Clinical Neurophysiological Correlates of Histopathological Abnormalities in Epilepsy Surgery

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Clinical Neurophysiological Correlates of Histopathological Abnormalities in Epilepsy Surgery

Klinisch Neurofysiologische Correlaten van Histopathologische Afwijkingen bij Epilepsiechirurgie

(met een samenvatting in het Nederlands)

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voor mijn ouders
voor mijn grootouders
voor mijn kleine neefjes

LIST OF ABBREVIATIONS

CAV	Cavernoma
CD / co-CD	Cortical dysplasia / coexisting cortical dysplasia
Cho	Choline
Cr+PCr	Creatine + phosphocreatine
CT	Computed tomography
DNT / DNET	Dysembryoplastic neuroepithelial tumour
ECoG	Electrocorticography
EEG	Electroencephalograpy
FCD	Focal cortical dysplasia
GFAP	Glial fibrillary acidic protein
GG	Ganglioglioma
GNT	Glioneuronal tumour
HLA	Human leucoyte antigen
MAP2	Microtubule-associated protein
MEG	Magnetoencephalography
MRI / fMRI	Magnetic resonance imaging / functional MRI
MRS / ^{1}H MRS	Magnetic resonance spectroscopy / proton MRS
MTS	Mesial temporal sclerosis
NAA	*N*-Acetylaspartate
NDL	Neurodevelopmental lesion
NeuN	Neuronal nuclear protein
PET	Positron emission tomography
SPECT	Single photon emission computed tomography

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CHAPTER 1

Introduction

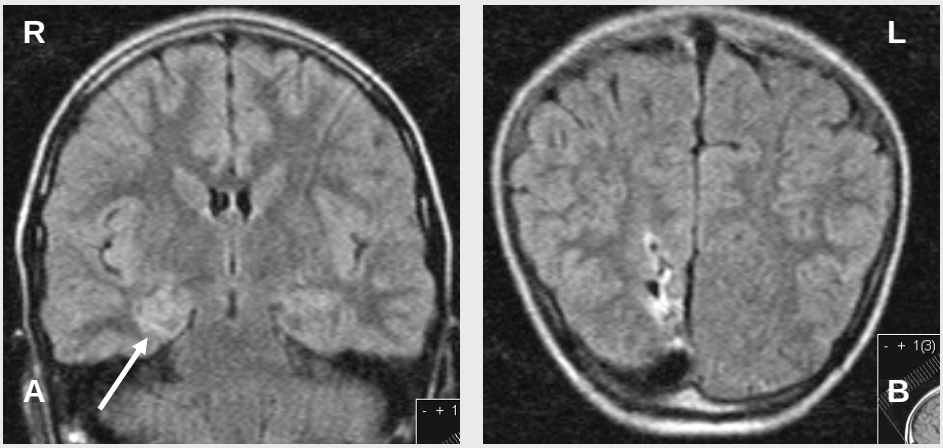
Many advanced techniques are used in the presurgical evaluation of patients in epilepsy surgery programmes. Unusual and unexpected findings should be investigated thoroughly in order to understand their meaning and significance, especially when they are associated with a poor surgical outcome or significant postoperative cognitive decline. We present a case as an example of a seemingly straightforward presurgical evaluation but in which multiple highly epileptogenic foci at different sites in the lateral temporal neocortex were detected during intraoperative neurophysiological investigations. Unfortunately, these foci could not be resected completely, resulting in operative failure.

CASE VIGNETTE

A 14-year-old boy was referred to the Dutch Collaborative Epilepsy Surgery Program for pharmacoresistant temporal lobe epilepsy. The seizures started when he was 12 and at referral they consisted of short episodes of staring, followed by fumbling movements of the fingers. He did not experience warning signs, and during a seizure he would be responsive but would answer questions inadequately. These episodes lasted for about 1 minute and were followed by a period of confusion that lasted about 5 minutes. There was amnesia for the event. Seizures occurred on a daily basis, often with clustering of several fits per hour. In the last 2 years, two antiepileptic drugs had been used without success.

The patient was one of a homozygous twin pair. His mother developed diabetes insipidus during the pregnancy. Delivery was at 39 weeks (forceps). Directly after birth, the child had apnoea and needed to be resuscitated. He was transferred to a neonatal intensive care unit for several days. The child had a prolonged febrile convulsion, with jerking of both arms and legs for about 10 minutes, when he was 3 years and showed compulsive behaviour between the ages of 10 and 12. Developmental milestones were normal and he received regular education. General physical and neurological examinations were normal. The patient was left-handed. His twin brother, who did not experience perinatal difficulties, was right handed and did not have epilepsy.

Figure 1. MRI (FLAIR, coronal slices). A: 4 cm posterior to the temporal pole). This was interpreted as a slightly swollen hippocampus with increased signal intensity (arrow). B: coronal slice, 9 cm posterior to temporal pole). Gliosis with loss of tissue in the right median occipital region consistent with infarction due to perinatal ischemia.



The patient's brain MRI showed some atrophy with a discrete area of gliosis in the right median occipital area, which was considered to be of perinatal origin, and slight swelling of the posterior hippocampus with some increased signal intensity (Figure 1). There were no clear signs of mesial temporal sclerosis or cortical dysplasia. A glioneuronal tumour, a low-grade astrocytoma, or a hamartoma in the right medial temporal region was diagnosed. Surface EEG showed bitemporal interictal sharp waves and spikes (mid- to posterior temporal), but the ictal discharges were clearly right-sided temporal. Preoperative neuropsychological testing revealed a normal total IQ (101), verbal IQ (103), and performance IQ (101). Language, memory, and learning were normal. A unilateral sodium amobarbital test in the right carotid artery (Wada test) showed the left hemisphere to be dominant for language and to support adequate memory functioning.

On the basis of these findings, it was concluded that the patient suffered from lesional right temporal lobe epilepsy with neocortical features. Accordingly, a right temporal lobectomy with intraoperative EEG monitoring, i.e. acute

electrocorticography (ECoG), was performed to determine the extent of the resection. After trepanation and opening of the dura mater, a grid of electrodes was placed directly over the exposed cortex and a strip of electrodes was inserted underneath the temporal lobe until the distal contacts reached the mesial temporal areas. On ECoG four independent discrete epileptogenic foci were identified. These foci showed typical discharge patterns, consisting of rhythmical spiking during most of the recording time with an almost pacemaker-like appearance, in the lateral temporal neocortex (Figures 2 and 3). Isolated spikes occurred independently at several sites in the lateral and inferior temporal neocortex and at the mesial temporal area. Intraventricular ECoG recordings in the lateral ventricle at a later stage during resection confirmed the presence of isolated spike complexes over the hippocampus.

A large temporal lobectomy with complete amygdalohippocampectomy was performed, with resection of the superior temporal gyrus (7 cm), medial temporal gyrus (8.5 cm), and inferior temporal gyrus (7 cm). A final ECoG recording revealed an epileptic focus with a continuous rhythmical 5 Hz discharge at the posterior-inferior border of the resection, just posterior to Labbé's vein (figure 5), and sporadic spikes on the superior temporal gyrus, posterior to Labbé's vein. As a more posterior resection, with ligature of Labbé's vein, carries a significant risk of postsurgical deficits, further resection was not performed. Postoperatively, the patient continued to have his habitual fits and, now after 2 years of follow-up, the procedure must be judged unsuccessful.

Extensive and detailed neuropathological examination of the neocortex that showed the continuous spiking pattern revealed an abnormal cortical architecture, a hallmark of cortical dysplasia, without other clear abnormalities. The hippocampus showed an ischaemic scar with no signs of tumour or mesial temporal sclerosis (Figures 5 and 6).

Figure 2. Preresection ECoG. The grid electrodes cover the anterior part of the lateral temporal neocortex. Two discrete spike foci show continuous spiking: 1) 200-300 µV continuous spiking occurring at 2 Hz at electrode G4 on the inferior temporal gyrus, and 2) 400-500 µV continuous spike-and-wave activity occurring at 1-2 Hz at electrode G7 on the medial temporal gyrus. Sample of 11 seconds, sensitivity 500 µV, 70 Hz, 0.1 s.

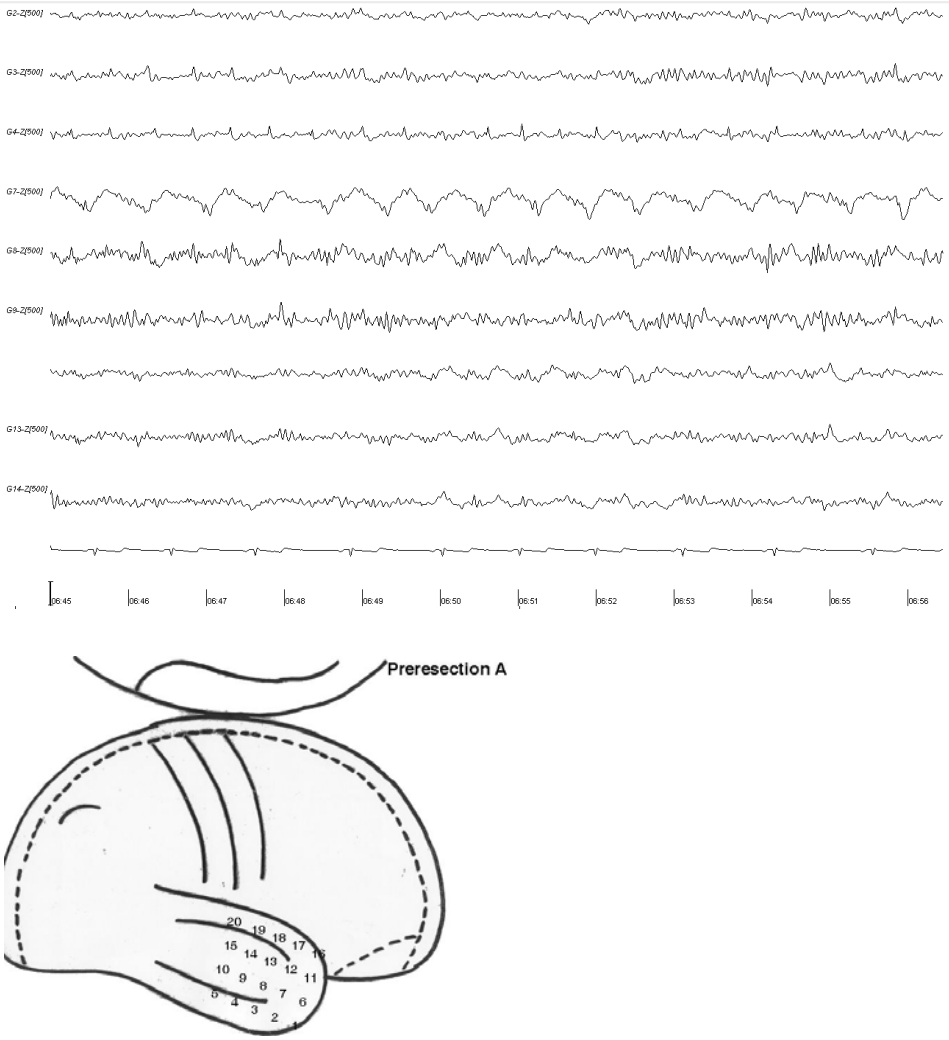
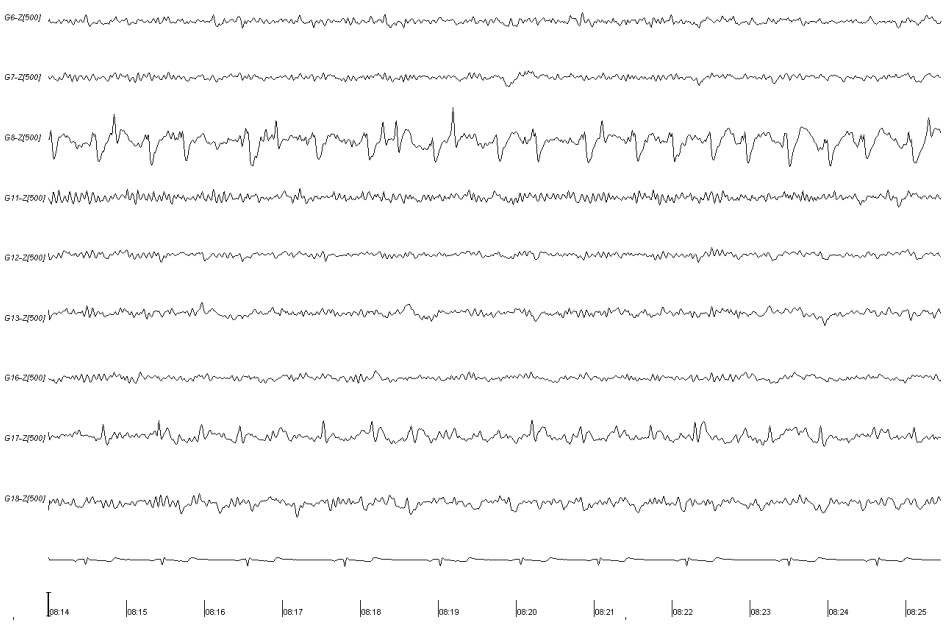


Figure 3. Preresection ECoG. The grid electrodes now cover the posterior part of the lateral temporal neocortex. There are two other discrete foci showing continous spiking. A focus with 2 Hz continuous spiking of 400-600 µV at electrode G8 (superior to midtemporal) and another 1-2 Hz continuous spiking focus of 300-500 µV at electrode G17 (posterior on the inferior temporal gyrus). Sensitivity 500 µV, 70 Hz, 0.1 s. Sample of 11 seconds.



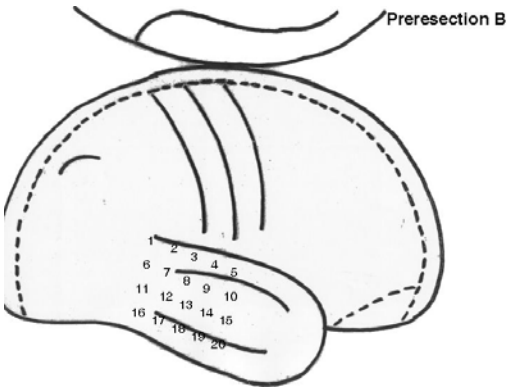
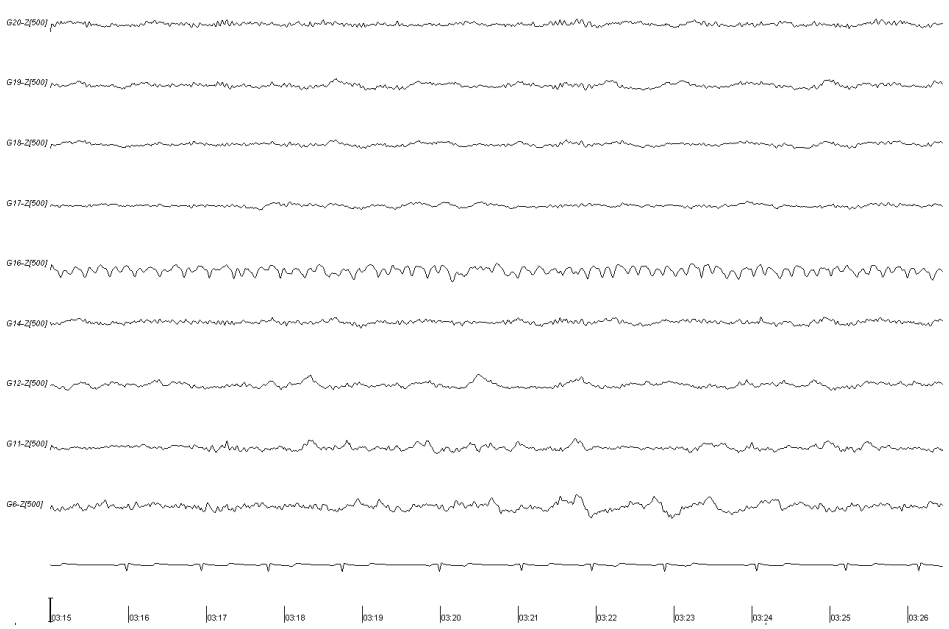


Figure 4. The postoperative electrocortiocogram shows a discharge of continuous rhythmical spike activity of 5-8 Hz at the border of the resection just posterior to Labbé's vein on the inferior temporal gyrus. Sensitivity 500 µV, 70 Hz, 0.1 s. Sample of 11 seconds. Presence of continuous spikes or recruiting discarges in the postresection EcoG is predictive of poor surgical outcome.



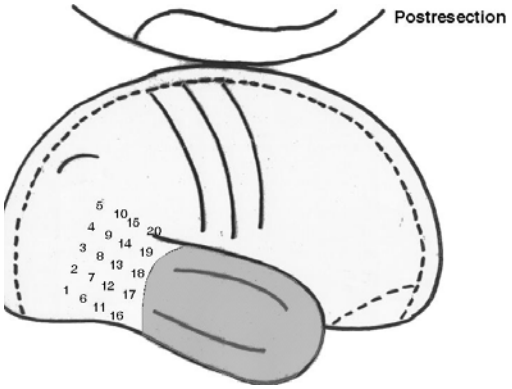
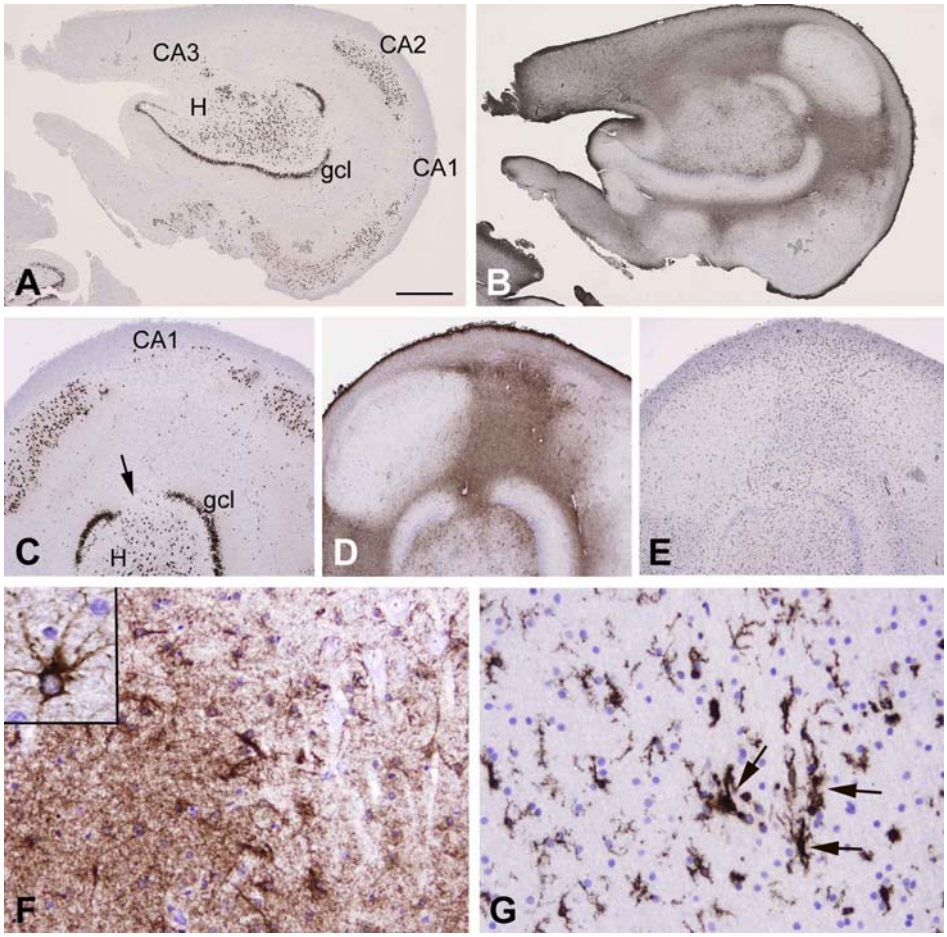


Figure 5. Surgical specimen from the hippocampus. Panels A and C: NeuN staining detects the neuronal cells, showing cell loss in the CA3 and CA1 regions. The CA2 subfield and hilar region are spared. Focal loss of the granule cells is observed (arrow in C). Panels B, D and F: GFAP staining showing astrogliosis in regions where neuronal loss is present (F, CA1 region). Insert in F shows high magnification of a GFAP positive reactive astrocyte. Panels E and G: HLA-DR staining detects microglial cells, showing activated microglial cells in regions where neuronal loss is present, such as the CA1 region (panel G, arrows). Granule cell layer (gcl); hilus (H). Scale bar in A: A and B, 1 mm; C-E: 500 µm; F-G, 100 µm. We would like to thank W.G.M. Spliet (neuropathologist; University Medical Center Utrecht, The Netherlands) for the collaboration in the collection of this case.

Figure 5. For color figure see page 164.



This case illustrates several important issues that are relevant to epilepsy surgery. Although it was thought that the patient suffered from temporal lobe epilepsy, due to a lesion in the posterior part of the hippocampus, the patient's medical history was such that other possibilities had to be considered. The patient had difficulties in the perinatal and neonatal period. Although a history of febrile convulsion and latency are typical for mesial temporal lobe epilepsy, the seizure frequency was not typical and the semiology was rather non-specific – the patient did not experience an aura. The patient's left-handedness was remarkable in the light of the right-handedness of his homozygotic twin brother. Also, MRI findings showed signs of extratemporal perinatal brain ischaemia without evidence of mesiotemporal sclerosis.

Neurodevelopmental lesions (for example, focal cortical dysplasia) are often found in patients with refractory focal neocortical epilepsy [Wyllie et al., 1996; Prayson, 2001] and are being detected more often as a result of advances in imaging technology [Sisodiya, 2000]. However, MRI does not always detect small cortical dysplasias, which are often detected only after careful and detailed histopathological examination of the surgical specimen. Congenital gliotic lesions and ischaemic scars may be associated with subtle cortical dysplasia in distant, normal-appearing (MRI) areas at multiple sites [Marin-Padilla, 2000].

