Epileptogenicity of cortical dysplasia in temporal lobe dual pathology: an electrophysiological study with invasive recordings

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Hippocampal sclerosis is often associated with macroscopic or microscopic dysplasia in the temporal neocortex (TN). The relevance of such a dual pathology with regard to epileptogenesis is unclear. This study investigates the role of both pathologies in the generation of ictal and interictal activity. Ictal (113 seizures) and interictal data from invasive EEG recordings with simultaneous depth electrodes in the hippocampus and subdural electrodes over the TN were analysed retrospectively in 12 patients with variable degrees of hippocampal sclerosis and different types of histologically confirmed temporal cortical dysplasia [all male, age at epilepsy onset <1–29 years (mean 9.6 years), age when invasive recordings were performed 6–50 years (mean 28.2 years)]. Of the seizures 41.3% arose from the amygdala/hippocampus complex (AHC), 34.7% from the TN, 22% were simultaneously recorded from AHC and TN (indeterminate seizure onset), and 2% from other regions. In three patients, seizure onset was recorded only from the AHC. In patients with severe hippocampal sclerosis only 12% of the seizures arose from the TN, whereas in patients with mild hippocampal sclerosis 58% arose from the TN. The type of cortical dysplasia, however, did not predict seizure onset in the AHC or TN. Propagation time from the TN to the AHC tended to be shorter (mean 7.4 s) than vice versa (mean 13.7 s). The most common initial ictal patterns in the AHC were rhythmic beta activity (<25 Hz) and repetitive sharp waves, and in the TN were fast activity (>25 Hz) and repetitive sharp waves. The interictal patterns over the TN were similar to those seen over extratemporal focal cortical dysplasias. Simultaneous recordings from the hippocampus and the TN strongly suggest that dysplastic tissue in the TN is often epileptogenic. The quantitative contribution of the hippocampus to seizure generation corresponded with the degree of hippocampal pathology, whereas different subtypes of cortical dysplasia did not affect its relative contribution to seizure generation and even mild forms of dysplasia were epileptogenic.

Keywords: hippocampal sclerosis; focal cortical dysplasia; invasive EEG recording; epileptogenesis

Abbreviations: AHC = amygdala/hippocampus complex; FCD = focal cortical dysplasia; mMCD = mild malformations of cortical development; MTD = mild mesial temporal damage; non-REM = non-rapid eye movement; TN = temporal neocortex

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Introduction

An association of hippocampal sclerosis with macroscopic or microscopic cortical dysplasia in the temporal lobe has recently been discovered as a quite common pathology and has come into the focus of interest. Histologically, dysplastic features such as columnar and laminar disorganization, clusters of disorganized and misshaped neurons and rarely also balloon cells are found in the neocortical temporal cortex in 10–50% of patients with hippocampal sclerosis (Prayson et al., 1996; Kasper et al., 2003; Diehl et al., 2004; Kalnins et al., 2004).

Although this dual pathology of the temporal lobe is frequently observed in epilepsy patients, the clinical significance of the dysplastic tissue in the neocortical temporal lobe, in particular its epileptogenesis, remains unclear (Reynolds, 1987; Raymond et al., 1994; Holmes et al., 1998; Huang et al., 1999; Thom et al., 2001). Reports on the post-operative outcome of these patients are controversial. Early studies reported that patients with hippocampal sclerosis and associated microscopic cortical dysplasia have a higher risk for seizure recurrences after epilepsy surgery (Engel, 1992;
Palmini et al., 1994) as compared with patients with mesial temporal sclerosis only. More recent investigations, however, could demonstrate that these patients can have a very favourable outcome provided that both pathologies were removed (Thom et al., 2001; Srikijvilaikul et al., 2003; Fauser et al., 2004; Kalnins et al., 2004). Post-surgical outcome data alone leave open questions regarding the relative contribution of both pathologies to ictogenesis. Simultaneous invasive recordings from both the hippocampus and the temporal neocortex (TN) may provide additional information on this topic and thus contribute to a better understanding of the clinical significance of such dysplastic tissue in the neocortical temporal lobe. Electroclinical data of invasive EEG recordings in patients with hippocampal sclerosis associated with microscopic cortical dysplasia of the temporal lobe have not been reported until now.

In the present study we analysed ictal (113 seizures) and interictal data in 12 patients with variable degrees of hippocampal sclerosis associated with different types of cortical dysplasia in the temporal lobe who underwent invasive video EEG recordings. All of them were simultaneously implanted with subdural strip electrodes or grid electrodes over neocortical areas (temporo-lateral/basal) and depth electrodes in the amygdala/hippocampus complex (AHC).

