution in most cases (Preusser et al., 2007, Sugita et al., 2008). Other diagnoses included two cases with non-specific changes (gliosis) despite very suggestive MRI appearances of FCD. No positive correlation was found between histopathological findings and post-operative outcome (\( P = 0.19 \), Fisher’s exact test).

In the group of patients for whom both MRI and histopathological diagnosis was available (\( n = 15 \)), we found that FCD was over-represented in the frontal lobe (6/15, 40%). Only five patients (33%) displayed an FCD in the temporal lobe and the remaining four (27%) were located in posterior regions. Other lesional types (DNET, ganglioglioma) were preferentially located in the temporal lobe.

Finally, after MRI or/and histopathological analysis, we retained the diagnosis of FCD in 30 patients and of NDT in six patients; these patients were included in the signal analysis study. When analysing post-operative outcome in this group, only 26 FCD and 5 NDT could be evaluated (three non-operated patients and two with a follow-up after <1 year); in the FCD group, 14/26 were in class I according to Engel’s score (55%), 4/26 were in class II (15%) and 8/26 were in class III or IV (30%). If we only consider patients with conventional curative surgery (excluding three palliative radiosurgical procedures, all in class IV) the proportion of FCD patients in class I was 61% (14/23 patients). When strictly considering FCD diagnosis assessed by histopathological findings (23 patients) and removing the two patients with <1 year follow-up, we found 57% patients (12/21) in class I, 19% (4/21) in class II, and 24% (5/21) in class III or IV.

SEEG signal analysis

SEEG recordings (average = 7.5 electrodes per patient) permitted to localize the epileptogenic zone in all selected patients; the frontal lobe was the most frequently involved at seizure onset (17 patients, 48%). The implantation of contralateral electrodes was required in the majority of patients (20/26) including 10/17 patients with the epileptogenic zone located in the frontal lobe, 4/9 patients with the epileptogenic zone in the temporal lobe, and 6/10 patients with the epileptogenic zone located in posterior regions.

For 19 patients (52.7% of all cases), seizure started in the right hemisphere and in the left hemisphere for 14 patients (38.8%). Rapid involvement (<1 s) of contralateral homotopic regions was observed in 3 patients.

Organization of the epileptogenic zone

In order to determine the epileptogenicity of analysed brain areas, we selected several cortical areas structures (hereafter named ‘structures’, seven per patient) that were crucial for understanding the anatomo-functional organization of involved systems. In agreement with the characteristics of our population, these structures differed from one patient to another (online supplementary table).

Among the recorded structures, some were considered as ‘lesional’ when contacts of the electrodes were localized in (or near) the lesion visible on MRI or disclosed neurophysiological features highly suggestive of FCD (such as focal slow waves or seizure like patterns) in the group with ‘negative-MRI’ (Chassoux et al, 2000). The EI was then calculated for each selected structure. Mean EI value, averaged over all the structures, was 0.379 (±0.35). Mean EI in lesional regions was 0.87 (±0.25) and 0.29 (±0.30) in ‘non-lesional’ structures (\( P < 0.001 \), Mann–Whitney). This result confirmed the intrinsic epileptogenic nature of the studied lesional sites. In addition, and as shown in Fig. 4A, values for FCD tended to be higher than values for NDT (\( P = 0.07 \), Mann–Whitney). Values for FCD are grouped around 1 (mean 0.85; median 1; SD 0.31), while more dispersion is observed for NDT (mean 0.60; median 0.56; SD 0.36). In addition, results suggest that intrinsic epileptogenicity is probably higher for FCD than neurodevelopmental tumour.