Although the ECoG abnormalities were very clear in this patient, the (extremely focal) continuous spiking patterns were not suspected from the preoperative scalp EEG recordings, which showed only the more widely distributed isolated spikes. Specific ECoG spiking patterns can be indicative of cortical dysplasia and therefore relevant to the operation strategy and surgical outcome. Unfortunately, such patterns are not always detected by scalp EEG because of the low conductivity of the skull, which forms a barrier between cortex and scalp.

Figure 6. For color figure see page 165.

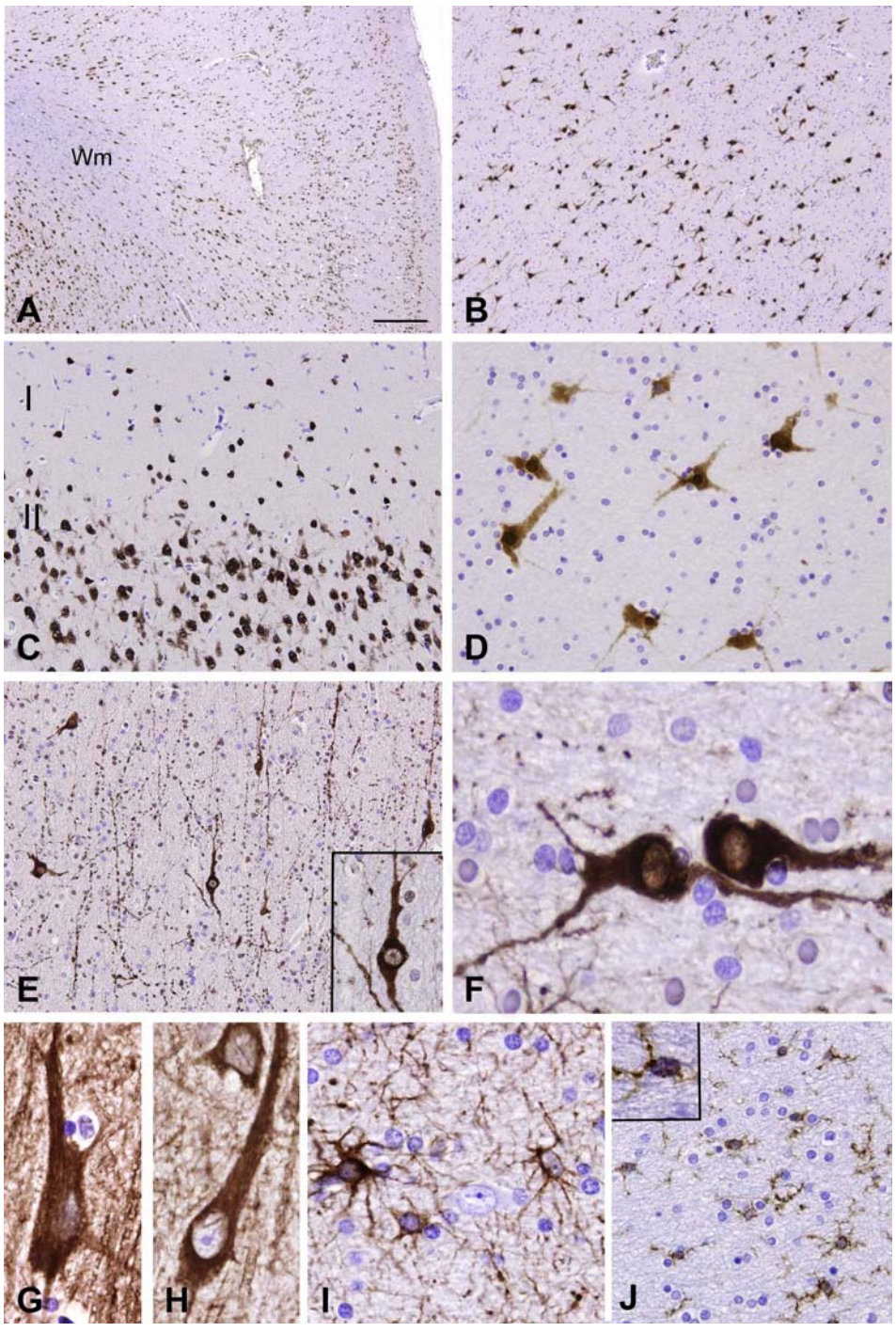


Figure 6 (opposite page). Temporal lateral neocortex. Cytological features of the surgical specimen from the temporal lobe. Panel A: NeuN staining, showing a disorganized cortex with abnormal clustering of neurons and blurring of the deep cortical border with the white matter. Panels B and D: white matter with ectopic neuronal cells (NeuN-positive). Panel C: loss of a clear margin between cortical layer I (molecular layer) and layer II, with NeuN-positive cells in layer I. Panel E and F: MAP2 staining in the white matter, showing a large number of neuronal cells with different size, morphology and orientation (tangential orientation in F). Panel G: high magnification of a MAP2 positive hypertrophic neuron within the cortex. Panel H: large neuron with an accumulation of neurofilament (2F11). Panel I: GFAP positive reactive astrocytes within the withe matter. Panel J: HLA-DR positive microglial cells within the white matter. (No detectable gliosis was observed in the grey matter; data not shown). Scale bar in A: A, 500 µm; B: 250 µm; C, E, 100 µm; D: 75 µm F: 25 µm; G-H, 50 µm. I: 30 µm; J: 50 µm.

Resective epilepsy surgery is a safe and effective treatment for selected patients with pharmacoresistant focal epilepsy, with as goal seizure control without the development of postoperative neurological or cognitive deficits [Carreño & Lüders, 2001]. Surgical series reported in the literature mainly consisted of patients with temporal or frontal lobe epilepsy [Kim & Spencer, 2000; Crandall & Mathern, 2001; Khan et al., 2001; Munari et al., 2001]. In general, the success rate of epilepsy surgery depends on whether ictal semiology is consistent with preoperative test results (including patient history, neurological examination, electroencephalography, MRI, neuropsychology, and, in some cases, MEG, PET, SPECT, functional MRI), so that the localization and extent of the epileptogenic zone can be estimated (i.e. the cortical area from which seizures arise and the removal of which leads to complete cessation of the patient's seizures [Carreño & Lüders, 2001]).

Important issues remain to be resolved, in order to improve the outcome of epilepsy surgery. For example, the identification of specific epilepsy syndromes that can be cured by epilepsy surgery, optimal neurophysiological demarcation of the epileptogenic zone, and the selection of patients who are at risk of postoperative cognitive decline.

Specific epilepsy syndromes with their underlying histopathological lesions have specific combinations of clinical, neuroimaging, and neurophysiological features.

Recognition of these syndromes during the presurgical assessment or intraoperative monitoring makes it possible to adapt the diagnostic evaluation and the operation strategy. For instance, in the syndrome of mesial temporal sclerosis, when ictal semiology, MRI findings, and non-invasive interictal and ictal scalp EEG findings are consistent (which is normally the case), 'standard' temporal lobectomy with complete amygdalohippocampectomy is sufficient to achieve excellent seizure control in the vast majority of the patients [Kim & Spencer, 2000; Uijl et al. 2006]. Low-grade tumours (especially glioneuronal tumours), malformations of cortical development (especially focal cortical dysplasia), vascular malformations (especially cavernomas), and gliotic brain lesions are other lesions encountered during epilepsy surgery [Bingaman & Cataltepe, 2001; Cosgrove, 2001]. Except for cavernomas, preoperative identification of the underlying histopathology by MRI is not always straightforward, and the presence of concomitant (dual) pathology in the mesial temporal structures can be misleading [Ruggieri, 2001; Jack, 2001]. Focal cortical dysplasia can be very subtle and is easily missed on MRI, even by experienced neuroradiologists. Low-grade astrocytomas share similar radiological features with glioneuronal tumours, which makes radiological differentiation between these entities impossible in most patients. Moreover, MRI cannot always distinguish between glioneuronal tumours and focal cortical dysplasia.

Non-invasive scalp EEG is helpful in identifying the side and lobe of seizure onset, but less so in delineating the area of cortex producing interictal epileptiform discharges [Hamer & Katsarou, 2004; Foldvary-Schaefer, 2004]. The use of more or special electrodes (nasopharyngeal), multiple recordings (including sleep recordings or with the use of other activation methods), and the timing of the EEG may increase the diagnostic yield but not the accuracy in localizing epileptogenic sources, for which (semi-)invasive EEG recordings are necessary, made with sphenoidal, foramen ovale electrodes, or subdural electrodes (ECoG) [Rosenow et al., 2004]. The morphology and repetition rate of interictal and ictal epileptiform activity in scalp EEG recordings cannot be used to predict the aetiology of the epilepsy. This is because of physical limitations: in order to detect an epileptiform spike with overlying scalp electrodes, at least 6 cm^2 of cortex needs to discharge synchronously. The distribution of epileptiform discharges is distorted by the

conductive properties of the meninges, cerebrospinal fluid, and skull [Hoekema et al., 2003]. Moreover, the scalp EEG may not detect interictal spikes arising from deep or midline structures. Thus, local network disturbances and their resulting spike patterns may escape detection by the scalp EEG.

The topographical relationship between a structural lesion and its irritative zone (that is, the cortical area producing interictal spikes, comprising the area from which the seizures arise) is highly variable. The irritative zone can best be defined by invasive recording with subdural electrodes (ECoG) or intracerebral depth electrodes. Intraoperative ECoG has been performed routinely in epilepsy surgery since the 1950s, when Penfield and Jasper published their pioneering work on epilepsy and the functional anatomy of the human brain [Penfield & Jasper, 1954]. After craniotomy and opening of the dura mater, they placed electrodes over the exposed cortex to register and to stimulate areas responsible for the patient's habitual seizures and to identify functionally important cortical areas (for example, language or motor areas). In this way, they localized the epileptogenic focus, which was subsequently resected, when possible. This approach allowed ECoG recordings from the cortex to be made before the actual resection and during the different stages of the procedure. Areas showing sharp (spike) activity were presumed to be epileptogenic.

ECoG and cortical stimulation are still used in epilepsy surgery [Lachhwani & Dinner, 2004; Schulz, 2004], although a more restricted use of ECoG has become fashionable with the advent of standardized surgical procedures, especially for mesial temporal lobe epilepsy with sclerosis, and also in circumscribed lesions, for which in some cases lesionectomy has been proposed [Morris III, 2001]. However, some form of invasive EEG is required in a significant proportion of patients with neocortical epilepsy, to establish the extent of the irritative or ictal onset zone.

Recently, careful study of the ECoG has revealed local epileptiform discharge patterns distinct from those usually seen in the scalp EEG. These patterns may be classified as "dense epileptiform patterns" and are indicative of a locally disturbed network acting as a spike generator. These generators may arise from a normal-looking cortex on preoperative MRI (see case vignette). The occurrence of such

patterns on intraoperative ECoG has implications for the surgical strategy and prognosis regarding postoperative seizure control.

Apart from seizure control, another important aim of the extensive presurgical evaluation is to preserve eloquent cortex function and to minimize postoperative functional deficits. A Wada test is currently used to assess hemispheric language functioning and hemispheric memory performance. Catheterization of the carotid artery and arterial injection of amobarbital leads to pharmacological inactivation of brain areas in the distribution of the carotid artery, which is presumed to mimic the potential effects of a lesion after surgery [Knake et al., 2004]. However, because of its invasive character, the Wada test is not without risk and non-invasive alternatives are being sought. In some patients it is possible to localize language function in a non-invasive manner with functional MRI [Rutten et al., 2002; Rutten et al., 2002]. However, functional MRI is not reliable enough to select those patients who are at risk of postoperative memory decline, i.e. patients with (mesio)temporal lobe epilepsy with insufficient memory compensation in the hemisphere contralateral to the epileptic focus.

The studies described in this thesis were carried out to resolve the above controversies, with the ultimate goal to improve the outcome of epilepsy surgery while keeping the risk of postoperative neurological or cognitive decline to a minimum. We tried to identify variables both in presurgical evaluation and in intraoperative ECoG monitoring that contribute to the identification of specific epilepsy syndromes (with their underlying pathology) and their surgical consequences. In addition, we searched for a non-invasive alternative to the memory part of the Wada test. The aims of the individual studies were as follows:

- To determine the prevalence of focal cortical dysplasia in a surgical series of consecutive patients with frontal lobe epilepsy and to correlate electroclinical and neuroimaging abnormalities with surgical outcome (chapter 2).
- To study the presence of dense epileptiform ECoG discharge patterns in focal cortical dysplasia and to establish the significance of these patterns and residual pathology for surgical outcome (chapter 3).

- To establish whether dense epileptiform ECoG discharge patterns also occur in other types of neurodevelopmental lesions (glioneuronal tumours) and whether there are common histopathological features associated with these patterns (chapter 4).
- To investigate whether dense epileptiform ECoG discharge patterns also occur in patients with cavernomas and whether the histopathological and demographic features of these patients are different from those of patients with a neurodevelopmental brain lesion (chapter 5).
- To determine whether memory scores for the Wada test in patients with mesial temporal sclerosis are associated with the neuronal integrity of medial temporal structures, as expressed by metabolite ratios from proton Magnetic Resonance Spectroscopy (chapter 6).

CHAPTER 2

Prognostic Factors in Presurgical Assessment of Frontal Lobe Epilepsy

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Abstract

OBJECTIVES

To determine predictors for surgical outcome in the presurgical assessment of frontal lobe epilepsy.

METHODS

Thirty seven patients were operated on for frontal lobe epilepsy between 1975 and 1996. Their medical records were reviewed for ictal semiology, age at onset, duration of the epilepsy, age at operation, preoperative interictal and ictal encephalographic findings, and abnormalities on neuroimaging and neuropsychological testing. In addition, type of resection and pathology were compared with surgical outcome.

RESULTS

Univariate statistical analysis showed that the presence of a focal abnormality on neuroimaging was associated with favourable outcome. The presence of the following ictal findings was associated with poor outcome: autonomic manifestations, eye deviation, head version contralateral to the operated side, and bilateral or multifocal ictal onset. Fifteen patients had secondarily generalised interictal discharges and, interestingly, their presence was not associated with poor outcome. Multivariate logistic regression showed that the presence of a focal abnormality on neuroimaging was significantly associated with a favourable outcome while contralateral head version was the only variable significantly associated with poor surgical outcome.

CONCLUSIONS

A focal abnormality on neuroimaging was the only variable which was significantly associated with a favourable surgical outcome, whereas contralateral head version was the most significant predictor for a poor outcome. The presence of generalised discharges before surgery was not associated with poor outcome.

Introduction

Frontal lobe seizures are often resistant to medical treatment but may be amenable to surgery, accounting for as many as 18% of those patients who undergo surgery for epilepsy [Binnie et al., 1992; Rasmussen, 1991]. However, outcome with regard to seizure control after frontal lobe surgery is generally poorer than after surgery for temporal lobe epilepsy. Although 56% of patients operated on for frontal lobe epilepsy experience a reduction in seizures [Rasmussen, 1991], only a minority remain seizure free after a long follow up period [Hajek, 1999]. The reasons behind these relatively poor results remain unclear. It has been suggested that the epileptogenic zone may be more extensive and difficult to identify in frontal lobe epilepsy [Talairach et al., 1992], because of either widespread pathology or fast propagation. Although the symptomatology of frontal lobe seizures has been widely reported [Penfield, 1954; Chauvel, et al. 1994; So, 1994; Bancaud et al., 1992; Williamson et al., 1986; Morris, 1991; Trottier et al., 1988; Saint-Hilaire et al., 1988], and the utilisation of multiple variables has been suggested to be useful in prediction of seizure relief after surgery for partial epilepsy [Dodrill et al., 1986; Armon et al., 1996; Guldvog et al., 1994], no clear features have been consistently reported as predictive of surgical outcome after frontal lobe surgery. Furthermore, the lateralising and localising values of some simple clinical signs, such as head version, have remained controversial since the time of Hughlings Jackson. Most series correlating electroclinical or neuroimaging signs with outcome after frontal lobe surgery study a small number of patients either in isolation or within a larger series including patients with temporal lobe epilepsy or other types of extratemporal epilepsies [Dodrill et al., 1986; Guldvog et al., 1994; Boon et al., 1991; Adler et al., 1991; Davies et al., 1993; Laskowitz et al., 1995; Cukiert et al., 1996; Bleasel et al., 1997; Chee et al., 1993; Swartz et al., 1998]. Unfortunately the few large series of patients with frontal lobe epilepsy do not attempt to correlate ictal signs, pathology, type of resection, neuroimaging, or neuropsychology rigorously with surgical outcome [Talairach et al., 1992; Bancaud et al., 1992; Cascino et al., 1992].

In this study we present findings from all patients who have had frontal lobectomies for epilepsy between 1975 and 1996 in the Maudsley Hospital and King's College Hospital, and correlate surgical outcome with age at onset, duration of epilepsy and age at operation, ictal symptomatology (clinical signs), interictal and ictal electroencephalographic findings, presence of abnormalities in neuroimaging, neuropsychology, type of resection, and pathology.

Patients and methods

PATIENTS

The clinical notes of all the patients who underwent a frontal lobectomy at our centre between 1975 and 1996 (42 patients) were reviewed retrospectively. Three patients had a follow up period shorter than 1 year and two had incomplete medical records. These five patients were excluded from the study, leaving 37 to be included.

The study comprised 18 males and 19 females. The age at onset of the epilepsy was between 0 and 19 years (mean 6.1 (SD 5.2)). The duration of the epilepsy at the time of operation ranged from 1 to 30 years (mean 10.6 (SD 7.9)). The age at operation was between 1 and 38 years (mean 16.8 (SD 10.4)). The period of follow up ranged from 1 to 19.5 years (mean 5.9 (SD 3.9)).

Although this was a retrospective study over two decades, the patients had all been treated by a team headed by the same neurosurgeon and two neurophysiologists. Detailed and standardised documentation was available.

OUTCOME

Surgical outcome was classified into four grades according to Engel [Engel et al. 1993]: I (free of disabling seizures), II (almost seizure free, still having three or less seizures per year), III (worthwhile improvement remaining with more than three seizures per year), IV (no worthwhile improvement). Outcome grades I or II were considered favourable. Outcome grades III or IV were considered poor.

CLINICAL SIGNS

Full and detailed eye witnessed seizure descriptions were recorded by the neurosurgeon (CEP) in every patient. In addition, 15 patients have undergone video telemetry because there were discrepancies between different tests in the presurgical assessment and more detailed information about lateralisation or localisation was found to be necessary. Seizure description by the patient or relatives in all cases and telemetry videotapes or reports from 15 patients were used to evaluate the ictal symptoms. In the 15 patients who underwent video telemetry, ictal signs from video telemetry were used for analysis regardless of whether they were reported in the notes.

The presence of the following clinical features was recorded: aura, staring, automatisms (oroalimentary, bimanual/bipedal, cursive), motor signs (head version, eye deviation, focal twitches, posturing/dystonia), secondarily generalised seizures, vocalisation, autonomic manifestations (flushing, pallor, tachycardia, palpitations, changes in respiratory rhythm, mydriasis, salivation, frightened appearance), incontinence, postictal confusion, postictal dysphasia, and Todd's paralysis. Patients with head version to one side were further analysed as to whether the direction of the version was ipsilateral or contralateral to the operated side.

COMPARISON BETWEEN HISTORY AND TELEMETRY

For the patients who had telemetry, the telemetry reports were compared with seizure descriptions in the clinical notes to check the reliability of ictal semiology reported in the history. This was done by counting the cases in which signs were present both in history and telemetry and whether their laterality was concordant.

ELECTROENCEPHALOGRAPHIC FINDINGS

Interictal

Of the patients studied, 33 had at least one preoperative scalp EEG record available for analysis. These were evaluated for the presence of (a) unilateral focal or unilateral multifocal epileptiform activity, (b) bilateral synchronous discharges, (c) bilateral independent discharges, and (d) unilateral focal or multifocal epileptiform activity with bilateral synchronous discharges.

Ictal

From the patients who underwent intracranial or scalp telemetry, the ictal record was analysed for the extent of ictal onset and classified into focal, bilateral, or multifocal.

NEUROIMAGING

All patients had neuroimaging before the operation. Twenty patients had only CT and seven patients only MRI. Ten patients had CT and MRI. Neuroimaging findings were classified as normal, focal, multifocal, unilateral diffuse, or bilateral.

NEUROPSYCHOLOGY

Twenty five patients had neuropsychological assessment including full scale IQ, performance IQ, and verbal IQ. One of the following tests was performed: WAIS-R, WISC-R, WAIS, short-WAIS, WISC, or WPPSI-R. In right handed patients, a discrepancy between performance and verbal IQ greater than or equal to 15 points was considered as lateralising. If verbal IQ was larger than performance IQ a functional abnormality in the right hemisphere was inferred. If performance IQ was larger than verbal IQ, an abnormality in the left hemisphere was suspected.

PRESURGICAL ASSESSMENT AND RESECTION

The side of operation and extent and topography of the resection were decided on the basis of history, neuroimaging, neurophysiological findings (including intraoperative electrocorticography), and neuropsychology. In patients with normal neuroimaging, the side of resection was decided on the basis of history in addition to the presence of interictal EEG abnormalities or results from intracranial ictal telemetry. Four types of resection were performed:

(1) Total lobectomy: removal of the frontal lobe sparing the motor strip.

(2) Polar lobectomy: removal of anterior third or half of the frontal lobe.

(3) Parasagittal: resection of the mesial and superior aspects of the frontal lobe.

(4) Convexity: resection involving only the lateral aspect of the frontal lobe.

PATHOLOGY

After resection, material from all patients was sent for neuropathological examination. Pathological findings in resected specimens were divided into seven groups: cortical dysplasia, neoplasm, scarring, vascular malformation, no lesion, Rasmussen's encephalitis and other.

OUTCOME VERSUS TIME

Date of operation was correlated with surgical outcome, to establish changes in outcome with time. The surgical outcome was studied in the patients who were operated on between: (a) 1975 and 1985, (b) 1985 and 1991, and (c) 1991 and 1996.

STATISTICAL METHODS

The two tailed Mann-Whitney test was used to establish differences in continuous variables (age of onset, duration, age at operation) between the two outcome groups.

An initial univariate analysis using χ^2 (one degree of freedom) or two tailed Fisher's exact probability tests, was carried out to identify the clinical features most likely to be significantly associated with surgical outcome. Fisher's exact test was used when the expected number of patients in one cell of the contigency table was less than five. Similarly, the presence of a focal abnormality on neuroimaging was correlated with surgical outcome. Results were considered significant for $p<0.05$.