Patients and methods
A total of 12 patients with pharmacoresistant epilepsy were included in the study, 11 of them with histologically confirmed dual pathology of the temporal lobe and 1 additional patient with histologically confirmed hippocampal sclerosis and typical MRI features of transmantle dysplasia. In all of them, invasive video EEG monitoring was performed simultaneously with subdural electrodes over the TN and depth electrodes in the AHC (see Presurgical evaluation) between May 1998 and October 2004. The data were analysed retrospectively.

Demographical data
All investigated patients were of male gender. The age at epilepsy onset ranged from <1 to 29 years (mean 9.6 years, median 8 years), and the age when invasive recordings were performed ranged from 6 to 50 years (mean 28.2 years, median 33 years).

Presurgical evaluation
Presurgical evaluation was performed in the Epilepsy Center at the University hospital of Freiburg, Germany. All patients underwent presurgical MRI. MRI scans were acquired with a 1.5 T scanner (Siemens magnetom Vision or Siemens Magnetom Symphony, Erlangen, Germany). The following sequences were performed: $T_1$-weighted images with and without gadolinium-DTPA, $T_2$-weighted images, fluid-attenuated inversion recovery images and magnetization-prepared rapid gradient echo sequences. Additionally, axial images were acquired with a modified angulation parallel to the long axis of the temporal lobe to evaluate the mesio-temporal structures. MRI criteria suggestive for focal cortical dysplasia were gyration anomalies, focal thickenings of the cortex, blurring of the grey–white matter junction, and abnormal cortical and subcortical signal intensity.

Invasive video EEG monitoring was indicated because patients were cryptogenic in the MRI (2 patients), had an additional lesion in the frontal lobe (2 patients), had cortical dysplasia temporo-posterior in the dominant hemisphere (1 patients), had a frontal semiology with hypermotor seizures and a wide fronto-temporal field of seizure onset on scalp EEG (3 patients), had a parieto-occipital or temporo-posterior seizure onset on scalp EEG (2 patients), had a bilateral seizure onset (1 patient) or because a very circumscribed resection was aimed at (1 patient).

Multicontact depth electrodes (Ad-tech®, Racine, WI) were inserted into the hippocampus from a posterior approach in all 12 patients. Depth electrode recordings were performed with 10 contacts in 10 patients and with 5 contacts in 2 patients. Two to four temporo-basal subdural strip electrodes and one to four temporo-lateral subdural strip electrodes were inserted in all 12 patients. Temporo-lateral double-stripe electrodes (6 patients) or grid electrodes (2 patients) overlying also temporo-posterior, occipital or parietal areas were used when seizure onset was suspected outside the temporal lobe. Additional fronto-basal (3 patients), fronto-lateral (3 patients) or interhemispheric subdural strip electrodes (2 patients) were used in patients with frontal semiology or an additional frontal lesion. Mean total number of recording sites was 58.5.

EEG recordings and analysis
EEG data acquisition was performed with a Neurofile NT digital video EEG system (It-med, Usingen, Germany), with 128 channels, 256 Hz sampling rate and a 16 bit analogue-to-digital converter. Data were band pass filtered between 0.53 and 80 Hz.

EEG-analyses were performed by two board-certified electroencephalographers. Mean video EEG recording period was 7 days (range 2–13 days). In each patient, the first 10 recorded seizures were analysed. In 4 patients, in whom <10 seizures were recorded, all available seizures ($n = 7$–$9$ seizures, see Table 1) were considered. Complex partial seizures, simple partial seizures and subclinical seizure patterns were included. The ictal pattern was analysed in the area of seizure onset and in the area of the second lesion after propagation (e.g. the AHC in seizures arising from the dysplastic TN or the dysplastic TN in seizures arising from the AHC). Ictal patterns were classified as rhythmic spikes/sharp waves, rhythmic $\alpha$ activity, rhythmic $\beta$ activity, rhythmic $\theta$ activity, rhythmic $\delta$ activity, fast activity ($>25$ Hz) including low amplitude fast activity (lafa) and depression in amplitude. In our analysis, we have classified electrographic patterns as subclinical ictal patterns if such patterns showed evolution in frequency and/or topography (in contrast to the interictal patterns without evolution shown in Fig. 1). Subclinical ictal patterns included in the analysis occurred after the initial day of placement of intracranial electrodes. Exclusion of subclinical seizures ($n = 13$) did not significantly change the overall results.