These findings prompted us to define an accurate cut-off of EI values above which we could reasonably postulate that a structure is highly ‘epileptogenic’. Figure 4B shows a box plot representation of EI values in the lesional and extra-lesional sites. Since lesional sites are also epileptogenic in this subset of patients, we established this limit as EI > 0.4. This value corresponded to the 90th percentile of EI values in the lesion. Therefore, most of the lesional sites disclose values greater than 0.4. This value is close to the cut-off value chosen in our previous study in patients with mesio-temporal lobe epilepsy (Bartolomei et al., 2008). However, as illustrated in Fig. 4B, a large number of structures in extra-lesional sites also have values greater than 0.4.
This strongly suggests that epileptogenicity extends beyond the limit of the visible lesion in a large number of patients.

We then studied, for each patient, the number of highly epileptogenic structures (involved in the epileptogenic zone) as defined by an EI value $\geq 0.4$ (denoted by $N_{el \geq 0.4}$). The mean $N_{el \geq 0.4}$ was 3.14 (±1.87) in the whole population.

We analysed the type of epileptogenic zone organization for each patient according to our definition of focal, network and bilateral epileptogenic zone organization as described above (see ‘Materials and methods’ section). Figure 5A discloses histograms of the distribution of $N_{el \geq 0.4}$ in the whole population. We found that 11 patients had only one epileptogenic structure ($N_{el \geq 0.4} = 1$), therefore disclosing a strictly focal epileptogenic zone organization (31%). Figure 1 shows one typical example of focal organization.

In 25 patients, more than one area belonged to the epileptogenic zone. Among them, 22 disclosed a network epileptogenic zone organization (61%) (see example in Fig. 2) and three a bilateral epileptogenic zone representation (8%) (see example in Fig. 3). Therefore, the majority of patients with FCD or NDT were characterized by a network organization of the epileptogenic zone. We observed a significant inverse relationship between EI values and distances between lesional site and other studied regions ($P < 0.0001$). However, the mean distances were not different considering sites disclosing high EI ($>0.4$) versus sites disclosing EI $<0.4$ ($Ei > 0.4$: mean $40.59 \pm 17$ mm; $Ei < 0.4$: $40.32 \pm 24$ mm, $P = 0.54$).

**Relationship between clinical data, histopathological parameters and epileptogenic zone organization**

We looked at whether the epileptogenic zone organization was correlated with clinical parameters. We first looked for a
correlation between epilepsy duration or age at epilepsy onset and the number of structures displaying a high El ($N_{EI > 0.4}$) using Spearman’s correlation test. No significant relationship was found for epilepsy duration ($P = 0.21$) or for age at onset ($P = 0.93$).

In the same way, we did not find significant differences in these two parameters between the three epileptogenic zone organization types ($P = 0.28$, age at onset; $F = 2.4$, $P = 0.09$ epilepsy duration, Kruskal Wallis). We were unable to find any statistical correlation between histopathological features and the organization of the epileptogenic zone (FCD versus other diagnoses, $P = 0.39$, Chi square; FCD I versus FCD II, $P = 0.72$, Chi square).

Since, in our first study using El quantification in mesio-temporal lobe epilepsy (Bartolomei et al., 2008), we found a relationship between epilepsy duration and the number of epileptogenic structures, we looked at whether differences could be found by separately analysing FCD affecting mesial temporal structures and FCD in other locations. Figure 6 shows the relationship between epilepsy duration and $N_{EI > 0.4}$ in the temporal lobe, frontal lobe and posterior locations (defined as epileptogenic area including the lesional site located in the occipital or/and parietal areas). No relationship was found in frontal and posterior location (frontal lobe $P = 0.96$; posterior regions $P = 0.97$, Spearman). In contrast, for mesial temporal localization, a significant relationship was found between the epilepsy duration and the number of structures displaying a high El ($P = 0.02$).

A test of logistical regression with multivariate analysis was performed to see if clinical features (sex, age at epilepsy onset, epilepsy duration, lobar location of epileptogenic zone, presence or not of a visible lesion on MRI) influenced the type of epileptogenic zone organization. We did not find any significant relationship for the analysed parameters [age at epilepsy onset: $P = 0.94$; epilepsy duration: $P = 0.29$; lobar location of epileptogenic zone (frontal: $P = 0.50$; temporal: $P = 0.89$; posterior: $P = 0.72$); presence or not of a visible lesion on MRI: $P = 0.76$].