At a second stage we designed a multivariate logistic regression model using surgical outcome as the dependent variable and the variables which seemed to correlate with surgical outcome after the univariate analysis as covariates. Covariates which showed prognostic value were identified with a forward stepwise approach. Independence of covariates was studied by incorporating their product (after coding as 0 or 1) into the multivariate logistic regression. The constant was forced to 0 in the regression equations as it provided a higher goodness of fit than non-zero constants (41.7 v 37.0). All statistical analysis was carried out with SPSS for Windows.

Table 1. Sex, age at onset of epilepsy, duration of epilepsy, and age at operation in relation to surgical outcome.

	Outcome		
	Good (n = 20)	Poor (n = 17)	Mann-Whitney test
Male : Female	10:10	8:9	
Age at onset	6.3 (5.0)	5.9 (5.4)	p = 0.73
Duration	9.7 (8.3)	11.7 (7.5)	p = 0.37
Age at operation	16.1 (11.5)	17.6 (9.3)	p = 0.48

Results

PATIENTS

Out of the 37 patients studied, 12 had outcome grade I, eight grade II, nine grade III, and eight grade IV. Thus, 20 patients (54%) enjoyed a favourable outcome and 17 (46%) had poor outcome. The age at onset of the epilepsy, the duration, and the age at operation for these two groups are listed in table 1. None of these variables showed significant differences between the two outcome groups when analysed with a two tailed Mann-Whitney test.

CLINICAL SIGNS

The relation between several clinical variables and surgical outcome is shown in table 2. Contralateral head version, eye deviation, and autonomic manifestations during seizures were significantly associated with poor outcome.

Table 3 shows the relation between direction of head version and surgical outcome. There was a significant relation between contralateral version and poor outcome (Fisher's exact test, two tailed, p = 0.002).

COMPARISON BETWEEN HISTORY AND TELEMETRY

Out of the 18 patients who had head version, 10 had video EEG telemetry of seizures. In two patients head version occurred to both sides in different seizures

Table 2. Relation between clinical signs and surgical outcome.

Symptom or sign	Outcome		
	Good (n = 20)	Poor (n = 17)	P
Aura	9	11	0.231
Staring	12	10	0.942
Vocalisation	11	5	0.117
Incontinence	8	4	0.286
2nd generalised seizures	8	8	0.666
Autonomic features	6	11	0.035*
Oroalimentary automatisms	5	2	0.416
Cursive automatisms	6	1	0.097
Bimanual/bipedal automatisms	8	9	0.431
Contralateral head version	1	9	0.002*
Ipsilateral head version	4	2	0.667
Eye deviation (any direction)	5	10	0.037*
Myoclonias/clonic movements	8	11	0.134
Posturing	13	11	0.985
Postictal confusion	6	7	0.478
Postictal dysphasia	3	3	1.000
Todd's paralysis	2	4	0.383

The significance level accepted as suggesting statistical differences between favourable and poor outcome was p<0.05. Variables found to be associated with either favourable or poor outcome are indicated with an asterisk.

(one patient had head version to both sides in one seizure whereas the other patient had version of the head sometimes to the left and sometimes to the right in different seizures); they were excluded from the comparison between the direction of head version and outcome. In three further patients unilateral head version was not reported in the history but was seen in seizures recorded on telemetry. In the four patients in whom unilateral head version was previously reported in the medical notes and seen during the telemetry, the direction of head version was consistent. In one patient unilateral head version was reported in the history but not seen on telemetry.

Table 3. Direction of head version in relation to surgical outcome.

	Outcome	
Head version	Good (n = 20)	Poor (n = 17)
Contralateral	1	9
Ipsilateral	4	2
Inconsistent	1	1
No version	14	5

The terms contralateral and ipsilateral refer to the direction of version with respect to the operated side. The term "inconsistent" refers to patients in whom head version occurred sometimes ipsilateral and sometimes contralateral to the operated side. When comparing contralateral head version with the rest, there is a very significant association between contralateral head version and poor outcome and between lack of contralateral head version and favourable outcome (contingency table 1, 9, 19, 8, Fisher's exact test, two tailed, p = 0.002).

Telemetry was carried out in 10 patients of the 24 who were considered to have ictal posturing and demonstrated posturing in nine. In five patients posturing was recorded in the notes and confirmed by telemetry. In four patients posturing was seen on telemetry, but not recorded in the medical history.

Nine patients who presented ictal myoclonias or clonic movements either on telemetry or in history had telemetry. Among these nine patients, such movements were seen on telemetry in seven patients and reported in the history of six patients. In four patients, jerking was recorded in the notes and confirmed by telemetry. In two patients jerks were described in the notes but not seen on telemetry. In three patients the jerks were present on telemetry but not reported in the history. In all four patients in whom jerks were reported in the notes and described by telemetry, both methods agreed on the laterality of jerks.

It therefore seems that medical history reliably reported presence and laterality of convulsive ictal signs although with lower sensitivity than telemetry. In only one instance was a discrepancy in laterality found.

Table 4. Relation between surgical outcome and epileptiform activity on interictal scalp EEG.

	Outcome	
Interictal EEG	Good (n = 16)	Poor (n = 17)
Unilateral	5	8
Bilateral synchronous	5	2
Bilateral independent	1	0
Unilateral and bilateral synchronous	4	4
No epileptiform discharges	1	3

ELECTROENCEPHALOGRAPHIC FINDINGS

Interictal

Twenty one patients had unilateral focal or unilateral multifocal discharges in their preoperative interictal EEG, all of them lateralised to the operated side. One patient showed only a focal excess of slow activity with no epileptiform discharges in the right frontal area. This patient had a favourable surgical outcome. Interictal EEG findings were not predictive of surgical outcome (table 4).

Ictal

Among the 15 patients with ictal EEG on telemetry, nine had intracranial recordings with subdural or intracerebral electrodes. Eleven patients (including nine with intracranial EEG recordings) had focal seizure onset. Five of them had a favourable outcome whereas six patients had a poor outcome. Three patients had bilateral and one patient had multifocal seizure onset and these four patients had poor outcome. Two of these four patients had a focal abnormality on neuroimaging (oligodendroglioma, scar secondary to an abcess), one had multiple unilateral abnormalities and one had normal neuroimaging.

NEUROIMAGING

Twenty patients had a focal abnormality on neuroimaging. Seventeen patients had normal neuroimaging or presented non-focal abnormalities. Eleven of these had normal imaging of which four had a favourable outcome; two patients had multifocal abnormalities, both of them with a poor outcome; three patients had

unilateral atrophy, one of them had a favourable outcome; one patient had bilateral atrophy and a favourable outcome.

Among the 20 patients who presented focal abnormalities on neuroimaging, 14 had favourable outcome. However only six of the 17 patients with no focal abnormalities on neuroimaging enjoyed a favourable outcome. These proportions were significantly different (χ^2, 1 df, p = 0.035).

NEUROPSYCHOLOGY

Among the 25 patients who underwent neuropsychological testing, eight showed a lateralised deficit which suggested a dysfunction of the subsequently operated hemisphere in three patients. Among the three patients with psychometry lateralised to the operated side, two patients enjoyed favourable outcome and one patient had poor outcome. Among the five patients who showed neuropsychological preoperative deficits implicating the non-operated side, two had favourable outcome and three had poor outcome.

PRESURGICAL ASSESSMENT AND RESECTION

Eleven patients had normal neuroimaging. Of these, four patients were operated on the basis of history and clear focal interictal EEG abnormalities, three of them were operated on before telemetric recordings were available and one did not have seizures during repeated 2 week telemetries. Seven patients were operated on the basis of findings from intracranial ictal recordings.

The relation between type of resection and surgical outcome was as follows: nine patients had a total lobectomy, four of whom enjoyed a favourable outcome; nine patients had a parasagittal resection, four with favourable outcome; eight patients had a resection confined to the convexity, four of whom had a favourable outcome; and 11 patients had a polar lobectomy, of whom eight had a favourable outcome. Although the number of patients for each type is small, patients who underwent a polar resection seem to have done better. After a polar lobectomy 73% had a favourable outcome whereas only 46% of patients had favourable outcome after a total frontal lobectomy, a parasagittal resection or a resection confined to the convexity of the frontal lobe.

Table 5. Relation between pathology and surgical outcome.

	Outcome	
Pathology	Good (n = 20)	Poor (n = 17)
Cortical dysplasia	10	7
Neoplasm	3	3
Scarring	2	2
Vascular malformation	3	0
Rasmussen	0	2
Other pathology	2	1
No lesion found	0	2

In some patients functional procedures were performed in addition to resection at the time of the operation; one patient had in addition an anterior callosotomy and four had a procedure confined to the motor strip in addition to the resective surgery of the frontal lobe. The surgical outcome for the patient who had callosotomy was favourable. One of the four patients with multiple subpial transection had favourable outcome and three did poorly.

PATHOLOGY

The pathological findings in the resected material and the prognostic value of the different types of pathology in relation to surgical outcome are shown in table 5. No particular pathology seems to be significantly associated with favourable or poor outcome. Nevertheless, vascular malformations seem to have better outcomes, whereas Rasmussen's encephalitis and "no lesion" have by comparison worse outcomes. Patients with "other pathology" included one with poor outcome and pathology report of "abnormal brain, with suspicion of some unusual neurodegenerative disorder" and two patients with favourable outcome who were reported by the neuropathologist as Sturge-Weber syndrome, and extensive malformation reminiscent of tuberous sclerosis, partial pachygria (with microgyria), and dysplasia.

MULTIVARIATE LOGISTIC REGRESSION

The following covariates were used for the logistic regression model: autonomic features, contralateral head version, deviation of the eyes, and the presence of a focal abnormality on neuroimaging (Model χ^2 =13.8, 2 df, p = 0.0010, Goodness of fit = 41.7). The variables significantly associated with surgical outcome were presence of a focal abnormality on neuroimaging (b = 1.32, SE = 0.57, p = 0.021, R = 0.25) and contralateral head version (b = -2.75, SE = 1.12, p = 0.014, R = -0.28). Both variables were independent (p = 0.19).

POSTOPERATIVE COMPLICATIONS

The most common postoperative complication was hemiparesis, which was seen in eight patients and gradually improved in all cases, probably because it was secondary to cerebral oedema. One patient developed monoplegia of the right arm due to extradural haematoma and gradually improved although a mild weakness persisted. Eight patients developed pyrexia which resolved with antibiotics in four. The other four patients required removal of the bone flap and some form of cranioplasty. Two patients had dysphasia which in one patient resolved whereas the other patient was left with a mild dysphasia secondary to a cerebrovascular accident. One patient had a CSF leak through the left nostril which required reopening of the craniotomy and patching of the dura with a graft of fascia lata. One patient developed buzzing sensations in the left ear. Eighteen patients did not have any postoperative complications.

OUTCOME VERSUS TIME

In the period from 1975 to 1985, 12 patients (mean (SD) follow up period 9.5 (4.5) years) were operated on and six had favourable outcome. From 1985 to 1991, 13 patients (mean (SD) follow up period 5.0 (1.6) years) were operated on and only five had favourable outcome. Of the 12 patients (mean (SD) follow up period 3.4 (1.8) years who were operated on between 1991 and 1996 nine had favourable outcome. In the last group there were three patients with a follow up period of one to two years, all of them with a favourable surgical outcome.

Discussion

Some variables were significantly associated with surgical outcome. A focal abnormality on neuroimaging was associated with a good result. The presence of autonomic manifestations, eye deviation, contralateral head version, and bilateral or multifocal ictal onset was associated with poor outcome. A multivariate logistic regression model showed that only contralateral head version and the presence of a focal abnormality on neuroimaging had a significant prognostic value.

There was a significant association between version contralateral to the operated side and poor outcome. This may seem surprising as head version has traditionally been interpreted as suggestive of seizure onset contralateral to the direction of version since the early experiments involving electrical stimulation of the frontal lobe in primates and human patients [Ferrier, 1874; Penfield, 1941; Penfield, 1954]. There are several cortical and subcortical mechanisms by which both ipsilateral and contralateral head version can be induced (for an excellent discussion, see Ochs [Ochs et al., 1984]). For instance, electrical stimulation of the frontal eye fields and supplementary motor cortex tends to induce contralateral version [Penfield, 1954] whereas stimulation of the superior temporal gyrus, premotor, and primary motor cortex is associated with version towards the stimulated side [Ferrier, 1874; Rasmussen et al., 1948]. Thus, during a clinical frontal seizure, where widespread areas of the cortex may be rapidly activated, both ipsilateral and contralateral version could in principle be induced. In fact, some authors have mentioned the poor localising value of head version for establishing laterality in partial seizures [Ochs et al., 1984; Robillard et al., 1983; Quesney, 1986], whereas others found head version to be a significant lateralising sign [Bleasel et al., 1997; Chee et al., 1993; McLachlan, 1987; Fakhoury et al., 1995; Kernan et al., 1993; Quesney et al., 1990; Wyllie et al., 1986]. Curiously, among the second group of authors, who found a significant association between head version and the location of seizure onset, there is a marked discrepancy as to whether head version occurs ipsilateral or contralateral to seizure onset. There are three main factors which seem to explain these differences: (a) the lobe involved at seizure onset, (b) the quality of head version and its timing with respect to seizure

onset or secondary generalisation, and (c) the methodology used to identify seizure onset. Ochs et al. studied the direction of head version with simultaneous intracranial or scalp electroencephalographic recordings in 106 seizures from 43 patients with partial epilepsy [Ochs et al., 1984]. Ipsilateral head version was found in 53 seizures and contralateral head version was seen in 41 seizures, this difference was not significant. However, in the 17 seizures with clear frontal onset in the EEG, the head deviated to the ipsilateral side in 14 seizures and to the contralateral side in only three seizures ($\chi^2 = 7.12$, 1 df, $p < 0.01$), suggesting that at least in frontal lobe epilepsy, head version may have localising value to the ipsilateral side. Similarly, Quesney found that in 56 seizures with ictal electroencephalographic changes strictly confined to one frontal lobe, ipsilateral head version was seen in 36 seizures and contralateral version in 20 [Quesney, 1986]. However, McLachlan found that out of 25 patients regarded as having frontal lobe epilepsy by electrocencephalographic and neuroimaging criteria, 24 had contralateral head version and only one had ipsilateral head version according to reliable witnesses or to the patients themselves [McLachlan, 1987]. It could be argued that findings from history taking could not be sufficiently reliable, as it is based on witnesses' accounts. However, when favourable surgical outcome rather than diagnostic procedures is used to lateralise seizure onset, Quesney et al found in a retrospective study of "pure" frontal lobe epilepsy (composed of patients rendered seizure free after frontal lobe surgery), that unilateral head version was a lateralising sign to the side contralateral to version if present early in the seizure and without any other motor manifestation [Quesney et al., 1990]. It has also been suggested that in patients with frontal lobe seizures who remain conscious during head version, often occurring as the initial ictal manifestation, the direction is usually contralateral to the epileptic focus [Quesney, 1986].

Discrepancies regarding version could be explained by the findings of Kernan et al. and Fakhoury and Abou-Khalil who found that early isolated version in partial seizures which finishes before secondary generalisation tends to be ipsilateral whereas version taking place more than 120 seconds into the seizure or just before secondary generalisation is more likely to be contralateral [Fakhoury et al., 1995; Kernan et al., 1993]. This can be explained if we assume that widespread areas of

the ipsilateral frontal lobe are recruited during the development of secondary generalisation, including those areas responsible for contralateral head version. Such fast propagation responsible for contralateral version could be associated with poorer outcome, as in the case in temporal lobe epilepsy [Lieb et al., 1986].

The vast majority of patients had unilateral focal or unilateral multifocal discharges in their interictal EEG. This is not surprising considering that this was one of the criteria used in deciding to perform surgery [Binnie et al., 1992; Polkey et al, 1995]. However, 15 patients had secondarily generalised or bilaterally synchronous discharges. Interestingly, such discharges were not associated with poor outcome, by contrast with the findings by Lieb et al in temporal lobe epilepsy [Lieb et al., 1981]. These authors reported that out of nine patients operated on for temporal lobe epilepsy who presented with bilaterally synchronous discharges in their scalp interictal EEG, none had a favourable outcome, perhaps suggesting a frontal onset or early frontal involvement. In fact, it has long been established that secondarily generalised discharges can arise from localised areas of the frontal lobes [Loiseau, 1992] and also that they could spread very rapidly and almost explosively [Williamson, 1992]. Indeed, frontal lobe epilepsies with generalised bilateral synchrony can be improved by frontal resections [Stefan et al., 1988] and as many as 65% of patients who remained seizure free 5 years after surgery for frontal lobe epilepsy had bilaterally synchronous discharges in their preoperative interictal EEG [Rasmussen, 1983].

The four patients with bilateral or multifocal ictal onset had poor outcome, regardless of the presence of a focal abnormality on neuroimaging in two subjects. Similar findings have recently been reported elsewhere [Swartz, 1998] and emphasise that the presence of localised abnormalities on neuroimaging, although being a predictor for good outcome, does not necessarily imply a favourable result, particularly when discrepancies between structural and functional tests exist.

In our centre outcome has improved since 1991. Although follow up periods are necessarily shorter for patients operated on more recently, this is probably not the main factor contributing to the improvement of outcome as only three patients among those operated on later than 1991 had a follow up period shorter than 2 years. The most important factors in improving surgical outcome are likely to be

advances in surgical techniques and presurgical assessment, including the advent of neuroimaging.

The present study has implications for presurgical assessment of frontal lobe epilepsy. It seems that in addition to localising signs and symptoms, prediction of outcome requires the identification of factors which specifically appear to be associated with favourable outcome. For instance, the presence of autonomic manifestations during seizures was associated with poor outcome. Given the rapid seizure propagation in frontal lobe epilepsy, early symptoms can arise from areas located far from or contralateral to the initial functional abnormality, and the association between such findings and outcome may not be obvious. Thus some predictors of outcome should be found empirically as, in addition to the location and extent of the epileptogenic zone, they may also depend on the pathways and speed of propagation. Because in most centres, the number of patients with frontal lobe epilepsy is relatively small, statistically significant associations are difficult to obtain although strong, nearly significant trends are often seen. Convergence of multiple methodologies in localising functional and structural abnormalities could be the best predictor for outcome and it appears that convergence of both structural and functional techniques is desirable to obtain favourable outcome. Prospective studies considering several diagnostic methods in all patients are necessary.

CHAPTER 3

Relevance of Residual Histologic and Electrocorticographic Abnormalities for Surgical Outcome in Frontal Lobe Epilepsy

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Abstract

OBJECTIVES

To estimate the significance of residual electrocorticographic and neuropathologic abnormalities on seizure control after surgery for frontal lobe epilepsy with the purpose of determining their relevance in deciding the extent of the surgical procedure.

METHODS

The presence of epileptiform discharges in intraoperative electrocorticograms (ECoGs) and the nature and extent of neuropathologic abnormalities were reviewed for 35 patients who underwent frontal lobe resections for the treatment of epilepsy at our institution. The relations between surgical outcome and presence of the following features were studied: (a) presence of abnormal tissue at the limits of the resection; (b) presence of sporadic spikes and seizure patterns in the preresection ECoG; (c) their abolition in the postresection ECoG; and (d) the topography of residual discharges with respect to the margins of the resection.

RESULTS

18 patients had focal cortical dysplasia (FCD), and 17 had other abnormalities (non-FCD). Ten FCD patients and 11 non-FCD patients experienced a favourable outcome. Seizure patterns were significantly more common in patients with focal cortical dysplasia than in those without, with a sensitivity of 94% and a specificity of 75%. Abolition of seizure patterns was associated with a favourable surgical outcome ($p = 0.031$). Abolition of sporadic spikes or their presence in the postresection ECoG did not influence outcome. There was no clear relation between outcome and location of residual sporadic discharges. Seizure patterns persisted in the postresection ECoG in three FCD patients, were located at the margins of the resection in all three, and these patients had a poor outcome. Incomplete removal of abnormal tissue was not associated with a poorer outcome in either patient group or in the complete sample.

CONCLUSIONS

Seizure patterns were significantly more common in patients with cortical dysplasia, and their abolition on postresection ECoG recordings was associated with a favourable surgical outcome. Persistence of sporadic ECoG spikes and incomplete removal of histologic abnormalities did not affect outcome significantly.