Additionally, interictal activity was investigated in the TN. Interictal activity was classified as isolated spikes, repetitive spike pattern, paroxysmal fast pattern and slow repetitive spike pattern (Boonyapisit et al., 2003) (Fig. 1). Interictal patterns were analysed during wakefulness and during non-rapid eye movement (non-REM) and REM sleep. As additional recordings with scalp electrodes were not available for the whole recording period and the first 10 seizures were considered, an analogous correlation of ictal data to wakefulness and sleep was not performed.
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>MRI diagnosis</th>
<th>Histology</th>
<th>Number of evaluated seizures</th>
<th>Seizure onset</th>
<th>Propagation time</th>
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<tbody>
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<td>1</td>
<td>Cryptogenic</td>
<td>FCD 1b, HS Wyler 1</td>
<td>10</td>
<td>TN: 5</td>
<td>TN-&gt; AHC: 1.2 s</td>
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<td>2</td>
<td>FCD left temporal</td>
<td>FCD 2b, HS Wyler 1</td>
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<td>TN: 9</td>
<td>TN -&gt; AHC: 11.4 s</td>
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<td>3</td>
<td>FCD temporo-polar, insular, mesiofrontal left, HS left</td>
<td>FCD 1b, HS Wyler 3</td>
<td>10</td>
<td>TN: 0</td>
<td>AHC -&gt; TN: 11.4 s</td>
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<tr>
<td>4</td>
<td>FCD occipito-temporal and frontoparasagittal, HS right</td>
<td>HS Wyler 3</td>
<td>10</td>
<td>TN: 0</td>
<td>AHC -&gt; TN: 1.5 s</td>
</tr>
<tr>
<td>5</td>
<td>Very discrete FCD temporo-polar, discrete HS left</td>
<td>FCD 1b, HS Wyler 1</td>
<td>9</td>
<td>TN: 7&lt;sup&gt;*&lt;/sup&gt;</td>
<td>TN -&gt; AHC: 6.0 s</td>
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<tr>
<td>6</td>
<td>FCD temporo-polar, HS right</td>
<td>FCD 1b, HS Wyler 3</td>
<td>7</td>
<td>TN: 0</td>
<td>AHC-&gt; TN: 33.4 s</td>
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<tr>
<td>7</td>
<td>FCD temporo-polar, HS right</td>
<td>FCD 1a, HS Wyler 3</td>
<td>10</td>
<td>TN: 6&lt;sup&gt;**&lt;/sup&gt;</td>
<td>TN -&gt; AHC: 14.0 s</td>
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<td>AHC -&gt; TN: 34.4 s</td>
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<td>mMCD, HS Wyler 3</td>
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<td>Undecided</td>
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<td>11</td>
<td>FCD temporo-occipital bilaterally</td>
<td>FCD 1b, HS Wyler 1</td>
<td>7</td>
<td>TN: 1</td>
<td>TN -&gt; AHC: 4.4 s</td>
</tr>
</tbody>
</table>

FCD; focal cortical dysplasia (for classification according to Palmini see section Neuropathological examination, page 4). mMCD; mild malformation of the cortical development, HS; hippocampal sclerosis (for classification according to Wyler see section Neuropathological examinations, page 4). AHC; amygdala/hippocampus complex, ID; indeterminate onset (simultaneously recorded in TN and AHC), CL; contralateral to the operated site, TN; dysplastic temporal neocortex; *These numbers include subclinical seizure patterns. Patient 5: TN: seven seizures were all subclinical seizure patterns. Patient 7: TN: six seizures included two clinically manifested seizures and four subclinical seizure patterns with identical seizure onset pattern. AHC: two seizures were both subclinical seizures.
Surgical procedures
Epilepsy surgery was tailored according to the ictal and interictal results of invasive EEG recordings. Interictal activity was considered, as former studies could show that the extent of interictal epileptiform activity may be a more accurate estimate of the epileptogenic region compared with either the seizure onset region or the pathologic substrate (Bautista et al., 1999). In four patients an anterior temporal lobe resection including an amygdalohippocampectomy was performed, and five patients underwent an anterior temporal lobe resection with posterior extension including amygdalohippocampectomy. In two patients an extended temporal pole resection including amygdalohippocampectomy and in one patient a selective amygdalohippocampectomy were performed.

In four patients (nos 1, 2, 9 and 12) with predominantly or only TN seizure onset an amygdalohippocampectomy was recommended because of the fast spread of ictal activity into the AHC (<2 s) or the immediate involvement of both structures (indeterminate seizure onset) (Table 1). In these cases we considered the AHC as having a reduced seizure threshold and as a possible part of the epileptogenic region. Patients were informed about the risk of post-operative memory impairment and the patients gave their consent.