In addition, when comparing FCD and NDT, the number of structures displaying a high El ($N_{EI > 0.4}$) was not significantly different even though we observed a tendency for NDT to be more focal (mean $N_{EI > 0.4} = 2.1 \pm 1.8$) than FCD (mean $N_{EI > 0.4} = 3.8 \pm 1.7$) ($P = 0.08$, Mann–Whitney).

### Relationship between epileptogenic zone organization and surgical outcome

We then looked at whether the epileptogenic zone organization was a potential factor influencing surgical outcome. The number of epileptogenic structures ($N_{EI > 0.4}$) was not significantly different with regard to surgical outcome (SF = 3.2, NSF = 3.4; $P = 0.80$). We observed a trend for a difference in seizure outcome according to the type of organization ($P = 0.06$, Chi square, Fig. 5B). Indeed, 57% of patients with network organization and 87% with focal organization were seizure-free, while none of those with bilateral organization became seizure-free.

### Discussion

This article is based on the study of 36 patients suffering from focal pharmacoresistant epilepsy related to FCD or NDTs, investigated with SEEG during their pre-surgical evaluation. The main objective was to quantify the epileptogenicity of the lesional...
lesion is crucial for a good post-operative outcome, and increases published results [different population sizes, patient selection (heterogeneous and this may explain the discrepancies between included in these different studies were, however, notably mean follow-up of 4 years. Moreover, all FCD-I patients with pathological features and post-operative outcome, but the fact surgery (about 40% class I) has also been reported in older other studies, ranging from 64% to 79% (Chassoux et al., 2000; Tassi et al., 2001; Colombo et al., 2003; Alarcon et al., 2006; McConigal et al., 2007). Another interesting fact is that six cases in the present series had FCD-II (‘Taylor-type FCD’), a result that differs from previous studies where FCD was of type I when MRI was normal (Kresk et al., 2008a; Chassoux, 2008).

In the whole FCD group, 55% were in class I according to Engel’s score, but if we focus on the post-operative outcome in the patients who underwent curative surgery, the results were slightly better (61% in class I). This post-operative outcome is close to the proportion of FCD patients in class I observed in other studies, ranging from 64% to 79% (Chassoux et al., 2000; Tassi et al., 2001; Urbach et al., 2002; Cohen-Gadol et al., 2004; Kral et al., 2007). Less favourable outcome after FCD surgery (about 40% class I) has also been reported in older studies (Sisodiya, 2000).

In our population, no relationship was found between histopathological features and post-operative outcome, but the fact that the FCD-II group was over-represented in our population is an important bias. However, post-operative outcome in our FCD-I group was good as 4/6 patients (67%) were in class I after a mean follow-up of 4 years. Moreover, all FCD-I patients with complete resection of the lesion were in class I. The populations included in these different studies were, however, notably heterogeneous and this may explain the discrepancies between published results [different population sizes, patient selection (children/adults), follow-up duration, or histopathological classification].

Our study confirms that, in FCD, complete resection of the lesion is crucial for a good post-operative outcome, and increases the percentage of patients in class I from 57% to 76%. The importance of this factor has already been demonstrated in FCD (Chassoux et al., 2000; Edwards et al., 2000; Cohen-Gadol et al., 2004; Krsek et al., 2009) and other lesional types, like NDTs (Aronica et al., 2001, 2007; Lee et al., 2001; Nolan et al., 2004). Another important positive prognosis factor is an older age at epilepsy onset (after 8.5 years old), a finding previously described (Palmini et al., 1991; Hirabayashi et al., 1993; Polkey, 1996; Wyllie, 1998).