Introduction

Frontal lobe epilepsy, a common form of partial epilepsy, is often refractory to medical treatment, and accounts for as many as 30% of those patients who undergo presurgical assessment for epilepsy [Binnie et al., 1992; Rasmussen et al., 1991]. However, the proportion of patients with favourable outcome with regard to seizure control after frontal lobe surgery is generally lower than that after surgery for temporal lobe epilepsy. Although some 56% of patients operated on for frontal lobe epilepsy experience a reduction in seizures [Rasmussen, 1991], only a minority remain seizure free after a long follow-up period [Hajek, 1988]. The reasons behind these relatively poor results remain unclear, but it has been suggested that the epileptogenic zone may be more extensive and difficult to identify in frontal lobe epilepsy [Talairach et al., 1992], either because of widespread pathology or because of fast propagation of discharges. Although the clinical, electroencephalographic, and neuroimaging manifestations of frontal lobe epilepsy have been widely studied [Penfield et al., 1954; Williamson et al., 1986; Trottier et al., 1988; Saint-Hilaire et al., 1988], the identification of preoperative factors predictive of surgical outcome has proved elusive, and no features have been consistently reported as predictive [Dodrill et al., 1986; Armon et al., 1996; Guldvog et al., 1994]. Ferrier et al. [Ferrier et al., 1999] have recently reported that a focal abnormality on neuroimaging (as opposed to diffuse, multifocal, or no abnormalities) is perhaps the single factor most predictive of favourable outcome, and Wennberg et al. [Wennberg et al., 1999] have proposed that complete excision of the lesion as confirmed by neuroimaging is of paramount importance. This suggests that the extent of removal of abnormalities visible on neuroimaging may be related to prognosis, as indeed has been repeatedly reported in the case of focal cortical dysplasia (FCD) [Hirabayashi et al., 1993; Palmini et al., 1991; Palmini et al., 1997]. Present advances in neuroimaging allow the identification of focal abnormalities in vivo with an increasing degree of sensitivity [Sisodiya et al., 1995; Sisodiya et al., 1996; Sisodiya et al., 1997], and complete resection of the lesion has been reported to be the single most important factor in achieving good seizure control after surgery for FCD [Palmini et al., 1991; Palmini et al., 1994;

Palmini et al., 1995]. However, when widespread or multifocal frontal lesions are identified on neuroimaging, complete resection of the lesion may not be achieved, either because of involvement of functionally eloquent areas [Hirabayashi et al., 1993; Palmini et al., 1991; Guerrini et al., 1992] or because histologic abnormalities may extend beyond the limits of the lesion as determined by neuroimaging. Indeed the presence of FCD at a microscopic level outside the visible magnetic resonance imaging (MRI) lesion or subtle dysplasia in remote areas has been postulated to explain less favourable seizure control in patients with FCD [Sisodiya et al., 1995]. The question then arises as to whether the extent of the surgical procedure should be guided by the location and extent of electrophysiologic abnormalities and/or by the distribution and histologic nature of the lesion as determined intraoperatively. A further complication emerges from the fact that the prognostic significance of residual spikes on postresection electrocorticographic (ECoG) recordings has long been debated, at least in the case of temporal lobe epilepsy (for discussion, see Fiol et al. [Fiol et al., 1991]). Some authors maintain that residual epileptiform discharges in postresection ECoG recordings have unfavourable long-term prognostic significance [So et al., 1989; Jennum et al., 1993; Kanner et al., 1995; Wennberg et al., 1998], whereas others dispute their predictive value [McBride et al., 1991; Cascino et al., 1995; Kanazawa et al., 1996; Tran et al., 1997]. As these series comprised mainly patients submitted to temporal lobe surgery, the significance of residual spikes after frontal lobe surgery and their relation to residual pathologic abnormalities is uncertain, although one study suggests that surgical failure is more likely in the presence of large epileptogenic zones and postexcision residual spiking [Salanova et al., 1994]. We have studied retrospectively the relation between postsurgical seizure control, persisting ECoG abnormalities, and the presence of histologic abnormalities extending to the limit, and by implication probably beyond, the margins of the resection in 35 of all 42 patients who underwent frontal resections because of refractory epilepsy between 1975 and 1996 in the Maudsley and King's College Hospitals. As FCD was the most common pathologic abnormality, accounting for half of the patient sample, and showed fairly characteristic radiologic, electroencephalographic, and

histopathologic features, patients were subclassified into those with FCD and those without (non-FCD).

Patients and methods

PATIENTS

The series derives from the 42 patients who underwent a frontal lobectomy for epilepsy between 1975 and 1996 at the Maudsley or King's College Hospitals. Three patients had a follow-up period <2 years, and two had incomplete medical records. These five patients were excluded from the study. In addition, two patients had Rasmussen's encephalitis and were also removed from analysis because of the progressive nature of this condition, leaving 35 patients in the present series. No patient had stigmata of tuberous sclerosis. The period of follow-up ranged from 2 to 19.5 years (mean, 6.0 years; SD, 3.8 years). Pathologic examination carried out on the surgical specimen showed that 18 patients had FCD, and 17 patients had other pathology (non-FCD). A more detailed account of the clinical features seen in this series of patients has been reported elsewhere (see chapter 2) [Ferrier et al., 1999; Hirabayashi et al., 1993]. Although this was a retrospective study over two decades, the patients had all been treated by a team headed by the same neurosurgeon, one neuropathologist, and two neurophysiologists. Detailed and standardized documentation was available.

PREOPERATIVE INVESTIGATIONS

All patients had at least one preoperative interictal scalp EEG. Standard chlorided silver-cup electrodes were applied according to the Maudsley system [Margerison et al., 1970], which is a modification of that described by Pampiglione [Pampiglione et al., 1956]. Most records lasted between 1 and 2 h and included a period of sleep. All patients had neuroimaging before the operation. Nineteen patients had only computed tomography (CT) examination, seven had only MRI, and nine had both. In addition, 14 patients underwent video telemetry either because neuroimaging was normal, or because the different tests used for lateralisation

and/or localisation of seizure onset yielded incongruent results. In eight of these 14 patients, prolonged recordings with subdural or intracerebral electrodes, and functional mapping with electrical stimulation were obtained to decide the side and extent of the resection.

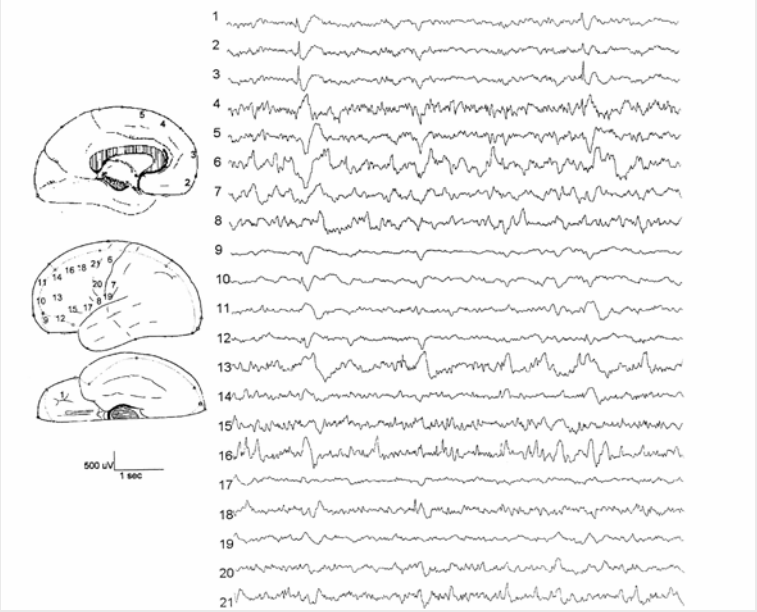
ELECTROCORTICOGRAPHY

Among the 33 patients who had preresection ECoG recordings, 30 also had postresection recordings. A frontal craniotomy was performed under general anaesthesia, which was maintained with nitrous oxide and isoflurane [Hewitt et al., 1984], and electrodes were placed on the surface of the brain. Up to 21 flexible saline wick electrodes [Penfield et al., 1954] were placed over the exposed convexity and, when necessary, eight or four contact flexible strip electrodes were often introduced subdurally in contact with the medial, polar, or orbital aspects of the frontal lobes and occasionally toward parietal or lateral temporal regions. If epileptiform discharges were not observed or scanty during the early stages of each recording, isoflurane level in inspired air was adjusted (between 0.25 and 1%) until discharges were observed. Records were analysed visually and displayed with reference to a selective common average reference from which electrodes most actively involved in epileptiform discharges were excluded. Throughout the article, the term spike will be used to describe sharp waveforms, including spikes, sharp waves, spike-and-slow-wave complexes, sharp-and-slow-wave complexes, according to the recommendations of the International Federation of Societies for Clinical Neurophysiology [Noachtar et al., 1999].

Discharges have been classified into:

1. Sporadic spikes: Spikes recorded at one or more sites and occurring at irregular time intervals, usually >2 s (Figure 1). This term is equivalent to "epileptiform pattern" or "epileptiform discharge," following the terminology of Noachtar et al. [Noachtar et al., 1999].
2. Seizure patterns: This term follows the international terminology [Noachtar et al., 1999] and does not imply that clinical ictal events occurred. In the present context, it refers to the presence of rhythmic electrographic phenomena, usually

Figure 1. Example of sporadic spikes involving the orbital and polar aspects of the left frontal lobe. Discharges remained after resection, and the patient had poor outcome.



persisting for >1 s, which could take three forms that largely correspond to those described by Palmini et al. [Palmini et al., 1995]: (a) Continuous spikes: continuous or almost continuous rhythmic regular spikes of variable frequencies, typically 1–10 Hz, lasting for several minutes or throughout the record (Figure 2); (b) Bursts of rhythmic spikes: sudden bursts of rhythmic regular spikes, occurring at 1–10 Hz and lasting for several seconds (Figure 3); (c) Trains of fast activity: build-up of trains of fast activity, occurring intermittently, often followed by rhythmic spikes.

PRERESECTION RECORD

For each patient, the position of the electrodes was drawn on brain maps by the neurosurgeon and the neurophysiologist. Records lasted for 10–12 min. During the second half of the preresection record, activation with thiopentone sodium in a dose sufficient to induce burst suppression (≤350 mg) was carried out.

Figure 2. Example of seizure pattern consisting of continuous spikes. Continuous spikes remained after resection, and the patient had poor outcome.

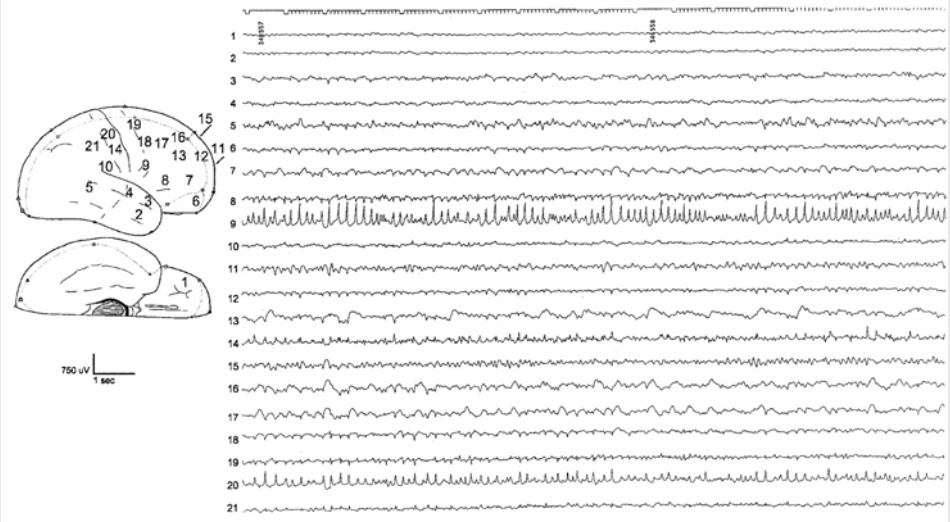
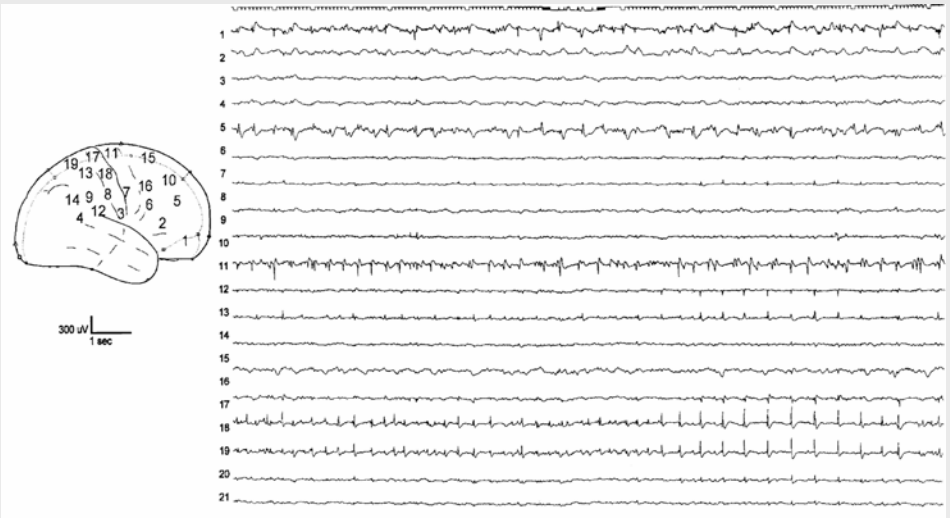


Figure 3. Example of seizure pattern consisting of bursts of rhythmic spikes. Bursts remained after resection, and the patients had poor outcome.



POSTRESECTION RECORD

An ECoG recording, lasting for 5–10 min, was obtained immediately after the resection. If the record showed persisting epileptiform discharges, either the resection was extended or additional multiple subpial transections were performed, after which a further ECoG recording was obtained. For analysis, the final record was considered the postresection ECoG. The topography of discharge patterns was studied in relation to resection margins. Discharges were considered to be at the margins of the resection if they were recorded from the remaining brain located within 0.5 cm from the margins.

SURGERY AND SURGICAL OUTCOME

The side, extent, and location of the resection were decided on the basis of the clinical history, neuroimaging, neurophysiologic findings (including scalp EEGs and intraoperative ECoG), and neuropsychology. Surgical outcome was classified in four grades [Engel et al., 1993]: I, free of disabling seizures; II, almost seizure free (three or fewer seizures per year); III, worthwhile improvement (but more than three seizures per year); and IV, no significant improvement. Grades I and II were considered a favourable surgical outcome, whereas grades III and IV were considered poor. Of the 18 FCD patients, 10 (56%) had a favourable outcome, whereas eight (44%) had poor surgical outcome. Among the 17 non-FCD patients, 11 (64.7%) experienced a favourable outcome, and six (35.3%) had poor outcome.

NEUROPATHOLOGY

All specimens were removed en bloc for histologic diagnosis and assessment of resection margins. Specimens were formalin-fixed for 1–3 days before slicing at right angles to the cortical surface at 0.5- to 0.7-cm intervals. After macroscopic examination and photography, tissue was processed for paraffin embedding, cut at 7- to 14-μm thickness, and stained with haematoxylin/eosin, Luxol Fast Blue/Nissl, and Glees silver impregnation. In addition, specific immunochemical staining including that with antisera to glial fibrillary acidic protein and electron-microscopic studies were sometimes performed [Janota et al., 1992].

Diagnostic criteria of FCD were those described by Taylor and Falconer [Taylor et al., 1971]. Typical features of FCD included laminar disorganisation and abnormally large nerve cells. The pathologic diagnosis was based on the presence of abnormally large neurones arranged singly or in clusters, possessing inappropriately oriented perikaryal processes, intermixed with variable proportions of abnormally large astrocytes, and, rarely, diagnosis was based on the presence of only abnormally large neurones or astrocytes [Janota et al., 1992]. Fibrillary gliosis, Rosenthal fibres, and cavitation were observed on occasions, and considered secondary degenerative phenomena. The essential criteria for FCD are therefore more restrictive than those used by Mischel et al. [Mischel et al., 1995] but allow greater uniformity of diagnosis.

All specimens were examined immediately after surgery with the purpose of determining the nature and extent of the underlying lesion, if any. Thus although this was a retrospective study, examination of resection margins to estimate if complete removal of the lesion had been achieved was an objective of neuropathologic examination throughout data collection, and reliable documentation was available in 15 FCD and in 15 non-FCD patients. Two non-FCD patients showed absence of neuropathologic abnormalities, leaving 13 non-FCD patients in whom the extent of removal of pathologic abnormalities could be studied. Removal of pathologically abnormal tissue was assumed to be incomplete if abnormalities extended to the cut surface.

STATISTICAL METHODS

The two-tailed Mann–Whitney test was used to establish differences in continuous variables (age of onset, duration, operation age) between the two outcome groups. Univariate analyses using $\chi 2$ (1 degree of freedom) or two-tailed Fisher's exact probability tests were carried out to identify the dichotomous variables significantly associated with surgical outcome. Fisher's exact test was used when the expected number of patients in one cell of the contingency table was fewer than five. Results were considered statistically significant if the p value reached a level < 0.05. All statistical analysis was carried out with SPSS 10.0 for Windows.

Results

DEMOGRAPHIC AND CLINICAL FEATURES OF THE PATIENT POPULATION

Among the 18 patients with FCD, the mean age at onset of epilepsy was 3.0 years (SD, 3.3 years), the mean age at operation was 11.5 years (SD, 7.0 years), and the mean duration of epilepsy was 8.5 years (SD, 6.0 years). In the 17 non-FCD patients, the mean age at onset of epilepsy was 9.5 years (SD, 4.9 years), the mean age at operation was 23.5 years (SD, 10.0 years), and the mean duration of epilepsy at the time of surgery was 13.9 years (SD, 8.5 years). The age at onset of epilepsy and the age at operation were significantly younger for the FCD patients ($p = 0.0002$ and $p = 0.0009$, respectively). The duration of epilepsy at the time of surgery was not significantly different between groups ($p = 0.057$).

ELECTROCORTICOGRAPHY

The relation between outcome and presence, absence, and abolition of each discharge type observed in pre- and postresection recordings is shown in Table 1 for FCD, non-FCD, and all patients.

PRERESECTION ECoG

Among the 17 FCD patients who had ECoG, 11 showed sporadic spikes, and 16 had at least one seizure pattern: nine patients showed continuous spikes, six had bursts of rhythmic spikes, and four showed trains of fast activity. Most commonly, patients showed one or more seizure patterns together with sporadic spikes elsewhere.

Among the 16 non-FCD patients who had an ECoG, 12 showed sporadic spikes, one patient had continuous spikes, two patients had bursts of rhythmic spikes, and one patient showed trains of fast activity (only after pharmacologic activation). Twelve of the 16 non-FCD patients did not show seizure patterns.

The presence of seizure patterns in the preresection ECoG showed a weak, nonsignificant trend toward an association with favourable outcome in non-FCD patients ($p = 0.077$) and in the whole pool of patients ($p = 0.055$). This suggests

that seizure patterns may be related to the epileptogenic zone, because this trend may become significant in larger samples. As most FCD patients had seizure patterns, no statistical association with outcome can be established in this group.

Significant associations were found between ECoG and neuropathologic abnormalities. Sporadic spikes showed a weak, nonsignificant negative association with FCD (11 of 17 with FCD vs. 12 of 16 in non-FCD patients; $\chi 2 = 0.41$, 1 df, $p = 0.52$; Table 1). However, a strong and significant positive association was found between presence of seizure patterns and focal cortical dysplasia (16 of 17 with FCD vs. four of 16 in the non-FCD group; $\chi 2 = 16.49$, 1 df, $p = 0.000049$). This means that identification of seizure patterns has a sensitivity of 16 of 17 (94%) and a specificity of 12 of 16 (75%) for detecting FCD in patients operated on because of frontal lobe epilepsy. The positive predictive value of seizure patterns is 16 of 20 (80%), and the negative predictive value is 12 of 13 (92%). Conversely, the presence of sporadic spikes has a sensitivity of 11 of 17 (65%) with a specificity of four of 16 (25%), a positive predictive value of 11 of 23 (48%), and a negative predictive value of four of 10 (40%). The findings clearly show that seizure patterns are predictive of FCD, whereas there is no clear association between sporadic discharges and type of pathology.

POSTRESECTION ECOG

All 17 patients with FCD and ECoG had a postresection record (nine with favourable outcome). Of the three patients who showed no spikes in the postresection ECoG, two enjoyed a favourable outcome. Three patients (all with poor outcome) showed only seizure patterns consisting of continuous spikes, which were present at the margins of the resection. Eleven patients showed only sporadic spikes, seven with a favourable outcome. Sporadic spikes were located at the margins of the resection in seven patients (two with poor outcome). Abnormalities in the remaining four patients (two with a favourable outcome) were located away from the resection and consisted of sporadic spikes.

Table 1. Relations between surgical outcome and discharge type on ECoG records.

	Condition	Good	Poor	P	
Before resection					
FCD (n = 17)					
Seizure patterns	P	9 (6)	7	0.47	F
	NP	0 (0)	1		
Sporadic spikes	P	6 (4)	5	1.00	F
	NP	3 (2)	3		
Non-FCD (n = 16)					
Seizure patterns	P	4 (2)	0	0.077	F
	NP	4 (2)	8		
Sporadic spikes	P	5 (3)	7	0.57	F
	NP	3 (1)	1		
All (n = 33)					
Seizure patterns	P	13 (8)	7	0.055	χ^2
	NP	4 (2)	9		
Sporadic spikes	P	11 (7)	12	0.71	F
	NP	6 (3)	4		
After resection					
FCD (n = 17)					
Seizure patterns	P	0 (0)	3	0.82	F
	NP	9 (6)	5		
Sporadic spikes	P	7 (5)	4	0.34	F
	NP	2 (1)	4		
Non-FCD (n = 13)					
Seizure patterns	P	1 (0)	0	1.00	F
	NP	6 (4)	6		
Sporadic spikes	P	5 (3)	4	1.00	F
	NP	2 (1)	2		
All (n = 30)					
Seizure patterns	P	1 (0)	3	0.32	F
	NP	15 (10)	11		
Sporadic spikes	P	12 (8)	8	0.44	χ^2
	NP	4 (2)	6		
Discharge abolition or persistence (all patients)					
Seizure patterns	Persistent	0	3	0.031*	F
(n = 20)	Abolished	13 (8)	4		
Sporadic spikes	Persistent	7 (5)	8	1.00	F
(n = 20)	Abolished	2 (1)	3		

Statistically significant results are indicated with an asterisk. FCD, Focal cortical dysplasia; F, Fisher's exact test; χ^2, chi-square test, 1 df; P, present; NP, not present. The number in brackets under the column "good outcome" shows the number of seizure-free patients.

Table 2. Relation between surgical outcome and persistence of histologic abnormalities.

	Good	Poor	p	
FCD (n = 15)				
Not totally removed	7 (5)	6	0.49	F
Removed	2 (1)	0		
Non-FCD (n = 13)				
Not totally removed	5 (3)	3	1.00	F
Removed	3 (2)	2		
Neoplasm (n = 6)				
Not totally removed	3 (2)	2	-	-
Removed	0 (0)	1		
Scar (n = 3)				
Not totally removed	1 (1)	1	-	-
Removed	0 (0)	1		
Vascular malformation (n = 3)				
Removed	3 (2)	0	-	-
Sturge-Weber (n = 1)				
Not totally removed	1 (0)	0	-	-
All (n = 28)				
Not totally removed	12 (8)	9	0.50	F
Removed	5 (3)	2		

FCD, Focal cortical dysplasia; F, Fisher's exact test; —, sample too small for statistical analysis. The number in brackets under the column "good outcome" shows the number of patients who remained seizure free.