Neuropathological examinations
After excision, the tissue was fixed for 12–24 h in 10% buffered formalin, embedded in paraffin and sectioned. Staining was carried out using haematoxylin–eosin, periodic acid–Schiff and Kluever–Barrera myelin stain. For selected cases, additional special stains (Elastica-van-Gieson, Reticulin, Bodian) were used. Additional immunohistochemical stainings were performed with antibodies...
against neurofilament to visualize the orientation of neurons and to depict dysmorphic neurons or ectopic white matter neurons and against synaptophysin, another neuronal marker. Glial fibrillary acid protein (GFAP) and vimentin immunohistochemistry was performed in order to better visualize astrogliosis and/or balloon cells. Moreover, the proliferation marker Ki-67, the pan-leucocyte marker leucocyte common antigen and the microglial marker CD68 were applied.

Histological dysplastic features were classified as suggested by Palmini and Lüders (2002).

Dyslamination was the inclusion criterion for the diagnosis of focal cortical dysplasia (FCD) type 1: FCD 1a was defined as a blurred transition between different cortical layers, in our patient group most commonly seen between layers III and IV or layers V and VI. In these zones we observed a relatively homogenous population of neurons and a moderately increased cell density. Occasionally, dyslamination was characterized by a numerical reduction of pyramidal neurons and granule cells and clusters of misplaced neurons (e.g. an increased number of pyramidal neurons in layers I or II with abundant ectopic neurons in the white matter). FCD 1b was diagnosed if the laminar disorganization was more prominent and occurred together with cytoarchitectural abnormalities such as immature neurons (a population of neurons with a large nucleus and a thin rim of cytoplasm) and/or giant neurons.

Abundant heterotopic white matter neurons in the absence of a dyslamination were described as mild malformations of cortical development (mMCD).

Dysplastic tissue with the additional occurrence of dysmorphic neurons was classified as FCD 2a, and dysplastic tissue with the additional occurrence of balloon cells as FCD 2b.

The histological grading of hippocampal pathology was classified according to Wyler et al. (1995). Grade 1: mild mesial temporal damage (MTD) with gliosis and <10% or no hippocampal neuronal dropout involving sectors CA1, CA3 and/or CA4 of hippocampal pyramidal cell layer. Grade 2: moderate MTD with gliosis and 10–50% neuronal dropout involving sectors CA1, CA3 and/or CA4 of hippocampal pyramidal cell layer. Grade 3: moderate to marked MTD with gliosis and >50% neuronal dropout involving sectors CA1, CA3 CA4 of hippocampal pyramidal cell layer but sparing CA2. Grade 4: marked MTD with gliosis and >50% neuronal dropout involving all sectors of hippocampal pyramidal cell layer.

Statistical analysis

For comparison of propagation times in seizures arising from the hippocampus and seizures arising in the dysplasia the two-tailed t-test was used. For comparison of the location of seizure onset in patients with severe and mild hippocampal sclerosis the chi-square test was used. P-values <0.05 were regarded as statistically significant.

Results

Histology, MRI and outcome

Histological and MRI findings are summarized in Table 1. Of the 12 patients six showed mild hippocampal sclerosis (Wyler 1) and six showed severe hippocampal sclerosis (Wyler 3). In the neocortical temporal lobe, in two patients abundant white matter neurons were the only histological dysplastic feature (mMCD), and in one patient FCD 1a, in seven patients FCD 1b and in one patient FCD 2b were seen. In one further patient the area showing MR features of cortical dysplasia was not removed as invasive recordings did not show ictogenesis arising from this area. In this patient, however, the MRI findings were highly suggestive for FCD 2b in temporo-posterior localization.

In 6 out of 12 patients the FCD and the hippocampal sclerosis were visible in MRI. In 3 out of 12 patients only the FCD and in 1 patient only hippocampal sclerosis was detectable in MRI. Of the 12 patients 2 had no imaging abnormalities. Sensitivity of MR scanning for correct detection of hippocampal sclerosis was higher when more severe forms of neuronal damage were present.

Post-surgical outcome was favourable in most cases. Post-surgical outcome was classified according to Engel and Rasmussen (1993) and was related to the latest follow-up visit (range 6–36 months, mean 18 months). Of all the patients, seven were completely seizure free (Engel Ia), two had only simple partial seizures or a running down of seizure frequency with complete seizure freedom over 2 years (Engel Ib and Engel Ic), one patient had >90% seizure reduction (Engel II), one patient with contralateral seizure onset had considerable reduction of seizure frequency (≥75%) (Engel III), and one patient with both neocortical and hippocampal seizure onset did not benefit from epilepsy surgery (Engel IV). Patients with severe hippocampal sclerosis were all Engel I (three patients Engel Ia, one patient Engel Ib and Ic each). In the patient group with mild hippocampal sclerosis three patients were Engel Ia, and one patient Engel II, III and IV each.