Quantification of the epileptogenic zone and intrinsic epileptogenicity

We propose a quantification of brain structure epileptogenicity associated with FCD or NDT. The quantity is based on signal analysis of rapid discharges (high frequency oscillations) observed at seizure onset (Allen et al., 1992; Alarcon et al., 1995; Wendling et al., 2003; Worrell et al., 2004; Jirsch et al., 2006). To this aim, we have used a quantity that combines the signal energy in defined frequency bands (appearance of beta–gamma oscillations concomitantly with the attenuation of slower alpha–theta oscillations) and the delay with which rapid discharges occur. It is noteworthy that several experimental (Traub et al., 2001) and computational modelling (Wendling et al., 2005) studies have also demonstrated the existence of a relationship between the epileptogenicity of the neuronal tissue and its propensity to generate fast oscillations. EI values were found to be higher in the lesional sites for a great majority of patients. This result adds further confirmation that FCD and NDT are intrinsically epileptogenic as suggested by earlier reports (Ferrer et al., 1992; Mattia et al., 1995, Palmini et al., 1995, Morioka et al., 1999; Hong et al., 2000; Otsubo et al., 2005). In addition, this result indicates that the EI method is well-suited to quantify the epileptogenicity of a brain structure. Furthermore, our statistical analysis showed that intrinsic epileptogenicity in FCD tends to be higher than in NDT, a result in agreement with previous studies (Palmini et al., 1995; Rosenow et al., 1998).

Even if the lesional sites are generally the ones disclosing highest epileptogenicity, our study highlights the fact that, in these patients, distant sites may also show early involvement by rapid discharges. As mentioned above, these properties allow these regions to be defined as highly epileptogenic and, therefore, part of the epileptogenic zone. According to this assumption, we defined the three different types of organization of the epileptogenic zone: ‘focal’, ‘network’ and ‘bilateral’. The ‘focal’ category was defined by a very focal onset within a single epileptogenic structure. This could be seen as corresponding to the classical notion of an epileptic ‘focus’ and accounted for 31% of our patients. In 8% of cases we observed a bilateral organization, these three cases corresponding to posterior epilepsies. The majority of patients (61%) had a more complex organization (‘epileptogenic network’), with at least two distant sites disclosing high epileptogenicity. This number is particularly high with regard to previous studies that generally consider that in FCD, the lesional and epileptogenic zones tend to co-localize, albeit without quantification of this aspect (Chassoux et al., 2000; Tassi et al., 2001, 2002; Kresk et al., 2008a, b).
In addition, it is now well-established that the epileptogenic zone can be more extended than the visible lesion on MRI (Ferrier et al., 2001; Tassi et al., 2002, Colombo et al., 2003, Francione et al., 2003, and/or histopathological findings (Tassi et al., 2001). In the paper by Chassoux et al. (2000), using the same SEEG approach, ~20% of patients with FCD were considered to have a larger epileptogenic zone than the dysplastic cortex. In a more recent paper (Widdess-Walsh et al., 2007) the role of subdural grid evaluation for FCD was studied. The authors found that a diffuse, non-localized onset was found in 30% of cases and that a complex pattern (with two or three sites of onset) may be observed in 41% of patients.

Nevertheless, despite the fact that it is has been suggested that the epileptogenic zone is often larger than the visible lesion, a focal organization is still considered to be the rule in FCD. Our study is the first to quantify precisely the epileptogenicity of these lesions and thus to demonstrate that the epileptogenicity may affect remote regions, distant from the lesional site. In addition, the extent of the epileptogenicity appears to be a prognostic factor for post-operative outcome since a focal organization was associated with a better Engel's score. On the opposite, bilateral epileptogenicity was always associated with unfavourable outcome.