Among the 16 non-FCD patients who had an ECoG, 13 had a postresection ECoG, of whom seven enjoyed a favourable outcome. Three patients did not have spikes in the postresection ECoG, of whom only one had a favourable outcome. Among the remaining 10 patients, only one seizure pattern consisted of nonmarginal bursts of rhythmic spikes that were not seen in the preresection ECoG. These were regarded as secondary to surgical injury, and the patient had a favourable outcome. The remaining nine patients had sporadic spikes. These were nonmarginal in one patient (with poor outcome), marginal in five (three with favourable outcome), and involved marginal and nonmarginal electrodes in three patients (two with favourable outcome).

In summary, sporadic discharges were nonmarginal in eight patients (four with favourable outcome) and were restricted to the margins in 12 patients (eight with favourable outcome). The difference between these two proportions is not statistically significant (Fisher's exact test, $p = 0.9$).

ABOLITION OF ECOG DISCHARGES

Abolition of discharges was defined as failure to record discharges in the postoperative ECoG in a patient in whom discharges had been observed in the preoperative ECoG. Only patients showing discharges in the preresection record have been considered in this section. Abolition of seizure patterns could be studied in 20 patients. The association between abolition of seizure patterns and favourable outcome was statistically significant ($p = 0.031$). Abolition of sporadic spikes could be studied in 20 patients, and there was no significant association between abolition of sporadic spikes and outcome.

NEUROPATHOLOGY

The extent of histologic abnormalities could be studied in 15 specimens of patients with FCD. In two patients, the abnormality was completely removed, and both patients experienced a favourable outcome. In the remaining 13 patients, the lesion was not completely removed, and seven enjoyed a favourable outcome.

Among the 15 non-FCD patients for whom pathology records could be studied, two patients showed no lesion and had poor outcome. For the remaining 13 patients who showed abnormalities on neuropathologic examination, Table 2 shows the relation between surgical outcome and removal of neuropathologic abnormalities. Among the six patients with neoplasms, a dysembryoplastic neuroepithelial tumour (DNET) was identified in two, an astrocytoma in two, an oligodendroglioma in one patient, and an oligoastrocytoma in one patient. The lesion was incompletely removed in five patients, of whom three nonetheless experienced a favourable outcome (two with DNET and one with astrocytoma). The patient in whom the neoplasic tissue (oligodendroglioma) appeared to be completely removed had poor outcome. All the vascular malformations were completely removed and had good outcome.

No significant relation was found between outcome and complete or incomplete removal of histologic abnormalities in either patient group or in the complete sample.

Discussion

It appears that both structural and functional abnormalities can show different forms or grades at different sites within the same patient, and the question then arises as to what should be considered significant abnormalities that should be treated to increase the likelihood of achieving good seizure control. Whereas incomplete removal of the histologic lesion (whether dysplastic or nondysplastic) does not appear to be associated with poor surgical result (Table 2), the predictive value of persisting ECoG discharges depends on their type. Abolition of seizure patterns after resection was associated with good outcome (Table 1). In addition, our findings confirm that seizure patterns in ECoG recordings are significantly more frequently associated with FCD than with other pathology, as previously reported by Palmini et al. [Palmini et al., 1997; Palmini et al., 1995].

The question arises as to what should be regarded as a predictor for poor outcome in postresection ECoG records and, therefore, whether action can be undertaken intraoperatively to improve surgical results. Although the presence of sporadic spikes in the postresection ECoG did not correlate with poor outcome, all three patients (all with FCD) whose seizure patterns persisted in the postresection ECoG had poor outcome. This sample is too small to test for statistical significance, but similar findings have been reported by Palmini et al. [Palmini et al., 1995] and Dubeau et al. [Dubeau et al., 1998], who found poor outcome in those patients in whom seizure patterns persisted after resection. Indeed, the findings in our series become significant when abolition or persistence of seizure patterns is considered, instead of just their presence in the postresection ECoG (Table 1). It thus appears that changes in the incidence of ECoG events as a response to surgery is a more sensitive predictor of outcome than is just their presence in postresection recordings. This confirms the findings by McBride et al. [McBride et al., 1991], who

found that even though absence of spikes in postresection ECoG records was not associated with favourable outcome, a reduction >50% in the incidence of discharges after resection (or transection) was associated with good outcome.

In contrast, the presence of sporadic spikes in the postresection ECoG does not appear to predict poor outcome. Similar results have been reported in other ECoG series [McBride et al., 1991]. It has been suggested that discharges remaining at the margins of the resection do not appear to have prognostic value and may be secondary to injury due to the surgical procedure, whereas those persisting far from the resection margins seem to associate with poor outcome [Wennberg et al., 1999; Wennberg et al., 1998; Tran et al., 1997]. Patients with FCD were not included in the series by Tran et al. [Tran et al., 1997] and made up only a small proportion of the patients included in the series reported by Wennberg et al. [Wennberg et al., 1998]. In our series, which includes a larger proportion of patients with FCD, the topography of remaining sporadic discharges did not relate to outcome. In addition, persistence of seizure patterns in the postresection ECoG occurred only at the margins of the resection and was associated with a poor surgical outcome, presumably because such seizure patterns were generated by remaining epileptogenic dysplastic tissue rather than because of injury. These findings suggest that the type of discharge pattern persisting in the postresection ECoG may be as relevant in predicting outcome as its topography with regard to resection margins.

It is surprising that incomplete removal of histologic abnormalities was not associated with poor outcome, particularly as the presence of a focal lesion in neuroimaging appears to be the single most significant factor associated with good outcome in the same series (see chapter 2) [Ferrier et al., 1999]. This emphasizes that not all structural abnormalities in the same lesion are equally epileptogenic, and the ECoG may aid in the identification of the most epileptogenic regions, as more extensive pathology may be missed by MRI. Indeed the use of ECoG in this series may explain why incomplete removal of histologic abnormalities was not associated with a poorer outcome. Technical factors are unlikely to be responsible, as incomplete removal of neuropathologic abnormalities was unequivocal when abnormal tissue was observed at a resection margin. Conversely, assessing

removal of the lesion as complete was less reliable because not all the cut surface could be examined microscopically. Assessing the value of complete removal of dysplastic tissue in our series is particularly difficult, as only two patients showed resection margins free of dysplastic tissue. In non-FCD patients, complete removal of the lesion does not appear to imply a favourable outcome, except in the three patients with vascular lesions in whom the abnormality was completely removed and who had good outcome.

It is concluded that whereas abolition of seizure patterns appears to be desirable to achieve a favourable outcome, persistence of sporadic spikes and incomplete removal of histologic abnormalities do not imply a poorer outcome. The usefulness of intraoperative ECoG in guiding epilepsy surgery has been questioned [McBride et al., 1991]. However, concrete indications may emerge if specific pathology, topography, or discharge patterns are studied.

CHAPTER 4

Electrocorticographic Discharge Patterns in Glioneuronal Tumours and Focal Cortical Dysplasia

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Abstract

OBJECTIVES

To determine whether highly epileptiform electrocorticographical discharge patterns occur in patients with glioneuronal tumours (GNT) and focal cortical dysplasia (FCD) and whether specific histopathological features are related to such patterns.

METHODS

The series consists of operated patients with pharmacoresistant epilepsy due to FCD or GNT between 1992 and 2003. Electrocorticography was reviewed for presence of continuous spiking, bursts, recruiting discharges or sporadic spikes. Surgical specimens were reviewed for the presence of balloon cells, (co-existing) cortical dysplasia and relative frequencies of neurons, glia and microglia.

RESULTS

Continuous spiking was seen in 55% vs 12% of patients with FCD and GNT respectively ($p = 0.005$). Bursts and recruiting discharges were seen in a similar proportion of patients with FCD or GNT. 91% of patients with continuous spiking showed (co-existing) cortical dysplasia in contrast to 42% of patients without this pattern ($p = 0.004$). The presence of balloon cells, and glia or microglia content were not associated with discharge patterns.

CONCLUSION

Continuous spiking, bursts, and recruiting discharges occur in patients with FCD and GNT. Continuous spiking was seen significantly more often in patients with FCD. When continuous spiking is found with GNT it is likely to be associated with dysplastic regions with a high neuronal density.

Introduction

Focal cortical dysplasia (FCD) and glioneuronal tumours (GNT), such as ganglioglioma (GG) and dysembryoplastic neuroeptihelial tumour (DNT), are well-known causes of focal symptomatic epilepsy. Focal cortical dysplasia was firstly described by Taylor et al. [Taylor et al., 1971] as being characterised by laminar disorganisation of the neocortex, leading to disruption of the normal architecture, often in combination with cellular abnormalities, such as dysmorphic neurons, giant neurons and balloon cells. Recent classification systems classify cortical dysplasia as FCD with or without balloon cells [Barkovich et al., 2001; Palmini et al., 2004; Lawson et al., 2005]. Since balloon cells are believed to result from maldifferentiation of cells at a very early (stem cell) stage, FCD with balloon cells is classified as a malformation of cortical development due to abnormal proliferation whereas FCD without such cells is classified as a malformation due to abnormal organisation [Barkovich et al., 2001]. Another classification system dichotomises FCD into type 1 and type 2 [Palmini et al., 2004]. Type 1 represents dysplasia without dysmorphic neurons or balloon cells whereas type 2 represents dyslamination with dysmorphic neurons (i.e. FCD as originally described by Taylor et al. [Taylor et al., 1971]). The absence or presence of balloon cells further subdivides type 2 into type 2A and type 2B respectively [Palmini et al., 2004].

GNTs are mixed low-grade tumours with neuronal and glial components and are considered an extreme form of FCD [Palmini et al., 2004]. Malignant transformation is rare and low-grade GNTs are considered a malformation of cortical development due to abnormal proliferation, together with cortical hamartomas of tuberous sclerosis, FCD with balloon cells and hemimegalencephaly [Barkovich et al., 2001]. Neurons within the tumours are clustered abnormally and laminar disorganisation, which is a key feature of FCD, can occur in the neocortex surrounding these low-grade tumours in over 80% of the cases [Daumas-Duport et al., 1988; Takahashi et al., 2005; Sakuta et al., 2005; Morris et al., 1998; Kleihues & Cavanee, 2000; Foldvary-Schaefer et al., 2004].

On preoperative EEG examination, patients with FCD or GNT may show focal, multifocal or widespread epileptiform discharges [Raymond et al., 1995; Raymond

& Fish, 1996; Chan et al., 1998; Kutsy, 1999; Sisodiya, 2000; Bautista et al., 2003]. The outcome of epilepsy surgery, in terms of seizure control, is less favourable in patients with FCD than in patients with other lesional epilepsies, including low-grade glioneuronal tumours, possibly because of remote or subtle microscopic dysplasia outside the visible MRI lesion [Sisodiya et al., 1995]. This suggests that the laminar disorganisation of GNT is less extensive or epileptogenic than that of FCD. These differences may underlie the difference in surgical outcome in these patients.

Acute intraoperative electrocorticography (ECoG) provides a unique opportunity to assess the epileptogenicity of exposed areas of the cortex during surgery. The technique is based on the assumption that epileptiform discharges recorded from the cortex are indicators of local cortical involvement in an epileptogenic network and are also related to interictal spikes recorded during presurgical surface EEGs. While there are several reports on ECoG spike discharge patterns in FCD, with persistence of seizure patterns or ictal-like and/or continuous epileptiform discharges in postresection ECoG recordings being predictive of poor surgical outcome [Palmini et al., 1995; Ferrier et al., 2001], less is known about the ECoG spike discharge patterns in patients with GNT, often because only small patient samples have been investigated [Kirkpatrick et al., 1993; Prayson et al., 1993; Rosenow et al., 1998; Lee et al., 2000; Nishio et al., 2001; Kameyama et al., 2001; Seo & Hong, 2003]. Because of the common neurodevelopmental origin and features (cortical dysplasia) of GNT and FCD, patients with these disorders may have similar electrocortocographic abnormalities, abnormalities which may determine the extent of the resection and surgical outcome. Indeed, Binnie et al. [Binnie et al., 2000] reported that highly epileptiform ECoG discharge patterns are also seen in patients with DNT, but that such patterns occur less frequently in this type of pathology when compared with FCD.

We think that the highly epileptiform discharge patterns originally described in patients with FCD are also present in patients with GNT. If this is the case, these discharge patterns may be associated with specific histological features (i.e. tumour cell types), intrinsic features (i.e. densities of glia, microglia or neurons), or the presence of cortical dysplasia surrounding the tumour. Associations between

electrophysiological and histological findings might provide insight into the epileptogenicity and/or pathophysiology of refractory focal epilepsies. In the present study, we investigated whether highly epileptiform discharge patterns on the intraoperative ECoG indicative of cortical dysplasia were also present in GNT.

Patients and methods

The database of the Dutch Collaborative Epilepsy Surgery Program was searched for patients who had a final diagnosis of FCD or GNT (DNT or ganglioglioma). In all patients refractory focal epilepsy was the cause of admission to the program.
Between 1992 (August) and 2003, 545 patients were operated on for pharmacoresistant epilepsy in our center. Of these, 18 patients had a postoperative tissue diagnosis of FCD and 77 patients had a postoperative tissue diagnosis of GNT (28 DNT and 49 GG). In the present study, patients were included if they had undergone lesion resection with intra-operative ECoG recording. The ECoG records and pathology specimens had to be available for analysis. Only cases that contained sufficient amount of perilesional zone (i.e. cortex adjacent to the lesion that did not include the visible microscopical infiltration zone) were included. Eleven patients with FCD and 43 patients with a GNT (12 DNT, 31 GG) met the inclusion criteria, representing 61% and 56% of all patients with FCD or a GNT, respectively. The proportion of excluded patients did not differ significantly between these two groups (FCD vs GNT, $p = 0.69$, χ^2, 1df). Relatively more patients with a DNT than with a GG did not meet the inclusion criteria, but this difference was not statistically significant (DNT vs GG, $p > 0.05$, χ^2, 1 df). Surgical outcome was assessed after 1 year using the Engel classification [Engel et al., 1993].

PRESURGICAL EVALUATION

All patients underwent phase I investigations consisting of non-invasive tests, including history, medical, neurological and neuropsychological assessment, structural neuroimaging (1.5 T MRI according to a dedicated protocol [Meiners, 2002], and extensive interictal and ictal EEG studies with video monitoring. None of

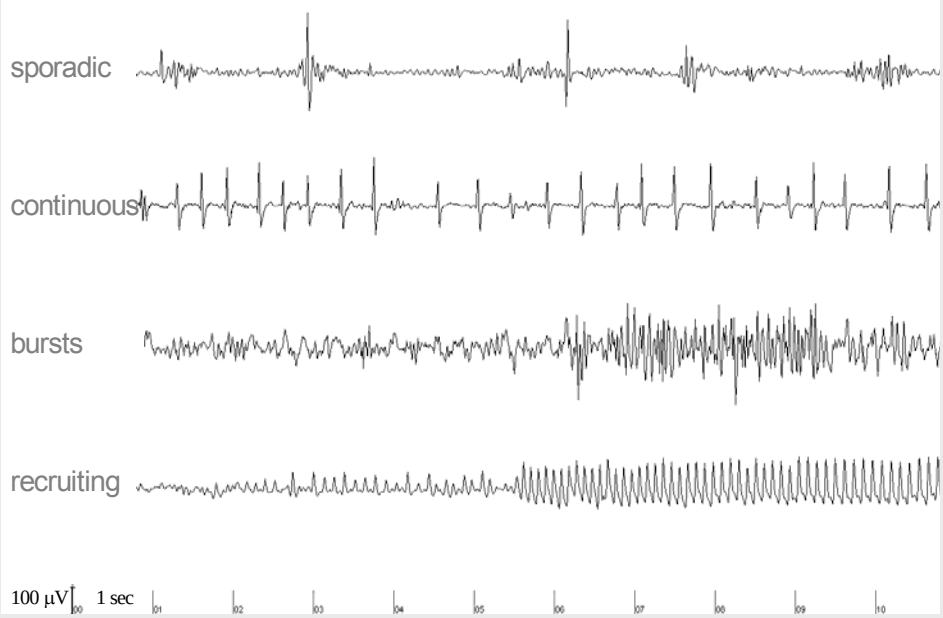
the patients were suspected to have co-existing dysplasia on neuroimaging during the presurgical evaluation. Psychiatric assessment and MEG studies (on experimental basis) were performed on indication. In Phase II, an intracarotid sodium amytal test (Wada test), interictal PET, (inter)ictal SPECT, fMRI and intracranial chronic EEG studies were performed on indication [van Veelen et al., 1990].

INTRAOPERATIVE ELECTROCORTICOGRAPHY

Intraoperative ECoG was performed routinely during surgery [Leijten et al., 2005]. The extent of the resection was based on findings from preoperative tests. In recent years surgical procedures were performed using image based intraoperative neuronavigation. Surgery was performed under general anaesthesia using intravenous propofol as the only anesthetic agent and continuous intravenous sufentanyl as analgesic. After opening of the dura mater, saline wick or silicon (5x4-) grid electrodes, with intercontact distances of 10 mm were placed on the exposed surface of the cortex. An effective number of 15 to 30 electrodes were used in each patient but it should be noted that electrodes were usually repositioned during the procedure resulting in a larger sampling area. The mesial and inferior temporal regions were assessed with the insertion of two 7-contacts electrode strips subtemporally reaching to the mesial regions [Binnie et al., 1998; Polkey et al., 1989]. Prior to ECoG recording the propofol infusion was discontinued; the patient remained on sufentanyl. Five to ten minutes of ECoG were sampled for classification of epileptiform abnormalities after the effects of propofol on the ECoG had abated with the requirement of a continuous background ECoG pattern and the patient not yet awake. The anesthesia conditions were uniform in all patients over the examined period of time. On indication, patients were awakened after the craniotomy for functional mapping of Wernicke's or Broca's areas.

In this study, the preresection record consisted of all available ECoG material before the final resection, excluding the part when the patient had been awakened to perform functional mapping. The duration of ECoG recordings varied from 5 to 15 minutes. The preresection ECoGs were reviewed using classification criteria

Figure 1. Examples of ECoG discharge patterns.



mainly based on those of Palmini et al. [Palmini et al., 1995](Figure 1): 1) sporadic spikes, spikes occurring at irregular time intervals at several sites; 2) continuous spiking, spikes occurring rhythmically at regular time intervals for at least 10 seconds, the interval between two subsequent spikes being 1 second at the most (frequency $\geq$ 1 Hz); 3) bursts of spikes, sudden occurrence of spikes for at least 1 second with a frequency of 10 Hz or more; 4) recruiting discharges, rhythmic spike activity characterised by increased amplitude and decreased frequency (electrocorticographic seizure). To avoid interpretation bias, the ECoG recordings were reviewed for the presence of one or more of these patterns by two clinical neurophysiologists (FL and AH) independently, both having experience in the field of epilepsy surgery monitoring for over a decade. The ECoG reviewers were aware of the inclusion criteria of this study but they were blinded for all patient information. Only neocortical epileptiform discharges were considered for analysis. Consensus was reached in cases of disagreement by common assessment.

Tissue preparation

Specimens were fixed in 10% buffered formalin, embedded in paraffin, sliced into 5-μm sections and mounted on organosilane (3-aminopropylethoxysilane; Sigma, St. Louis, MO)-coated slides. Representative sections were stained with haematoxylin-eosin and other markers, as described below.

Diagnosis of focal cortical dysplasia or glioneuronal tumour

Two neuropathologists (EA and WS) independently evaluated the samples, and confirmed the diagnosis of FCD or GNT (i.e. GG or DNT). For FCD the classification recently proposed by Palmini et al. was used for grading FCD into type 1, type 2A or type 2B [Palmini et al., 2004]. GG and DNT were diagnosed according to the revised WHO classification of tumors of the nervous system [Kleihues & Cavanee, 2000]. Histologically, GGs were composed of a mixture of atypical neuronal cells (cells without uniform orierentation, abnormal shape, often with vesicular nuclei, proment nucleoli) and neoplastic astrocytes (fibrillary astrocytes of varying cellularity and strongly GFAP staining) and showed a broad spectrum of histopathological features (see Figure 2). DNT showed a complex nodular or multinodular intracortical architecture with a typical heterogeneous cellular composition. They contained a complex mixture of neuronal cells, astrocytes and a prominent population of oligodendroglia-like cells (Figure 2).

Imunocytochemistry

Glial fibrillary acidic protein (GFAP; polyclonal rabbit, DAKO, Glostrup, Denmark; 1:2000), vimentin (mouse clone V9, DAKO; 1:400), synaptophysin (polyclonal rabbit, DAKO; 1: 200), neuronal nuclear protein (NeuN; mouse clone MAB377, IgG_1; Chemicon, Temecula, CA, USA; 1:1000), microtubule-associated protein (MAP2; mouse clone HM2, IgG_1; SIGMA, St. Louis, MO, USA; 1:100 and polyclonal rabbit, Chemicon; 1:1000) HLA-DR (mouse clone Tal1b5, Sigma, USA; 1:100) and CD68 (mouse monoclonal; DAKO; 1:1000) and CD31 (EN-4, IgG_1;

Sanbio, Uden, The Netherlands; 1:500) were used in the routine immunocytochemical analysis of epilepsy specimens.

Immunocytochemistry was carried out as previously described [Aronica et al., 2003; Aronica et al., 2001]. Single-label immunocytochemistry was performed using the avidin-biotin peroxidase method (Vector Elite) and 3,3-diaminobenzidine as chromogen. Sections were counterstained with haematoxylin. Sections incubated without the primary antibody (Ab) with pre-immune sera were essentially blank.

Evaluation of histological features

Two representative paraffin sections per case of GNT or FCD were evaluated for the presence or absence of associated laminar disorganisation within the surgical specimem. For the cases of GNT associated laminar disorganisation was evaluated in the perilesional zone that is, cortex adjacent to the lesion outside the microscopical infiltration zone. All specimens that were examined contained a sufficient amount of perilesional zone. This associated disorganisation in the perilesional zone is termed coexisting cortical dysplasia (coCD). Large neurons and/or balloon cells could be present in these dysplastic areas, and thus coCD could be classified into type 1, 2A and 2B according to the classification scheme of Palmini et al. [Palmini et al., 2004]. The relative frequencies (densities) of neurons, microglial and astroglial cells were calculated within ten representative fields of NeuN and GFAP, Tal1b5 and haematoxylin-eosin (HE)-stained (adjacent) sections of each lesion at a magnification of X 250, using an ocular grid as previously described [Aronica et al., 2001]. Neuronal cell bodies were differentiated from glia and glioneuronal balloon cells on the basis of morphology. For the GNTs the evaluation was performed in the center of the lesion. The results (labeling indices) were expressed as number of NeuN-, GFAP- and Tal1b5-labeled cells per total number of cells and were assigned semiquantitavely to three categories of relative frequencies as an estimate of the densities: 1) less than 10%, 2) 10%-30% and 3) more than 30%. Only neurons in which the nucleus could be clearly identified were counted. Balloon cells have eccentric nuclei and ballooned opalescent eosinophilic

cytoplasm. Sections stained with NeuN and GFAP and Tal1b5 adjacent to those used for HE staining were also studied.