Ictal onset zones and spread

A total of 96 seizures from 10 patients were quantitatively evaluated, and 17 seizures in 2 additional patients (nos 10 and 11) are described separately.

Of the evaluated seizures 41.3% arose from the AHC (Fig. 2A and B) and 34.7% from the dysplastic TN (Fig. 2C). In 22% of the evaluated seizures, seizure onset was indeterminate as it was simultaneously recorded over both areas, the AHC and the TN (Fig. 2D). In these seizures, larger networks were obviously very early activated. Although seizure semiology did not differ between seizures with definite hippocampal or extrahippocampal onset as compared with seizures with indeterminate onset in the same patient, an analysis of the time lag between electrographic seizure onset and initial behavioural signs or symptoms showed that in two patients (nos 6 and 7) seizures with initial electrographic patterns in both regions had a more rapid onset of clinical manifestations. Of the evaluated seizures 2.0% arose from the contralateral hemisphere.

Of the seizures arising from the AHC 70% propagated into the dysplastic TN and of the seizures arising from the dysplastic TN 72.4% propagated into the AHC. On patient level, in three patients all evaluated seizures arose only from the AHC. In the other patients, seizures arose in various combinations from the AHC and/or the TN and/or were simultaneously recorded over both areas (indeterminate
seizure onset). Only one of the five patients with Wyler 3 pathology had independent TN seizure onset (Table 1).

Seizure onset from the AHC was significantly more frequent in patients with severe hippocampal sclerosis ($P < 0.0001$), and seizure onset from the TN was significantly more common in patients with mild hippocampal sclerosis ($P < 0.0001$). In five patients with severe hippocampal sclerosis (Wyler 3), 78% of the evaluated seizures arose from the AHC only, 10% had indeterminate seizure onset and 12% arose from the dysplastic TN only. In the five patients with mild hippocampal sclerosis (Wyler 1) 4% of the evaluated seizures arose from the AHC, 34% had indeterminate seizure onset and 58% arose from the dysplastic TN (Fig. 3).
Regarding the types of focal cortical dysplasia, seizure origin was highly variable. In two patients with severe FCD 2b, seizure onset was nearly complementary. In one of them (no. 2) 90% of the seizures arose from the dysplastic TN and 10% from the hippocampus. In the other patient (no. 4), 100% of the evaluated seizures arose from the hippocampus.

In eight patients with mild dysplastic features in the TN (classified as mMCD, FCD 1a and FCD 1b) seizure onset zones varied considerably. In four of them, none of the seizures arose from the dysplastic TN alone, 32.2% had indeterminate seizure onset and 67.5% of the seizures arose from the AHC. In the other four patients (including one patient with mMCD), the...
Fig. 2 (A) Example of seizure onset (arrow) with rhythmic sharp waves in the amygdala and anterior hippocampus. (B) Example of seizure onset (arrow) with rhythmic beta activity in the amygdala and anterior hippocampus. (C) Example of a seizure from Patient 1: seizure onset (first arrow) is seen with a fast activity in the temporo-basal neocortex, temporo-anterior lateral neocortex and entorhinal cortex. After 1 s (second arrow) the seizure has propagated in the AHC in which a rhythmic beta activity appears. Immediately before seizure onset rhythmic spikes are seen over the temporo-basal neocortex, temporo-anterior lateral neocortex and entorhinal cortex, which were frequently observed interictally. (D) Example of seizure onset (arrow) with fast activity, the onset of which is simultaneously recorded over neocortical and mesial temporal areas (indeterminate seizure onset). (E) Example of a seizure from Patient 7 showing interaction between neocortical and hippocampal regions in seizure generation. In this example seizure onset is seen with a beta activity in the temporo-basal and temporo-anterior lateral neocortex (first arrow). Simultaneously with seizure onset there is a decrement of the amplitudes in the hippocampal depth electrode. One second before the seizure activity is seen in the hippocampus, the temporo-basal and temporo-lateral beta activity disappears (second arrow). With the onset of the rhythmic beta activity in the hippocampal electrode contacts (third arrow), low amplitude fast activity is recorded over the temporo-basal neocortex. (F) Example of a seizure from Patient 10. In this patient an electrographic status epilepticus limited to the intrahippocampal electrode contacts (panel 1) was observed during the complete period of video EEG monitoring. This rhythmic spiking showed repeated transition into other ictal patterns every 10 min (panel 2). Infrequently low amplitude fast activity (arrow) was recorded from the temporo-basal cortex resulting in a clinical seizure (panel 3). In this case, it was impossible to decide whether this low amplitude fast activity was related to the preceding ictal pattern in the hippocampus.
majority of seizures (64.5%) were generated in the dysplastic TN, 23.5% had indeterminate seizure onset and only 8.5% arose from the AHC alone.