Interestingly, we found a propensity for patients with frontal lesions to develop a network epileptogenic zone organization rather than a focal one. These findings are in agreement with human in vivo studies showing large functional connections within the frontal lobes and between the two frontal lobes (Lacruz et al., 2006). Besides, in our study, posterior cases often show bilateral organization. It is known that posterior epilepsies tend to present diffuse or even bilateral interictal spikes on surface EEG (Gavaret et al., 2008). Only a few studies (Krsek et al., 2008b) have reported that, in FCD patients, ictal EEG can show early bilateral discharge, but to our knowledge no case with bilateral posterior ictal onset in a patient with FCD has yet been reported. Rapid multilobar involvement has been more frequently described (Chassoux et al., 2000). The extension of the epileptogenic zone to involve contralateral homotopic structures by a secondary epileptogenic process appears to be the most probable mechanism. The high functional and anatomical connectivity between posterior regions (Clarke and Miklossy, 1990; Riedel et al., 2004; Peltier et al., 2007; Teipel et al., 2008) may support this phenomenon. We cannot, however, rule out the possibility that posterior cases with bilateral seizure onset could be due to bilateral FCD, but, in these particular cases, as the patients are never operated bilaterally, we do not have any histopathological data available from the contralateral lobe. Indeed, bilateral FCD can occur (Hong et al., 2000), especially in posterior regions (Chassoux et al., 2000; Fukui et al., 2001; Francione et al., 2003; Fogarasi et al., 2004).

In our FCD population, we failed to identify clear clinical or histological factors influencing the type of organization of the epileptogenic zone. In contrast to previous observations in mesio-temporal lobe epilepsy (Bartolomei et al., 2008), we did not find a correlation between epilepsy duration and the extension of the epileptogenic zone. However, this result may be due to differences in the localization of the epileptogenic zone. Indeed, a significant trend for a relation between epilepsy duration and extension of the epileptogenicity ($N_{E1>0.4}$) was observed in the cases affecting mesial temporal lobe. This result is in agreement with previous studies showing a positive correlation between epilepsy duration and development of pharmacoresistance, in lesions such as DNET and gangliogliomas, mainly affecting the temporal lobe (Weissman et al., 1996; Itoh et al., 1997; Lanzieri et al., 1997; Chassoux et al., 2000; Aronica et al., 2001; Hennessy et al., 2001; Valenti et al., 2002; Luyken et al., 2003; Nolan et al., 2004). The underlying mechanisms are probably related to the synaptic alterations observed during secondary epileptogenesis (Khallov et al., 2003). The features observed in the ‘network’ organization of the epileptogenic zone are indeed reminiscent of those seen in secondary epileptogenesis processes, which occur not only at the site of a lesion but also in distant areas in animal models (Morrell, 1959; Wilder et al., 1969) and in humans (Morrell, 1985, 1989).

It is interesting that secondary epileptogenesis is easier to induce in limbic temporal lobe structures than in other sites in the brain (Niedieck et al., 1990, Hirsch et al., 1991a,b; Parent et al., 1997; Bertram, 2007) and can lead to a mirror focus (Wilder et al., 1969; Morrell, 1985). These processes seem to mainly affect younger subjects, in both animal (Fanelli and McNamara, 1986) and human studies (Morrell, 1985), thus suggesting that the earlier the onset of epilepsy, the higher the risk of secondary epileptogenesis.

**Concluding remarks**

This study has concluded that the EI can be a useful tool for quantifying and defining the epileptogenicity in FCD and neuro-developmental tumour. We found that many cerebral structures are involved at seizure onset (on average, more than three per patient). A majority of patients (61%) had a network epileptogenic zone organization, showing that most of these ‘focal’ lesions display an epileptogenic zone that involves other structures, often distant ones; bilateral organization can also be seen, especially in posterior FCD. The precise determination of the epileptogenic zone is an important prognostic factor and with the help of the EI, we could confirm that epileptogenic zone organization influences surgical outcome. Furthermore, the number of epileptogenic structures increased with epilepsy duration in the mesio-temporal epileptic cases, which raises the issue of secondary epileptogenesis in this population of pharmaco-resistant epileptic patients.

**Supplementary material**

Supplementary material is available at *Brain* online.

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