STATISTICAL ANALYSIS

Student t-tests were used to analyse differences between mean age at onset, age at operation and duration of epilepsy in patients with FCD or GNT. χ^2 or Fisher's exact tests were used for difference in location of the lesion (temporal vs. extratemporal) and assessment of surgical outcome in relation to different underlying pathology.

For the analysis of ECoG discharge patterns versus histological diagnosis, the number of patients in each group showing these patterns was counted. All possible combinations of presence or absence of these ECoG discharge patterns were counted (only recruiting discharges, only continuous discharges, only bursts, recruiting and continuous discharges, recruiting discharges and bursts, etc.). In this way a table was constructed with mutually exclusive rows.

For analysis of histological features (such as cortical dysplasia and cell typing) versus ECoG discharge patterns, a second table with mutually exclusive rows was constructed. These rows consisted of all possible combinations of cortical dysplasia and densities of neurons, migcroglia and glia of more than 30%. The columns consisted of the specified ECoG discharge patterns.

χ^2 tests were used for 2x2 contingency tables. Fisher's exact test was used if one of the expected values in the cross tables was less than 5. Results were considered statistically significant if the p-value was less than 0.05.

Table 1. Patient characteristics.

	FCD	GNT
Number of patients	11	43
Male : female	6 : 5	26 : 17
Right : left	9 : 2	19 : 24
Temp : extratemp[1]	3 : 8	37 : 6
Age at onset[2]	1.0 (0 – 30.0)	11.0 (0 – 26.0)
Age at operation[3]	13.0 (0 – 50.0)	29.0 (1.0 – 55.0)
Duration of epilepsy	12.0 (0 – 44.0)	16 (0 – 39.0)
% seizure free after one year	64%	74%

FCD = focal cortical dysplasia; GNT = glioneuronal tumour. Age at onset, aget at operation and the duriation of epilepsy are expressed as medians; [1]$p < 0.001$, Fisher's exact test, 1 df, [2]$p < 0.05$, Student's T-test, [3]$p < 0.10$, Student's T-test.

Results

PATIENT CHARACTERISTICS

Fifty-four patients met the inclusion criteria (11 FCD, 43 GNT (i.e. 12 DNT, 31 GG)). Table 1 shows the characteristics of these patients. FCD was located in extratemporal areas more often than were GNTs (Fisher's exact test, $p < 0.001$). The median age at onset of seizures and age at operation were lower in FCD than in GNT (Student's T-test, $p < 0.05$ and $p < 0.10$, respectively). There was no statistically significant difference in duration of epilepsy between the two patient groups.

Surgical outcome was assessed after 1 year. Seven patients (= 64%) with FCD were seizure free (Engel I), as were 32 patients (= 74%) with a GNT. Relatively more patients with a GNT than with FCD were seizure free after 1 year, but this difference was not statistically significant ($p = 0.48$, χ^2, 1df). Eight patients, all with a GNT, had concomitant mesial temporal sclerosis.

Figure 2 (opposite page, color figure see page 166).

Histopathological feautures of glioneuronal tumours (ganglioglioma, GG; dysembryoplastic neuroepithelial tumour, DNT) and focal cortical dysplasia (FCD).

Panels A-D: Representative photomicrographs of ganglioglioma. A: Haematoxylin/Eosin (HE) staining of GG showing the mixture of atypical neuronal cells, lacking uniform orientation (arrows) and glial cells. B: NeuN detects the neuronal component. C: GFAP detects the astroglial tumour component. D: HLA-DR detects the presence of cells of the microglia/macrophage lineage.

Panels E-H: representative photomicrographs of DNT. E: HE staining of DNT showing a typical heterogeneous cellular composition, with floating neurons (arrow) surrounded by a prominent population of oligodendroglia-like cells. F: NeuN detects the neuronal component. G: GFAP detects few reactive astrocytes (arrow) between the GFAP-negative oligodendroglia-like cells. H: HLA-DR detects the presence of cells of the microglia/macrophage lineage.

Panels I-M: representative photomicrographs of FCD (type IIB). I: NeuN detects the neuronal component of the dysplastic cortex with disorganised radial and laminar architecture. J: HE-staining showing a group of large cells with pale eosinophilic cytoplasm and eccentric nucleus (balloon cells). K: coexisting cortical dysplasia (coCD) in a patient with a DNT; GFAP staining reveals balloon cells (arrows) and reactive astrocytes (arrow-heads) surrounding a dysmorphic neuron (asterisk). L: dysplastic neurons with accumulation of neurofilament. M: HLA-DR detects the presence of cells of the microglia/macrophage lineage.

N-R: Representative photomicrographs of GNT with coCD. N (HE staining): low-power micrograph showing the typical nodular structure of DNT. The insert in N shows NeuN positive floating neurons (arrows) surrounded by oligodendroglia-like cells. O (HE-staining): Low-power micrograph of GG. Insert in O shows the neuronal component of the tumor (NeuN positive, arrows) surrounded by tumour astrocytes. P-R: Low-power micrographs of coCD (dysplastyic cortex outside the microscopical infiltration zone). P: coCD type I (associated with DNT). Insert in P shows ectopically placed neurons (NeuN positive; arrows) in layer I. Q: coCD type IIA (associated with DNT). Insert in Q shows NeuN positive abnormally oriented dysplastic neurons. R: coCD type IIB (associated with GG). Insert in R shows a dysplastic neuron (NeuN positive, arrow) and two balloon cells (NeuN negative, arrow-heads). Scale bar in A: A 70 µm; B-E 35 µm; F 45 µm; G-H 35 µm; J 45 µm; K-M 35 µm; I, N-R 285 µm; insert in I 70 µm, inserts in N-O 150 µm, insert in P 120 µm, inserts in Q-R 100 µm.

Figure 2. For color figure see page 166.

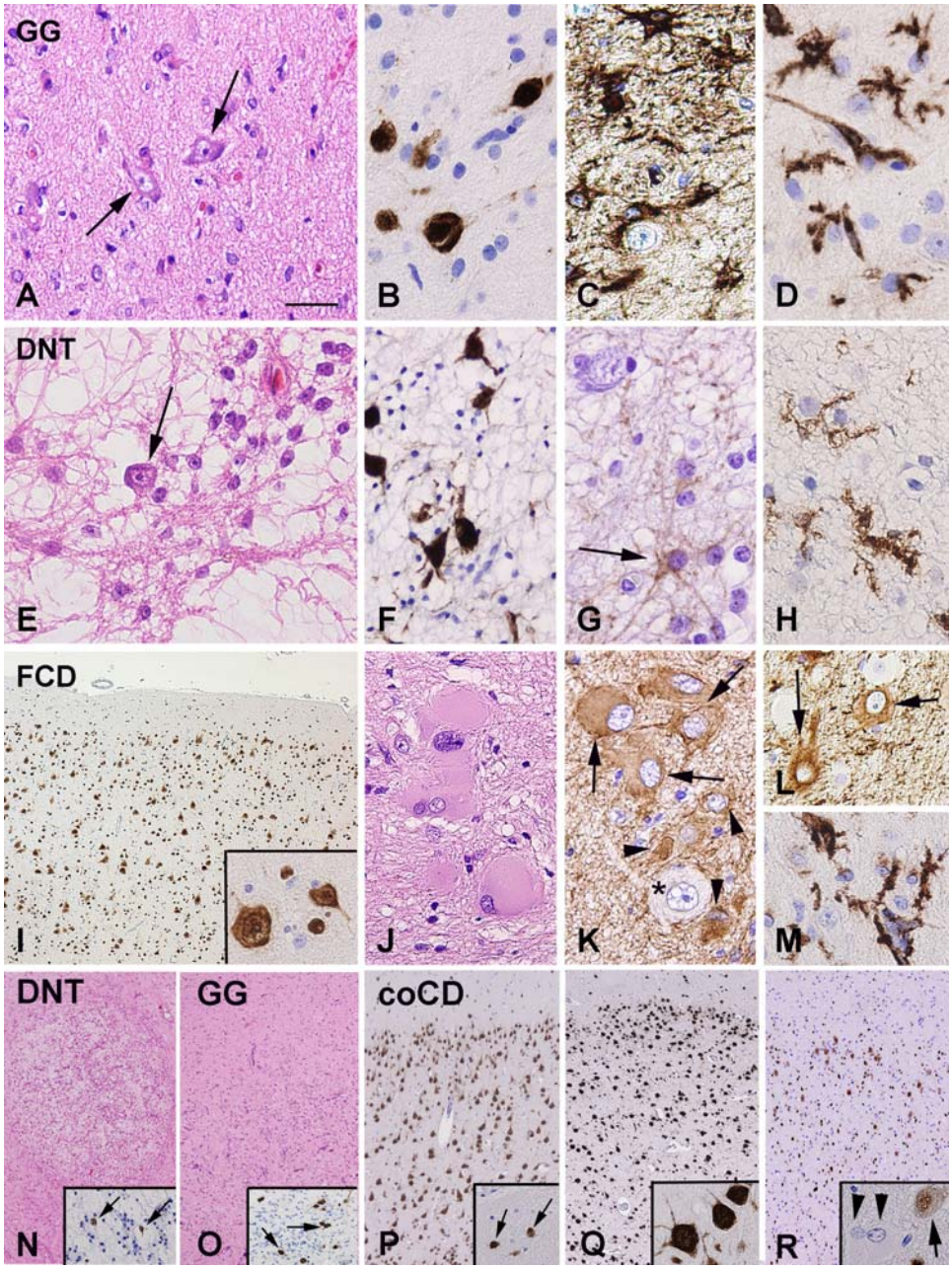


Table 2. Epileptiform discharge patterns and diagnosis.

N = 54	FCD n=11	GNT n=43
No (or only sporadic) spikes	5	27
Recruiting	0	2
Bursts	0	7
recruiting & bursts	0	2
Continuous	2	2
Recruiting & continuous	0	0
bursts & continuous	1	3
recruiting & bursts & continuous	3	0

Each entry in the table represents the number of patients and per patient group showing (any combination of) specificied epileptiform discharge pattern. FCD = focal cortical dysplasia; GNT = glioneuronal tumour.

Table 3. Continuous spiking and histological diagnosis.

N = 54	FCD n=11	GNT n=43
continuous spiking		
Present	6 (55%)	5 (12%)
not present	5 (45%)	38 (88%)

Patients with continuous spiking are grouped together. FCD = focal cortical dysplasia, GNT = glioneuronal tumour, p = 0.005, Fisher's exact test.

ELECTROCORTICOGRAPHIC DISCHARGE PATTERNS

Four patients did not have spikes in their ECoG, 48 patients had sporadic spikes, 11 patients had continuous spikes, 7 patients had recruiting discharges and 16 patients had bursts of spikes. In 20-30% a consensus conclusion was reached after discussion between the two neurophysiologists.

Table 4. Histological features and presence of continuous spiking, bursts or recruiting discharges.

	Continuous		Bursts		Recruiting	
	P n=11	NP n=43	P n=16	NP n=38	P n=7	NP n=47
Dyspl-, neuron-, mglia, glia-	0	2	2	0	1	1
Glia+	0	12	3	9	1	11
Neur+ & glia+	0	1	0	1	0	1
Glia+ & mglia+	1	8	2	7	0	9
Neur+ & glia+ & mglia+	0	2	1	1	1	1
Dyspl+	2	7	3	6	0	9
Dyspl+ & glia+	1	3	1	3	1	3
Dyspl+ & neur+ & glia+	5	1	3	3	3	3
Dyspl+ & mglia+	0	3	0	3	0	3
Dyspl+ & glia+ & mglia+	2	2	1	3	0	4
Dyspl+ & neur+ & glia+ & mglia+	0	2	0	2	0	2

The rows represent all possible combinations of histologic features and are mutually exclusive. Dyspl+ = presence of dysplasia (FCD or GNT with coCD); Dyspl- = absence of dysplasia; neuron+ = high content of neurons (≥ 30% within the lesion); neuron- = low content of neurons (<30% within the lesion); mglia+ = high content of microglia (≥30% within the lesion); mglia- = low content of microglia (<30% within the lesion); glia+ = high content of glia (≥ 30% within the lesion); glia - = low content of glia (<30% within the lesion). 'P' = present; 'NP' = not present.

HISTOLOGICAL DIAGNOSIS AND HISTOLOGICAL FEATURES

Forty-three patients had a diagnosis of GNT (12 DNT, 31 GG) and 11 patients had a diagnosis of FCD (three with type 2A and eight with type 2B). In 17 of the 43 GNTs (12 DNT, 5 GG) the surgical specimen contained dysplastic regions (coCD). Thus, there were 28 patients with cortical dysplasia (11 with FCD and 17 coCD next to a GNT). Out of the 12 patients with coCD next to a DNT four patients had coCD type 1, six patients had coCD type 2A and two patients had coCD type 2B. Of the five patients with coCD next to a GG, one had coCD type 2B while the remaining four had coCD type 2A.

Table 5a. The relation between presence of dysplasia and discharge patterns.

	Continuous		Bursts		Recruiting	
	P	NP	P	NP	P	NP
	n=11	n=43	n=16	n=38	N=7	n=47
Dyspl						
P	10[1]	18[1]	8	20	4	24
NP	1[1]	25[1]	8	18	3	23

Dyspl = dysplasia (FCD or GNT with coCD); 'P' = present; 'NP' = not present. Positive predictive value for continuous spiking and presence of dysplasia is 91% ([1]p = 0.004, Chi-square, 1 df).

Table 5b. Subytpes of cortical dysplasia (11 FCD, 17 GNT (12 DNT, 5 ganglioglioma)).

	Continuous		Bursts		Recruiting	
	P	NP	P	NP	P	NP
	n=10	n=18	n=8	n=20	n=4	n=24
FCD type 1	1	3	2	2	0	4
FCD type 2A	3	9	2	10	2	10
FCD type 2B	6	6	4	8	2	10

Subtypes of cortical dysplasia and relation with continuous spiking, bursts of spikes and recruiting discharges. 'P' = present; 'NP' = not present. There is no significant relation between discharge patterns and subtypes of dysplasia.

Of the 28 patients with cortical dysplasia (FCD and GNT with coCD), 4 had cortical dysplasia type 1, 12 had type 2A, and 12 had type 2B. Nine patients with FCD had balloon cells in the surgical specimen. Atypical large and pleomorphic cells similar to the balloon cells of FCD type 2B were observed within the GG of 6 patients. No patient with a DNT had such cells within the lesion. Forty patients had a high content of glia in the lesion, 20 patients had a high content of microglia, and 11 patients a high content of neurons

Table 6. Relationship between lesional content of neurons and discharge patterns.

	Continuous		Bursts		Recruiting	
	P	NP	P	NP	P	NP
	n=11	n=43	n=16	n=38	N=7	n=47
Neuronal content						
>= 30%	5[1]	6[1]	4	7	4[2]	7[2]
< 30%	6[1]	37[1]	12	31	3[2]	40[2]

Presence of continuous spiking or recruiting discharges was significantly related to a high content of neurons ([1]p = 0.035, Fisher's exact test; [2]p = 0.025, Fisher's exact test).

ELECTROCORTICOGRAPHY AND HISTOLOGICAL DIAGNOSIS

Preresection ECoGs were scored for the presence of one or more types of predefined neocortical epileptiform patterns. All but one patient had sporadic spikes, and so this epileptiform pattern was disregarded for analysis. No patients had only continuous spiking and recruiting discharges in the same recording. All other possible combinations of discharge patterns and the distribution within each patient group are shown in Table 2. Continuous spiking, bursts of spikes and recruiting discharges were seen in patients with FCD, but also in patients with GNTs.

Six of the 11 patients with FCD had continuous spiking (sensitivity for detecting FCD = 55%) while 38 of 43 patients without FCD (28 GG, 10 DNT) did not show continuous spiking (specificity for FCD = 88%). Of the 11 patients showing continuous spiking, 6 had a diagnosis of FCD (positive predictive value = 55%) and five patients had a GNT (3 GG, 2 DNT). Of the 43 patients without continuous spiking, 38 did not have a diagnosis of FCD (28 GG, 10 DNT, negative predictive value = 88%). Table 3 summarises the assocation between continuous spiking and histological diagnosis. Continuous spiking was seen significantly more often in patients with FCD than in patients with a GNT (p = 0.005, Fisher's exact test). No significant relationship between histological diagnosis and bursts or recruiting discharges was found.

If the eight patients with concomitant mesial temporal sclerosis were excluded from the analysis the same significant results were obtained, i.e. continuous spiking was related to FCD (p = 0.013, Fisher's exact test).

ELECTROCORTICOGRAPHY AND HISTOLOGICAL FEATURES

The combinations of histological features (cortical dysplasia and lesional content of neurons, microglia and astroglia) and the number of patients showing the specified epileptiform patterns are given in Table 4.

Of the 28 patients with cortical dysplasia, 10 had continuous spiking (sensitivity 36%). Of the 26 patients without cortical dysplasia, only 1 had continuous spiking (specificity 96%). In contrast, 10 of the 11 patients with continuous spiking had cortical dysplasia (PPV 91%), whereas 25 of the 43 patients without continuous spiking did not have cortical dysplasia (NPV 58%). Continuous spiking was significantly associated with the presence of cortical dysplasia (p = 0.004, χ^2, 1 df) (Table 5a), whereas there was no association between the presence of discharge patterns and subtypes of dysplasia (Table 5b).

Of the 11 patients with a neuronal density of more than 30%, 4 (36%) had recruiting discharges. In contrast, of the 43 patients with neuronal densities of less than 30% , 40 (93%) did not have recruiting discharges. A neuronal density of more than 30% was significantly associated with recruiting discharges (table 6, p = 0.025, Fisher's exact test). Furthermore, of the 11 patients with a neuronal density of more than 30%, 5 patients (45%) had continuous spiking, whereas 37 of 43 patients (86%) with a neuronal density of less than 30% did not have continuous spiking. A neuronal density of over 30% was significantly associated with continuous spiking (table 6, p = 0.035, Fisher's exact test).

Leaving out the eight cases with concomitant mesial temporal sclerosis did not change the results, i.e. continuous spiking was related to co-existing dysplasia (p = 0.008, χ^2, 1 df) and a neuronal density over 30% (p = 0.043, Fisher's exact test).

Discussion

ECOG DISCHARGE PATTERNS AND HISTOLOGICAL DIAGNOSIS

Various types of spike discharge patterns have been described in patients with FCD, but the lack of a generally accepted classification of ECoG discharge patterns has meant that different terms and definitions have been used. Palmini et al. reported that ictal or continuous epileptiform discharges (consisting of recruiting/derecruiting patterns, repetitive bursting patterns and (quasi)continuous rhythmic spiking) were related to cortical dysplasia [Palmini et al., 1995]. Since then, various reports on ECoG findings in cortical dysplasia have been published using different nomenclature and definitions, such as, *slow repetitive spikes* [Boonyapisit et al., 2003], *rhythmic spike discharges* [Chassoux et al., 2000], *seizure patterns* (consisting of continuous spiking, bursts of rhythmic spikes and trains of fast activity) [Ferrier et al., 2001], *continuous epileptogenic discharges* [Kameyama et al., 2001], *frequent or continuous rhythmic spiking* [Morioka et al., 1999], and *continuous frequent spiking* [Rosenow et al., 1998]. This difference in terminology makes direct comparison of these studies difficult. However, continuity and rhythmicity appear to be important characteristics of such patterns. Our continuous spiking pattern (occurring rhythmically at regular intervals, at least 1 Hz, for at least 10 seconds) was associated with a histological diagnosis of focal cortical dysplasia, a finding that is in agreement with previous findings.

In epilepsy surgery series, most low-grade tumours are GGs or DNTs. Several reports have described the clinical, neuroimaging and histological characteristics of these indolent GNTs [Prayson et al., 1993], but few investigators [Kirkpatrick et al., 1993; Raymond et al., 1994; Raymond et al., 1995; Ostertun et al., 1996; Daumas-Duport et al., 1999; Lee et al., 2000; Jorge et al., 2000; Aronica et al., 2001; Ildan et al., 2001; Nishio et al., 2001; Blumcke & Wiestler, 2002; Oishi et al., 2002; Luyken et al., 2003; Seo & Hong, 2003] have studied the ECoG spike discharge patterns of patients with a GNT, in contrast to those with FCD. Only a few studies report EEG and ECoG findings separately, and when they have, emphasis was mainly on the topography and distribution of the (inter)ictal discharge, and not on spike discharge patterns [Raymond et al., 1994; Raymond et al., 1995; Kameyama

et al., 2001; Luyken et al., 2003; Seo & Hong, 2003]. For example, Raymond et al. found that unequivocal spiking or sharp waves on the interictal scalp EEG were present in most patients with DNT but were concordant with the visible lesion in only three patients [Raymond et al., 1994]. The same authors found that 12 of 21 patients with DNT had focal or lateralized epileptiform discharges on the scalp EEG [Raymond et al., 1995]. Seo et al. reported that ictal onset- and irritative zones were localised perilesionally rather than intralesionally in patients with DNT [Seo & Hong, 2003]. Kirkpatrick et al. reported that 90% of patients with low-grade GNT had frequent ECoG epileptiform discharges in the preresection ECoG; however, these were not further specified [Kirkpatrick et al., 1993].