Two of the patients (nos 10 and 11) were not included in the quantitative evaluation.

In the first patient (Fig. 2F), EEG long-term recording revealed electrographic status epilepticus consisting of continuous 1/s rhythmic sharp wave activity limited to only the third electrode contact of the depth electrode in the anterior hippocampus during the complete 8 day period of invasive EEG monitoring and this could not be recorded by in the closely subdural electrode contacts. This rhythmic spiking showed repeated transitions into subclinical ictal patterns and a waxing and waning spatial distribution every 10–20 min. In addition, infrequently low amplitude fast activity was recorded from the anterior temporo-basal cortex, resulting in a clinically manifested complex partial seizure. It was impossible to decide whether this low amplitude fast activity was related to the ongoing ictal pattern in the hippocampus (Fauser and Schulze-Bonhage, 2004); thus, a classification as for the other patients could not be used.

In the second patient (patient no. 11) MRI revealed a bilateral cortical dysplasia in temporo-occipital localization. The left temporal lobe was resected because the majority of seizures were arising from that area: one seizure from the TN, three from the AHC and two with indeterminate seizure onset. Three seizures, however, were arising from the right temporal lobe: one from the TN and two with indeterminate seizure onset.

**Propagation times from the dysplastic TN into the AHC and vice versa**

Propagation times were separately determined in seizures arising from the AHC with propagation into the dysplastic TN and in seizures arising from the dysplastic TN with propagation into the AHC. In our patient sample, there was no significant difference between AHC to TN versus TN to AHC propagation times ($P = 0.5$); however, the former tended to be longer than the latter. In seizures arising from the dysplastic TN, propagation time ranged from 1 to 26 s, and the mean propagation time was 7.4 s. In seizures arising from the AHC, propagation time ranged from 1 to 76 s, and the mean propagation time was 13.7 s.

**Initial ictal patterns**

The initial ictal patterns in patients with dual pathology are shown in Figs 2 and 4. In seizures arising from the dysplastic TN (Fig. 4A), fast activity (>25 Hz) (50.5%) and repetitive sharp waves (35.6%) were the most common initial patterns. In the secondarily involved AHC (Fig. 4B) rhythmic beta activity (36.2%) was the most common pattern (Fig. 2C). Fast activity (>25 Hz), however, was rarely observed (7.3%).

In seizures arising from the AHC (Fig. 4C) rhythmic beta activity (<25 Hz) (47.1%) and rhythmic sharp waves (28.6%) (Fig. 2A) were the most common initial ictal patterns. Fast activity (>25%) was only seen in 4.2% of the evaluated seizures. In the secondarily involved dysplastic TN (Fig. 4D) fast activity (40.5%) was the most common pattern followed by rhythmic sharp waves (38.3%).

In seizures with indeterminate onset fast activity (>25 Hz) was the most common initial ictal pattern in the dysplastic TN (91.7%). In the AHC fast activity and rhythmic beta activity were both seen in 27.8% of seizures (Fig. 4E and F).

Few seizures were not included in the quantitative analysis as it was uncertain whether the ictal pattern seen in the AHC was related to the preceding ictal pattern in the dysplastic TN (Fig. 2E) or vice versa (Fig. 2F).

**Interictal patterns in the temporal neocortex**

Interictal patterns (Fig. 1) were evaluated during wakefulness, non-REM sleep and REM sleep in the electrode contacts overlying the dysplastic TN. The results are summarized in Table 2. Isolated spikes, a repetitive spike pattern (intermittent or almost continuous), and a paroxysmal fast pattern were frequently seen during wakefulness and non-REM sleep. A repetitive bursting pattern, however, was only seen in one patient during non-REM sleep. In this patient a FCD 2b (Taylor type) was diagnosed.

Localization of repetitive spike pattern, low amplitude fast activity and repetitive bursting pattern in the TN is shown in Figs 2 and 4. In seizures arising from the dysplastic TN, propagation time ranged from 1 to 76 s, and the mean propagation time was 13.7 s.

**Discussion**

The clinical significance of microscopic cortical dysplasia in the TN found in 10–50% of patients with hippocampal sclerosis is an issue of intense debate. In the present study 113 seizures in 12 patients with dual pathology of the temporal lobe who underwent invasive video EEG monitoring were investigated. Though patient numbers were limited in our study several conclusions may be drawn from our data.
Fig. 4 (A and B) Occurrence of different initial ictal patterns in the dysplastic TN and ictal patterns observed in the secondarily involved AHC in seizures arising in the TN. (C and D) Occurrence of different initial ictal patterns in the AHC and ictal patterns observed in the secondarily involved dysplastic TN in seizures arising in the amygdala/hippocampus complex. (E and F) Occurrence of different initial ictal patterns in the AHC and the dysplastic TN in seizures with indeterminate onset.
The quantitative contribution of the AHC to seizure generation seems to correlate strongly with degree of hippocampal pathology whereas a relation with different types of cortical dysplasia in the temporal neocortex was not evident.

Seizure onset from the AHC was significantly more frequent in patients with severe hippocampal sclerosis than in patients with mild hippocampal sclerosis \((P < 0.0001)\). Seizure onset from the TN, however, was significantly more frequent in patients with mild hippocampal sclerosis \((P < 0.0001)\). In contrast, the type of cortical dysplasia alone did not predict a temporo-neocortical or temporo-mesial seizure onset in our patient group. Any type of cortical dysplasia could be epileptogenic or could be electrically inert; for example, two patients with severe cortical dysplasia (FCD 2b) (histologically confirmed or suspected by MRI findings) behaved nearly complementarily, with preponderance of hippocampal seizure onset in one and preponderance of seizure onset in the TN in the other. The fact that areas of severe cortical dysplasia can be electrically inert is known from patients with tuberous sclerosis, in whom a leading tuber can frequently be identified whereas most of the additional tubers seem not to be epileptogenic. Similarly in patients with mild histological dysplastic features (classified as MCD, FCD 1a or 1b) the percentage of seizure onset from the dysplastic TN was highly variable and ranged from 0 to 78% per patient.

A preponderance of hippocampal seizure onset is not unusual in other multifocal epilepsies with hippocampal sclerosis (i.e. after viral encephalitis or traumatic brain injury) and does not exclude an additional extrahippocampal seizure onset zone. In this context, one study (Li et al., 1999) could demonstrate that in a group of patients with

<table>
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<th>Table 2</th>
<th>Interictal patterns in the dysplastic TN</th>
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<td>Awake</td>
<td>Non-REM</td>
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<td>Isolated spikes</td>
<td>12/12 patients (100%)</td>
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<tr>
<td>Repetitive spike pattern</td>
<td>8/12 patients (67%)</td>
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<tr>
<td>Paroxysmal fast pattern</td>
<td>5/12 patients (42%)</td>
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<td>Repetitive bursting pattern</td>
<td>0/12 patients (0%)</td>
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<tr>
<th>Table 3</th>
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<td>Patient no.</td>
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<td>Temporo-anterior, mid-temporal, temporo-posterior (basal and lateral)</td>
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<td>3</td>
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<td>5</td>
<td>Temporo-anterior (lateral), temporo-posterior (basal)</td>
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<td>Temporo-anterior (basal)</td>
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<td>Temporo-anterior (lateral + basal)</td>
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<td>11</td>
<td>Mid-temporal, temporo-posterior (left), mid-temporal (lateral) (right)</td>
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<td>Mid-temporal (lateral), temporo-posterior (basal)</td>
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extrahippocampal lesions (including cortical dysgenesis, tumours, contusions, infarcts and vascular malformations) associated with hippocampal atrophy, even if the atrophied hippocampus appeared to be the most epileptogenic structure, only 20% of the patients became seizure free after hippocampal removal. In our patient group with severe hippocampal sclerosis, however, all patients had a very favourable seizure outcome (Engel class I) after removal of the hippocampus and the neocortical areas of seizure onset and/or with severe interictal activity.

Although patients with severe and mild hippocampal sclerosis differ in the relative contribution of the AHC and the TN to seizure onset, there is an overlap between both groups

Even in our small patient group, we observed one patient with severe hippocampal sclerosis in whom the majority of seizures arose from the TN. Thus, in patients with severe hippocampal sclerosis and a dysplastic TN, seizure onset from the TN seems not to be an exception and is probably more common than in patients with mesial temporal sclerosis alone, in which seizure onset from the TN is reported in only 0–5% in most studies (Lieb et al., 1976; Delgado-Escueta and Walsh, 1983; Quesney, 1986; Morris et al., 1987; Maldonado et al., 1988; Sterling and O’Connor, 1989; So et al., 1989; Spencer et al., 1990; King and Spencer, 1995). These data, however, may be influenced by the preselection of patients for invasive EEG recordings; factors favouring an additional invasive EEG recording included seizure semiology, scalp EEG or MRI findings not typical for only temporo-mesial seizure onset. In patients with mild hippocampal sclerosis, the hippocampus played a less important role in the ictogenesis. However, 2 patients with mild hippocampal sclerosis were observed in whom one of the first 10 seizures arose from the AHC. The relative contribution of the AHC and the TN to ictogenesis in this patient group resembles reported percentages on patients with temporo-lateral convexity and thus do not directly reflect the structure where seizures arise from as compared with the exact point-of-onset. These dependencies may also be reflected in the scalp EEG (Ebersole and Pacia, 1996). However, all scalp EEG patterns are secondary to involvement of the temporo-lateral convexity and thus do not directly reflect the mesio-temporal seizure onset patterns investigated here.