We found that continuous spiking was the only pattern to be seen significantly more often, but not exclusively, in patients with FCD. Continuous spiking on ECoG has been described in other pathological entities as well. Indeed, as early as in 1949 Jasper reported rhythmic and periodic epileptiform discharges at ECoG in a patient with posttraumatic epilepsy and extensive gliosis [Jasper, 1949]. Thereafter, Rasmussen found that continuous epileptiform discharges were not uncommon in frontal lobe epilepsy, probably due to the high incidence of posttraumatic epilepsy in this group [Rasmussen, 1983]. Also, in a report on ECoG in frontal lobe epilepsy there were two clear examples of localized continuous epileptiform discharges due to brain gliosis [Wennberg et al., 1998]. Guerreiro et al. reported in a series of 30 patients with non-tumoral parietal or occipital lobe epilepsy that 7 of 8 patients with gliosis had continuous ECoG epileptiform discharges consisting of (semi-) continuous rhythmic spikes or sharp waves at frequencies ranging from 2 to 8 Hz [Guerreiro et al., 2003]. Little is known about the prevalence of a continuous spiking pattern (or other patterns originally attributed to cortical dysplasia) in chronic epilepsy caused by low-grade tumours. To our knowledge, this is the first systematic study to show that these discharge patterns are also prevalent in GNT, though less often than in FCD. As continuous spiking is not exclusively seen in patients with FCD but also in patients with other types of pathology, such as gliosis after traumatic brain injury or low-grade GNT, it may be a marker of epileptogenicity in general, indicating a common underlying pathophysiology or histology.

ECOG AND HISTOPATHOLOGICAL FEATURES

The origin of balloon cells, large cells containing large volumes of cytoplasm, is uncertain and these cells may stain for neuronal markers, glial markers, both, or neither. However, these cells are interpreted as having failed to differentiate at a very early (stem cell) stage and therefore seem to be excellent markers for malformations due to stem cell maldifferentiation [Robain, 1996].

The association between balloon cells and epileptogenicity, as expressed by spiking on ECoG, is unclear. From a histopathological point of view, balloon cells in cortical dysplasia represent a higher grade of cortical dysplasia (FCD type 2B), implying increased epileptogenicity but ECoG findings are not consistent about this. Rosenow et al. found that balloon cells in cortical dysplasia were associated with higher seizure frequency and more electrodes showing continuous frequent spiking, implying increased epileptogenicity [Rosenow et al., 1998]. On the other hand, Marusic et al. found that regions containing balloon cells show decreased epileptogenicity in eight patients with FCD involving perirolandic or Broca's area [Marusic et al., 2002]. We were not able to relate presence of balloon cells to highly epileptiform ECoG discharge patterns. This is in agreement by findings of Cepeda et al. who found that presence of balloon cells was not correlated with the grade of the ECoG abnormality [Cepeda et al., 2005]. In vitro experiments showed that these cells dit not display active voltage- or ligand-gated currents and did not appear to receive synaptic inputs, findings further supporting the assumption that balloon cells are not generators of epileptic activity [Cepeda et al., 2003]. Even so, application of large currents did not result in firing patterns in balloon cells, but application to firing potential in normal and cytomegalic neurons resulted in similar firing patterns for both types of neurons [Cepeda et al., 2005]. Experiments using patch clamp recordings showed that neurons (large or cytomegalic) may have intrinsic membrane properties that could play an important role in the generation of epileptic activity [Cepeda et al., 2003]. Our findings that a relatively high neuronal density in the lesion is associated with highly epileptiform discharge patterns such as continuous spiking or recruiting dischargers indicate that such a high density might be crucial for the tissue to be able to generate continuous spiking (and

recruiting discharges), at least for patients with FCD or a GNT. An increase in neuronal density can be the result of volume loss with a significant increase in the 'packaging density' of cells, especially large hypertrophic neurons as has been reported in cases of temporal lobe epilepsy. If this is also accompanied by increased perikaryal innervation from excitatory synapses, then neuronal hypertrophy could play an important role in the hyperexcitability of neocortical tissue [Bothwell et al., 2001]. The electrocorticographical reflection of this might be the generation of highly epileptiform discharge patterns such as continuous spiking or recruiting discharges.

Our findings regarding relations between neuronal (and glial) densities and epileptiform discharge patterns however should be interpreted with some caution since the relative densities were obtained by visual counting without the use of quantitative methods or controls.

POTENTIAL LIMITATIONS OF THE STUDY

A concern in present study could be that in 43% of cases in the cohort insufficient data were available and these cases were excluded. However, we found no differences between the proportions of excluded patients in both patient groups and we have no reason to believe that a systematic error occurred for exclusion of patients from either group in the period between 1992 and 2003. Therefore, we believe that the sample of included patients correctly represents all operated patients with a GNT or FCD. ECoG findings could perhaps be biased by the localization of the pathology (overrepresentation of FCD in extratemporal areas) and the younger age of patients with FCD. However, when considering dysplasia in general (thus FCD and co-existing dysplasia in cases with a GNT) there appears to be an equal distribution over the temporal and extratemporal lobes (15 temporal, 13 extratemporal). We also show that whereas earlier publications on FCD were focussed on extratemporal cses, the temporal neocortex is also capable of generating these epileptiform discharge patterns. Furthermore, although the age at onset of epilepsy was significantly younger for the patients with FCD, this was not the case for the patients with co-existing dysplasia as opposed to those without.

RELEVANCE FOR EPILEPSY SURGERY

Advances in neuroimaging have resulted in an increased recognition of FCD during the presurgical assessment of patients with chronic epilepsy. Grey matter thickening, homogeneous hyperintense signal in the subcortical white matter, a hyperintense signal that tapers as it extends to the lateral ventricle, and blurring of the grey matter–white matter interface are all features that can be present on MRI. However, changes can be subtle and easily missed, even by experienced neuroradiologists. Also, differentation from tumours is not always straightforward. The presence of continuous spiking on the ECoG might help distinguish between FCD and a GNT since we found that this pattern was quite specific (88%) for FCD, but with a rather low positive predictive value of 55%.

Our finding that continuous spiking was highly associated with (coexisting) cortical dysplasia in FCD or GNTs is important. Microscopic dysplastic abnormalities can exist beyond the border of the visible dysplastic lesion detected by high-resolution MRI. Consequently, these abnormalities can only be assessed on postoperative neuropathological examination. Our findings suggest that continuous spiking on preresection ECoG can predict the presence of (coexisting) cortical dysplasia in a high proportion of patients (91%) with a specificity of 96%.

In lesional epilepsy, the best results are obtained when structural and functional abnormalities are excised in toto. The relationship between epileptiform discharge patterns and histopathological changes is a strong argument for electrocorticographic tailoring of the resection, at least in patients with pharmacoresistant epilepsy due to FCD as well as GNT. Without ECoG, dysplastic changes may be missed in surrounding cortex that appears normal on preoperative MRI. Continuous spiking on the ECoG predicts the presence of (coexisting) cortical dysplasia, regardless of underlying pathology (FCD or GNT) and irrespective of the presence of concomitant mesial temporal sclerosis. It thus appears that assessment of type and topography of specific epileptiform discharge patterns is important to determine the extent of the resection. However, since we performed a retrospective, basic study on histopathological correlates of electrophysiological abnormalities, and in all cases maximal tailoring was performed, we cannot formally prove that tailoring to these discharge patterns has an impact on surgical

outcome. Our findings should serve as a starting point for further research on whether these discharge patterns mark a worse long-term surgical outcome, e.g. because microdysplastic changes may be multiple throughout the brain and other seizure types might arise.

CHAPTER 5

Electrocorticographic Discharge Patterns in Patients with a Cavernous Haemangioma and Pharmacoresistant Epilepsy

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Abstract

OBJECTIVES

Neurodevelopmental lesions (NDL) such as glioneuronal tumours and cortical dysplasia give rise to characteristic electrocorticographic discharge patterns. Because cavernomas, another congenital abnormality, are also associated with pharmacoresistant epilepsy, we wondered whether they exhibit discharge patterns similar to those occurring in NDL.

METHODS

Intraoperative electrocorticographic recordings from 19 cavernoma patients were reviewed for continuous spiking, bursts, or recruiting discharge patterns. The relative density of glia and microglia and the intensity of iron staining in surgical samples were evaluated. Results were compared with those from 54 patients with NDL.

RESULTS

Mean age at seizure onset and operation were higher in cavernoma than in NDL (22.5 and 36.4 vs. 10.0 and 25.2 years, $p < 0.01$). Electrocorticographic neocortical discharge patterns occurred equally in cavernoma and in NDL (53% and 41%, respectively). In cavernoma patietns hippocampal bursts occurred more often (41% vs. 14%; $p < 0.05$), and hippocampal continuous spiking was associated with longer duration of epilepsy (29.0 vs 11.0 years, $p < 0.01$). Neocortical continuous spiking was associated with lower age at seizure onset, especially in NDL (4.2 vs. 11.4 years, $p < 0.01$). In cavernoma a low microglia density was associated with neocortical bursts and hippocampal recruiting pattern. There were no associations between the intensity of iron staining and discharge patterns.

CONCLUSION

Neocortical discharge patterns occur in cavernoma as in NDL. Neocortical electrocorticographic patterns may indicate early onset of seizures, independent from pathology. Hippocampal patterns are common in cavernoma and may evidence secondary epileptogenesis. Amount of chronic bleeding in cavernoma is not contributory, but microglia may inhibit these patterns.

Introduction

Cavernous haemangiomas (cavernomas) represent 10-20% of cerebral vascular abnormalities and occur in up to 0.5% of the general population [Robinson et al., 1991]. When located supratentorially, they are highly epileptogenic, giving rise to seizures in about 65% (40-70%) of cases. Cavernoma-related seizures in the temporal lobe are often refractory to medical treatment [Moran et al., 1999]. Epilepsy surgery is considered if seizure semiology, interictal and ictal surface EEG recordings, and neuropsychological test results are consistent with the MRI location. The optimal surgical intervention consists of complete lesionectomy combined with resection of the adjacent epileptogenic area [Siegel et al., 2000; Stefan & Hammen, 2004]. Electrocorticography (ECoG) is often used to identify cortical areas that show active spiking, in order to tailor the resection [Stefan & Hammen, 2004].

Cavernomas consist of endothelium-lined vascular channels without mural muscular or elastic fibres, within a matrix of collagenous tissue that lacks neuronal elements [Simard et al., 1986]. Failure of the capillaries to form tight junctions results in chronic slow bleeding into the brain parenchyma [Robinson et al., 1999], so that the cavernoma is typically surrounded by haemosiderin deposits and gliosis [McCormick, 1966]. Because cavernomas do not show neoplastic features, they are assumed to be congenital. Indeed, cavernomas have been reported in fetuses and neonates [Houtteville, 1997; Detwiler et al., 1997; Zabramski et al., 1994; Moritake et al., 1985; Pozzati et al., 1989].

Neurodevelopmental brain lesions (NDL), such as cortical dysplasia and glioneuronal tumours, are intrinsically epileptogenic, and several studies have shown the presence of discharge patterns on ECoG, considered as highly epileptiform, over and at a distance from these lesions [Palmini et al., 1995; Ferrier et al., 2001; Ferrier et al., 2006; Kirkpatrick et al., 1993; Prayson et al., 1993; Rosenow et al., 1998; Lee et al., 2000; Kameyama et al., 2001; Seo & Hong, 2003]. We recently showed that continuous spiking and recruiting discharge types were associated with disorganization of cortical architecture and with high neuronal density, but not with the degree of gliosis [Ferrier et al., 2006].

Cavernomas lack neuronal elements and histopathological changes in the adjacent cortex would seem essential to the development of seizures. Indeed, interictal spike activity has been localized to the vicinity of cavernomas by magnetoencephalography [Stefan et al., 2004], and excellent seizure control has been achieved by lesionectomy of the cavernoma with its adjacent cortex stained by haemosiderin [Siegel et al., 2000; Baumann et al., 2006]. To determine whether cavernomas share ECoG features with dysplastic congenital lesions, and whether discharge patterns are associated with underlying histopathological changes, such as gliosis and iron deposition, we compared the intraoperative ECoG findings in cavernoma and NDL patients.

Materials and methods

The database of the Dutch Collaborative Epilepsy Surgery Program was searched for patients with a histologically confirmed diagnosis of cavernoma. In all patients refractory focal epilepsy was the reason for admission to the program. From 1996 until 2005, 24 cavernoma patients underwent lesionectomy or partial lobectomy. From five patients the intraoperative ECoG recordings were not available. Thus, the present series consists of 19 patients who underwent a tailored resection.

PRESURGICAL EVALUATION

All patients underwent phase I investigations consisting of non-invasive tests, including history, medical, neurological and neuropsychological assessment, structural neuroimaging (1.5 T MRI) according to a dedicated protocol [Meiners, 2002], and extensive interictal and ictal EEG studies with video monitoring. Psychiatric assessment and MEG studies (on a research basis) were performed on indication. Phase II included an intracarotid sodium amytal test (Wada test), interictal PET, (inter)ictal SPECT, functional MRI and intracranial chronic EEG studies on indication [van Veelen et al., 1990].

INTRAOPERATIVE ELECTROCORTICOGRAPHY

Intraoperative ECoG was performed routinely during surgery [Leijten et al., 2005]. Surgery was performed under general anaesthesia with intravenous propofol and

sufentanyl. After the dura mater was opened, saline wick or silicon (5x4-) grid electrodes, with intercontact distances of 10 mm (Ad-Tech, Wisconsin, USA), were placed on the exposed surface of the cortex. Fifteen to 30 electrodes were used in each patient, but it should be noted that electrodes were usually repositioned during the procedure, resulting in a larger sampling area. The mesial and inferior temporal regions were assessed by means of two 7-contact electrode strips inserted subtemporally, reaching the amygdalar and parahippocampal area [Binnie et al., 1998; Polkey et al., 1989]. Prior to ECoG recording the propofol infusion was discontinued. Five to fifteen minutes of ECoG were sampled for classification of epileptiform abnormalities after the effects of propofol had abated and the background pattern had become continuous. On indication, patients were awakened for further intraoperative electrostimulation to map Wernicke's or Broca's area.

In this study, the preresection record consisted of all available ECoG material before the final resection, excluding the part when the patient underwent functional mapping. The preresection ECoGs were reviewed using classification criteria mainly based on those of Palmini et al.[Palmini et al., 1995] (see chapter 4, Figure 1): 1) sporadic spikes, spikes occurring at irregular intervals at several sites; 2) continuous spiking, spikes occurring rhythmically at regular intervals for at least 10 seconds, the interval between two subsequent spikes being maximally 1 second (frequency $\geq$ 1 Hz); 3) bursts of spikes, sudden occurrence of spikes lasting at least 1 second with a frequency of 10 Hz or more; 4) recruiting discharges, rhythmic spike activity characterized by increased amplitude and decreased frequency (electrocorticographic seizure). To avoid interpretation bias, the ECoG recordings were independently reviewed for the presence of one or more of these patterns by two experienced clinical neurophysiologists (FL, AVH). The ECoG reviewers were aware of the inclusion criteria of this study but they were blinded for all patient information. Consensus was reached in cases of disagreement by common assessment. Discharge patterns occurring in the medial temporal areas were termed *hippocampal* whereas patterns occurring in the inferior/lateral temporal regions or in the convexity of the frontal lobe were termed *neocortical*.

HISTOPATHOLOGY

Tissue preparation

Specimens were fixed in 10% buffered formalin, embedded in paraffin, sliced into 5-mm sections, and mounted on organosilane (3-aminopropylethoxysilane; Sigma, St. Louis, MO)-coated slides. Representative sections were stained with haematoxylin-eosin, Perls' stain for Fe^{3+}, and immunocytochemical markers as described below.

Immunocytochemistry

Glial fibrillary acidic protein (GFAP; polyclonal rabbit, DAKO, Glostrup, Denmark; 1:2000), vimentin (mouse clone V9, DAKO; 1:400), neuronal nuclear protein (NeuN; mouse clone MAB377, IgG1; Chemicon, Temecula, CA, USA; 1:1000), HLA-DR (mouse clone CR3/43; DAKO, Glostrup, Denmark, 1:400; activated microglia, MHC class II), and anti-ferritin (polyclonal, DAKO, 1:1000) were used in the routine immunocytochemical analysis of epilepsy specimens. Immunocytochemistry was carried out as previously described [Aronica et al., 2003; Aronica et al., 2001]. Single-label immunocytochemistry was performed using the avidin-biotin peroxidase method (Vector Elite) and 3,3-diaminobenzidine as chromogen. Sections were counterstained with haematoxylin. Sections incubated without the primary antibody (Ab) with pre-immune sera were essentially blank. Two neuropathologists (EA and WS) independently evaluated the samples and confirmed the diagnosis of cavernous haemangiomas. Cavernous haemangiomas were characterized by closely packed, thin-walled blood vessels, lacking elastic tissue, and surrounded by haemosiderin deposits. The surrounding brain parenchyma showed reactive changes, including astroglial and microglial activation (Figure 1).

Evaluation of histopathological features

All labelled tissue sections were evaluated for the presence of staining for iron and the various markers. Two representative paraffin sections per case were stained and assessed. The intensity of iron staining was evaluated on a scale of 0-3 (0: -, no; 1: +/-, weak; 2: +, moderate; 3: ++, strong staining). The score represents the

predominant staining intensity found in each case. For analysis, staining intensity was stratified into *strong* (i.e. strong staining) and *weak* (i.e. no, weak, or moderate staining). The relative density of GFAP (astrocytes) and HLA-DR (microglia) positive cells was also evaluated semi-quantitatively and was assigned to three categories: 1) <10%, 2) 10%-30% and 3) >30%). For analysis, the relative density of glia and microglia cells was expressed as *high* (>30%) and *low* (0-30%) [Ferrier et al., 2006].

NDL GROUP

The NDL group consisted of 54 patients (43 patients with a glioneuronal tumour and 11 patients with focal cortical dysplasia) whose clinical characteristics, and ECoG and histopathological findings have been described elsewhere [Ferrier et al., 2006]. Glioneuronal tumours were diagnosed according to the revised WHO classification of tumours of the nervous system [Kleihues & Cavanee, 2000].

STATISTICAL ANALYSIS

The incidence of each discharge pattern was calculated by counting the number of patients with cavernoma or NDL that showed one or more of the specified patterns. Student's T-tests were used to compare average age at onset, age at surgery, and duration of epilepsy in patients with and without the specified discharge patterns. Associations between ECoG discharge patterns and histopathological features were studied using χ^2 with one degree of freedom (the two-sided Fisher's Exact Test was used if one or more of the expected values of the crosstabs was less than five). Statistical significance was reached if $p < 0.05$. No correction was made for multiple testing.

Figure 1. For color figure see page 167.

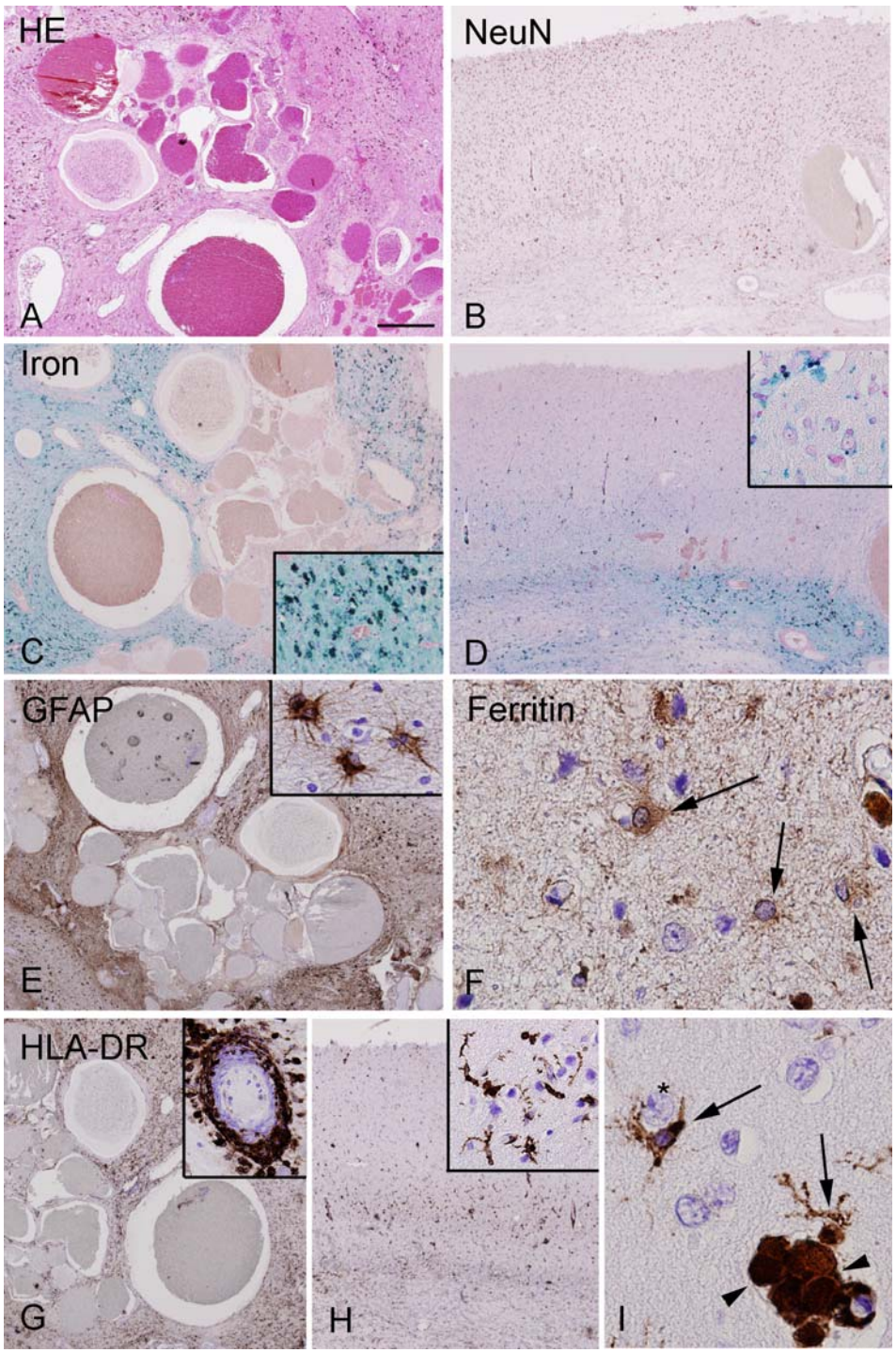

Figure 1 (opposite page, color figure see page 167).
Histopathological features of cavernous haemangiomas. A: Haematoxylin/Eosin (HE) staining showing tightly packed thin-walled blood vessels. B: neuronal nuclear protein (NeuN) staining of the cortex surrounding the vascular malformation. C: cavernous haemangioma with strong blue staining due to the deposition of haemosiderin (Perls' stain); the presence of Fe^{3+} is observed in macrophages surrounding the malformation (insert). D: Perls' stain showing the presence of Fe^{3+} in the perilesional cortex. E: GFAP staining around cavernous haemangioma with presence of GFAP-positive astrocytes (insert). F: Ferritin (major iron-binding protein)-positive glial cells within the perilesional cortex (arrows). G: HLA-DR staining showing the presence of activated and amoeboid microglia (insert) surrounding the malformation. H: HLA-DR immunoreactivity in the perilesional cortex showing both activated (insert in H and arrows in I) and amoeboid microglia (arrow-heads in I) also clustered around neurons (asterisk in I). Scale bar in A: A,B,C,D, E,G, H: 400 µm; F: 40 µm. I: 30 µm.