Propagation time of ictal activity tends to be shorter in seizures arising in the dysplastic temporal neocortex than in seizures arising in the hippocampus

Studies on propagation time of ictal activity from the TN into the hippocampus and vice versa are rare. One former study in patients with temporo-neocortical and temporo-mesial seizure onset (Brekelmans et al., 1995) reported a propagation time of 17.3 s from the neocortex into the limbic region and of 34.9 s from the limbic region into the neocortex. The aetiology of temporo-lateral seizure onset is not mentioned. Compared with that study, in our patient group with dual pathology of the temporal lobe propagation time of ictal activity from the temporo-mesial structures to the TN (13.7 s) and from the TN to the temporo-mesial structures (7.4 s) was shorter but showed a similar trend, however, without statistical significance. Additional factors such as different anticonvulsive drug regimes may contribute to these differences.

Initial ictal patterns differ between the AHC and the dysplastic TN

Comparing seizure onset patterns in the TN to seizure onset patterns in the AHC, in our patient group in accordance with earlier reports (Javidan, 1992), seizure onset patterns in the TN were characterized by higher frequency than in the AHC.

In the dysplastic TN, fast activity (>25 Hz) was the most commonly observed pattern, independently from the fact whether seizures were arising from this region or propagating into this region. Thus, also fast activity over the TN did not give any guarantee that the area displaying it is the initial seizure onset zone. In the temporo-mesial structures, rhythmic beta activity was the most common pattern, which was also independent from the fact whether seizures were arising from or propagating into the temporo-mesial structures. Fast activity, however, was very rarely observed in the AHC. More suggestive for a spread from another site into the temporo-mesial structures was a combination of different patterns within the temporo-mesial structures or an initial flattening of amplitudes.

The analysis shows that EEG patterns depended more on the structure where seizures arise from as compared with the exact point-of-onset. These dependencies may also be reflected in the scalp EEG (Ebersole and Pacia, 1996). However, all scalp EEG patterns are secondary to involvement of the temporo-lateral convexity and thus do not directly reflect the mesio-temporal seizure onset patterns investigated here.

Interictal patterns in FCD of the temporal lobe associated with hippocampal sclerosis resemble interictal patterns in FCD of extratemporal lobes but are less frequently observed

In our study, interictal patterns were evaluated during wakefulness and sleep (non-REM and REM sleep). A repetitive spiking pattern was seen in 75% of patients; however, only in three of them (25%) it was observed continuously or quasicontinuously. A repetitive bursting pattern was seen in only 1 patient (8.3%) with FCD type 2b (Taylor type) containing balloon cells and dysmorphic neurons. A former study in patients with FCD in extratemporal localization
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(Palmini et al, 1995) reported 35% of the patients with continuous or quasicontinuous rhythmic spiking and 30% of the patients with a repetitive bursting pattern. In that group, most of the patients had FCD type 2b (Taylor type) in the histological examination. Similarly, another study (Boonyapisit et al, 2003) correlated interictal patterns to the underlying pathological characteristics of the tissue and found that all above mentioned interictal patterns were most frequently seen in areas containing dysmorphic neurons. These findings suggest that the histological subtype may influence the interictal electrographic patterns more than the localization or the presence of dual pathology.

Conclusions

Simultaneous recordings from the hippocampus and the TN suggest that dysplastic tissue in the TN is often epileptogenic. The quantitative contribution of the hippocampus to seizure generation correlated strongly with the degree of hippocampal pathology, whereas different subtypes of cortical dysplasia did not affect its relative contribution to seizure generation in our patient group. Even tissue with mild dysplastic features (mMCD) in the TN could be epileptogenic. Moreover, the interictal patterns recorded over the dysplastic TN showed similarities to interictal patterns recorded over extratemporal focal cortical dysplasias, additionally supporting epileptogenicity of these areas. To get more detailed information on the significance of different types of tempo-neocortical dysplasia in patients with hippocampal sclerosis larger patient groups would be desirable.

Although MRI appears to be indicative of the relative role of the AHC in seizure generation, the variable combination of tempo-neocortical and limbic seizure onset warrants a precise definition of the epileptogenic area by invasive EEG recordings if a tailored resection is aimed at.

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References