Table 1. Patient characteristics. CAV = cavernoma, NDL = neurodevelopmental lesion. Age at onset, age at operation, and the duration of epilepsy are expressed as means with standard deviations (sd). Age at onset and age at operation were significantly higher in cavernoma patients (Student's T-test, $^1p < 0.01$).

	CAV	NDL
Number of patients	19	54
Male : female	8:11	32 : 22
Right : left	12:7	28 : 26
Temp : extratemp	17:2	40 : 14
Age at onset	22.5 (sd 11.4) [1]	10.0 (sd 7.8) [1]
Age at operation	36.4 (sd 11.9) [1]	25.2 (sd 13.1) [1]
Duration of epilepsy	14.0 (sd 9.5)	15.2 (sd 11.0)
% seizure free after one year	71%	72%

Results

CLINICAL CHARACTERISTICS

All patients had focal seizures, varying in frequency from daily to monthly, with or without secondary generalization. Cavernoma patients were significantly older than NDL patients at seizure onset and also at the time of surgery, so that the duration of epilepsy before surgery was comparable (see Table 1).

ECOG DISCHARGE PATTERNS

Of the 19 cavernoma patients, 17 had cavernomas located in the temporal lobe, all of them with ECoG recordings from the neocortex and mesial temporal structures. Of the 54 NDL patients, 40 had the NDL located in the temporal lobe, and 37 of them had ECoG recordings from both the neocortex and mesial temporal structures. Most cavernoma and NDL patients showed sporadic spikes, which were not considered a discharge pattern (Table 2). Hippocampal bursts were seen more frequently in cavernoma than in NDL patients. There were no other differences in the incidence of discharge patterns between the cavernoma and NDL patients (Table 2). When studying the occurrence of at least one of the discharge patterns at the neocortex we found no statistically significant differences between the cavernoma and NDL patients since 10 out of 19 (53%) cavernoma and 22 out of 54 (41%) NDL patients showed at least one of such patterns (χ^2, $p < 0.5$). In contrast, eight out of 17 (47%) cavernoma patients and eight out of 37 (22%) NDL patients showed at least one of such patterns at the hippocampal electrodes. This difference was almost statistically significant (χ^2, $p < 0.06$).

Presence of continuous spiking pattern was associated with specific demographic features. An early onset was significantly associated with neocortical continuous spiking in the NDL patients whereas there was a trend in the cavernoma patients ($p = 0.10$). When present in the hippocampus continuous spiking was associated with a longer duration of epilepsy before surgery (Table 3).

Table 2. Neocortical and hippocampal ECoG discharge patterns detected in cavernoma and NDL patients. There were no significant differences in the incidence of any of the neocortical discharge patterns between the patient groups. Hippocampal bursts occurred more often in cavernoma patients ([1]$p < 0.05$, χ^2, 1 df).

		CAV	NDL
neocortical	Sporadic spikes	17/19 (89%)	47/54 (87%)
	Recruiting	2/19 (11%)	7/54 (13%)
	Bursts	8/19 (42%)	16/54 (30%)
	Continuous	4/19 (21%)	11/54 (20%)
hippocampal	Sporadic spikes	14/17 (82%)	31/37 (84%)
	Recruiting	2/17(12%)	2/37 (5%)
	Bursts	7/17 (41%)[1]	5/37 (14%)[1]
	Continuous	2/17 (12%)	1/37 (3%)

Table 3. Demographics (mean, standard deviation) and the continuous spiking pattern in NDL and Cavernoma. In NDL patients the age at onset was significantly lower when neocortical continuous spiking was present ([1]$p < 0.01$, Student's T-test). In cavernoma patients the duration of epilepsy was significantly longer when hippocampal continuous spiking was present ([2]$p < 0.01$, Student's T-test).

NDL	Continuous neocortical		Continuous hippocampal	
	Present	Absent	Present	Absent
	N = 11	N =43	N = 1	N = 36
Onset	4.2 (3.1)[1]	11.4 (8.0)[1]	8	10.9 (8.4)
Age at operation	20.3 (15.0)	26.4 (12.4)	36	26.2 (12.8)
Duration	16.0 (13.4)	15.0 (10.4)	28	15.3 (10.3)

CAVERNOMA	Continuous neocortical		Continuous hippocampal	
	Present	Absent	Present	Absent
	N = 4	N = 15	N = 2	N =15
Onset	16.5 (5.7)	24.1 (12.1)	24.5 (10.6)	23.5 (12.0)
Age at operation	30.5 (13.2)	37.9 (11.5)	50.5 (0.7)	34.4 (12.2)
Duration	14.5 (9.7)	13.8 (9.7)	29.0 (11.3)[2]	11.0 (7.3)[2]

Table 4. Association between the relative density of microglia and discharge patterns (hippocampal recruiting and neocortical bursts) in cavernoma patients. A high content of microglia was associated with the absence of the hippocampal recruiting pattern and neocortical bursts ([1]$p < 0.05$, Fisher's Exact).

		Recruiting hippocampal		Bursts neocortical	
		Present	Absent	Present	Absent
		N = 2	N = 15	N = 8	N = 11
Microglia	> 30%	0[1]	13[1]	4[1]	11[1]
	< 30%	2[1]	2[1]	4[1]	0[1]

ECOG DISCHARGE PATTERNS AND HISTOPATHOLOGICAL FEATURES

In cavernoma patients, ECoG discharge patterns seemed correlated to relative microglia density (Table 4). None of these patients with a high relative density (> 30%) of microglia showed a hippocampal recruiting pattern, whereas both patients with such a pattern had a low density (<30%). Also, all cavernoma patients with a low density of microglia showed neocortical bursts, in contrast to only a few with a high density of microglia (Table 4). In contrast, in NDL patients the density of microglia was never associated with any of the discharge patterns. And neither was the relative astroglia density associated with any of the discharge patterns in either patient group. Intensity of iron staining was also not associated with any pattern in cavernoma patients (data not shown).

Discussion

OCCURRENCE OF EPILEPTIFORM ECOG DISCHARGE PATTERNS

Patients with pharmacoresistant epilepsy due to a cavernoma show highly epileptiform ECoG discharge patterns, such as continuous spiking, bursts of spikes, and recruiting discharges, similar to those seen in patients with NDL. Surprisingly, the incidence of these discharge patterns in the neocortex did not differ in both pathologies. To our knowledge, these ECoG abnormalities in cavernomas have not been described previously in a systematic manner. We conclude that these highly epileptiform ECoG patterns are not specific for focal cortical dysplasia as emphasized in the literature [Palmini et al., 1995; Boonyapisit

et al., 2003; Chassoux et al., 2000; Ferrier et al., 2001; Kameyama et al., 2001; Morioka et al., 1999; Rosenow et al., 1998]. We recently showed that the neocortex of patients with glioneuronal tumours (ganglioglioma and dysembryoplastic neuroepithelial tumour) may also generate such discharge patterns and signify dysplastic changes in the neocortex surrounding these tumours, suggesting common mechanisms of epileptogenesis in FCD and NDL [Ferrier et al., 2006]. However, in the present case of cavernomas, dysplastic changes do not occur. We think now that these discharge patterns are less related to underlying pathology and that they are indicative of an early seizure onset with specific neurodevelopmental consequences. Timing of the insult to the brain seems relevant. In NDL, the lesion is part of the developing brain proper, resulting in early structural and functional (dysplastic) changes in cortical areas that later may predispose to refractory epilepsy [Kuzniecky & Barkovich, 2001; Sisodiya, 2004; Barkovich & Raybaud, 2004; Marin-Padilla, 2000]. In cavernoma patients epileptogenesis and non-mitotic lesion expansion may result from progressive, intermittent or chronic bleeding and iron deposition around the lesion. One might argue that if significant (micro)bleeding occurs at a crucial stage of brain development this can result in similar functional changes as in NDLs. Our study lends some support to this notion. The expression of continuous neocortical spiking in the ECoG may be the marker of an early disruption of functional systems in the developing brain that has acquired intrinsic epileptogenicity.

EPILEPTIFORM ECOG DISCHARGE PATTERNS AND DURATION OF EPILEPSY

Our study indicates that hippocampal continuous spiking arises with a longer duration of epilepsy until surgery. It should be noted that statistical analysis is limited because of the low number of patients with hippocampal continuous spiking (two cavernoma and one NDL). The single NDL patient, however, had epilepsy for 28 years before surgery; which is comparable to the long duration of epilepsy in both cavernoma patients with hippocampal continuous spiking (mean 29.0 years) and far more than the average duration of epilepsy of NDL patients without hippocampal continuous spiking. If confirmed, the association suggests secondary epileptogenesis or perhaps even end-stage epileptogenesis that is, most likely,

irrespective of underlying pathology. This is consistent with the poor outcome of surgery in terms of seizure control of cavernoma patients with epilepsy of long duration [Casazza et al., 1996] and emphasizes the importance of early resection [Ferroli et al., 2006; Moran et al., 1999; Cappabianca et al., 1997; Cohen et al., 1995]. Our findings should be confirmed in larger patient sample to draw definite conclusions.

EPILEPTIFORM ECoG DISCHARGE PATTERNS, (MICRO)GLIA AND IRON

Cavernoma and NDL share some reactive gliosis, and thus gliosis might be implicated in the generation of discharge patterns. Indeed, continuous spiking has incidentally been described in patients with gliotic brain lesions [Guerreiro et al., 2003]. However, we could not relate the degree of gliosis to be associated at all with any discharge pattern, neither in cavernoma nor in NDL. In a previous study we found the same lack of association with microglia density in NDL [Ferrier et al., 2006], whereas in cavernoma patients, neocortical bursts and hippocampal recruiting discharges do seem associated with a low microglia density. This inverse relationship may imply an inhibitory role of microglia in cavernoma patients, in contrast with other studies in which microglia in general were found to enhance epileptogenesis (expressed by clinical parameters such as seizure frequency). Boer et al. recently showed that the number of activated microglia in the cortex was higher in individuals with epilepsy than in autopsy controls, and that the duration of epilepsy and seizure frequency correlated positively with the density of microglia in focal cortical dysplasia [Boer et al., 2006]. But this can be cause or effect and thus be interpreted in either direction.

Cavernomas are most likely congenital lesions [Houtteville, 1997; Detwiler et al., 1997; Zabramski et al., 1994; Moritake et al., 1985; Pozzati et al., 1989], and their chronic slow bleeding with subsequent iron deposition in adjacent cortex is thought to be essential to their epileptogenicity. However, we found no association between the extent of iron deposition and ECoG discharge patterns. As microglia may protect neurons by storing excess iron and by removing damaged cell constituents, epileptogenesis in cavernoma may be more complex than can be appreciated from

histological observations only. Pathophysiological factors involved in the generation of localized ECoG discharge patterns in cavernoma are far from clear.

RELEVANCE FOR EPILEPSY SURGERY AND FUTURE DIRECTIONS

This retrospective study was not meant to guide clinical decision making, but it suggests a few things that require further scrutiny. We provide additional, although indirect, evidence that resection be performed early in cavernoma patients with epilepsy. Our study shows that there is often a significant delay before cavernoma patients are referred for epilepsy surgery. While resection should include the surrounding haemosiderin-containing tissue in order to achieve favourable long-term seizure control [Baumann et al., 2006], ECoG seems a logical way to tailor the resection and identify epileptogenic areas. However, it would be interesting to know whether discharge patterns also exist in cavernoma patients without epilepsy and to perform a prospective study whether areas showing specific patterns should be included in the resection to improve seizure outcome. In ECoG, special care should be given to recordings from the mesial temporal site which may have become involved in temporal lobe cases. Comparative studies are needed to establish whether lesionectomy without ECoG early in the course of epilepsy is sufficient to prevent future seizures.

Conclusions

Electrocorticographical discharge patterns occur equally in cavernoma and NDL patients. In NDL these patterns are seen mainly in neocortex whereas in cavernoma these patterns are present in medial temporal structures to a similar degree. Earlier onset of seizures is associated with the presence of neocortical continuous spiking, suggesting an age dependent mechanism of epileptogenesis. Hippocampal continuous spiking seems to arise in the course of time, especially in temporal lobe cavernoma, probably reflecting secondary epileptogenesis. In cavernoma, the degree of iron staining is not associated with ECoG features, but absence of certain discharge patterns is related to high microglia density, suggesting a protective role of microglia.

CHAPTER 6

N-Acetylaspartate and Creatine Levels Measured by ^{1}H MRS Relate to Recognition Memory

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Abstract

OBJECTIVES

To investigate the relationship between recognition memory and metabolite levels in medial structures of the temporal lobes in the living human brain.

METHODS

Proton MRS (^{1}H MRS) and the intracarotid amobarbital test were performed in 16 epileptic patients found suitable for temporal lobectomy. All patients had mesial temporal sclerosis. Metabolite ratios between *N*-acetylaspartate (NAA), creatine and phosphocreatine (Cr+PCr), and choline-containing compounds (Cho) [NAA/(Cr+PCr), NAA/Cho, and NAA/(Cr+PCr+Cho)] were calculated for ^{1}H MRS voxels that included the amygdala, anterior half of the hippocampus, and underlying subiculum. Metabolite ratios were correlated with unilateral memory scores estimated by the intracarotid amobarbital test for words, objects, faces, and total score.

RESULTS

The total memory score, memory for objects and faces, and NAA/(Cr+PCr) were significantly lower for the hemisphere ipsilateral to the resection. The asymmetry indexes for NAA/(Cr+PCr) correlated with asymmetry indexes for words (rho = 0.82, p = 0.0001) and total memory (rho = 0.72, p = 0.002). Analysis of memory scores and metabolite ratios from all 32 hemispheres revealed a correlation between NAA/(Cr+PCr) and memory for words (rho = 0.45, p = 0.009). A correlation between memory for words and NAA/(Cr+PCr) existed in the contralateral (rho = 0.58, p = 0.019) and in the right (rho = 0.51, p = 0.045) hemispheres, and a trend was found in the left hemispheres (rho = 0.48, p = 0.06).

CONCLUSION

There is a correlation between memory for words and the NAA/(Cr+PCr) ratio from medial temporal structures in patients with mesial temporal sclerosis. The findings suggest that medial temporal structures and adjacent neocortex play a significant role in recognition memory in humans, particularly for words.

Introduction

The involvement of the hippocampal formation in memory functions has been recognized for decades, but its role in human memory has remained enigmatic since the now-classic work on the patient H.M. [Scoville et al., 1957] and the original description of mesial temporal sclerosis in temporal lobe surgical specimens by Falconer [Falconer, 1953]. As early as 1900, medial temporal structures were suspected to be involved in memory when "bilateral hippocampal softening" was described at autopsy in a patient who had had mainly memory deficits [Bechterev, 1900]. There is now ample experimental evidence suggesting that the medial region of the temporal lobe, including hippocampus and adjacent neocortex, plays a significant role in short-term memory processing in animals [Squire, 1992]. Indeed, some likely cellular and biochemical mechanisms have been identified in animals [Bliss et al., 1973; Bliss et al., 1973]. However, understanding of the cellular and biochemical mechanisms involved in human memory has proved elusive [Squire, 1992], and a number of issues remain unanswered with regard to the role of the human hippocampal formation in memory. In patients with temporal lobe seizures arising from the hippocampal formation in the hemisphere that predominantly supports memory, selective unilateral removal of the amygdala and hippocampus can provide substantial relief of their epilepsy with less memory impairment than if a more radical en bloc temporal lobectomy were performed [Wieser et al., 1982; Goldstein et al., 1993]. This suggests a role for extrahippocampal structures in supporting memory in patients with temporal lobe epilepsy.

There have been conflicting reports about the relation between memory performance and hippocampal cell counts or volumes. In patients with epilepsy who underwent temporal lobectomy, a significant correlation between presurgical verbal memory impairment and cell counts in hippocampal CA3 and CA1 areas has been described [Sass et al., 1990; Rausch et al., 1993]. However, no significant correlation was found between preoperative memory and hippocampal volumes as estimated by structural MRI, although these correlated with postoperative declines in verbal memory [Trenerry et al., 1993]. On the contrary, the Wechsler Logical

Memory percent retention scores correlated with left hippocampal volumes estimated by volumetric MRI, but this relationship existed only for patients who underwent a left temporal lobectomy [Lencz et al., 1992]. As both cerebral hemispheres can process information in parallel or independently, determination of hemisphere laterality for specific memory tasks is a major difficulty for in vivo localization of human memory and may explain some of the apparently contradictory results reported above. To avoid such ambiguity, we have measured memory performance during the intracarotid sodium amobarbital test, a procedure carried out routinely in our center on patients assessed for temporal lobe surgery to relieve their epilepsy [Morton et al., 1996]. The purpose of the intracarotid amobarbital test is to estimate and avoid potential neuropsychologic deficits associated with temporal lobe surgery. Unilateral intracarotid injection of sodium amobarbital prior to performance of memory tests permits estimation of unilateral memory function, thus permitting the study of the relationship between memory and ipsilateral in vivo brain measurements that can be obtained with modern neuroimaging techniques.

Proton MRS (^{1}H MRS) allows noninvasive in vivo estimation of tissue levels for various cerebral metabolites including *N*-acetylaspartate (NAA), creatine and phosphocreatine (Cr+PCr), and choline-containing compounds (Cho) in localized brain regions [Sanders, 1995]. Several lines of evidence, including the study of cell cultures, suggest that NAA is located primarily within neurons and their precursor cells, whereas (Cr+PCr) and Cho are found both in neurons and in glial cells [Urenjak et al., 1992; Urenjak et al., 1993]. Therefore, a reduction of NAA signal has been interpreted as reflecting neuronal loss or damage. Ratios between the peak areas of these metabolites [NAA/(Cr+PCr), NAA/Cho, NAA/(Cho+Cr+PCr)] are thought to reflect neuronal loss and gliosis and consequently yield quantitative measurements of the neuronal integrity. Indeed, a reduction in NAA has been found in clinical situations where neuronal loss is expected, such as infarcts, tumors, or partial epilepsy. Patients with epilepsy show reduced NAA/(Cho+Cr+PCr), NAA/(Cr+PCr), and/or NAA/Cho in medial temporal structures when compared with a population of normal subjects [Gadian et al., 1994; Cendes et al., 1994; Hetherington et al., 1995; Mendes-Ribeiro et al., 1998], and in patients

with temporal lobe epilepsy, such changes can be bilateral, with the epileptogenic temporal lobe being affected to a greater extent [Connelly et al., 1994].

We have studied the role of medial temporal structures in human memory by correlating unilateral memory function estimated by the intracarotid amobarbital test with ratios of NAA, (Cr+PCr), and Cho measured in medial temporal structures of patients assessed for temporal lobe surgery to relieve their epilepsy. ^{1}H MRS measurements included the amygdala, the anterior half of the hippocampus, and fields of the underlying subiculum. In the remainder of the text, these structures will generically be referred to as the medial temporal structures in order to simplify wording.

Patients and methods

PATIENTS

Sixteen patients were included in the study. These were consecutive patients who entered the epilepsy surgery program at our center and were selected for unilateral temporal lobectomy on the basis of clinical history, EEG findings (surface EEG including quinalbarbital-induced sleep recordings, foramen ovale, and/or scalp videotelemetry), MRI findings, and fluorodeoxyglucose PET investigations. The patient group consisted of eight men and eight women. Mean age at onset of their epilepsy was 5.8 years (SD = 4.3 years). Mean age at operation was 31.1 years (SD = 12.5 years), and mean duration of their epilepsy at the time of surgery was 25.1 years (SD = 12.4 years). Six patients were candidates for right temporal lobectomy and 10 for a left temporal lobectomy.

A brief neuropsychological test battery was administered to the patients. A short form of the Wechsler Adult Intelligence Scale–Revised, including Vocabulary, Comprehension, Similarities, Block Design, and Object Assembly, was used to measure intelligence. The mean IQ was 91.3 (SD = 14.8), with a mean Verbal IQ of 88.1 (SD = 10.6) and Performance IQ of 96.7 (SD = 20.2). Verbal short-term memory was tested using the Wechsler Memory Scale Logical Memory subtest, with immediate and delayed (1-hour) recalls. On immediate recall, the mean score

was 6.7 (SD = 3.1), whereas for delayed recall, it was 4.1 (SD = 3.1). Visuospatial short-term memory was tested using the copy and delayed drawing form of the Rey Osterreith Figure test, with a 40-minute delay. The mean percentage recall was 43.7 (SD = 19.5).

On structural MRI, all 16 patients had mesial temporal sclerosis ipsilateral to the side of operation (in 2 patients, the diagnosis was established after volumetric measurements). In addition, one patient showed widespread neocortical temporal atrophy.

All patients had interictal EEG recordings, including a sleep period induced by quinalbarbital (100 to 200 mg). Eleven patients showed unilateral discharges restricted to the temporal region ipsilateral to the resection. One patient did not show epileptiform discharges, one showed generalized discharges, one showed bilateral independent discharges, and one had widespread frontoparietotemporal discharges. Ten patients had videotelemetry, nine with intracranial foramen ovale and scalp EEG recordings. Habitual seizures were captured in all 10 patients. In patients with foramen ovale recordings, seizure onset was observed at the foramen ovale electrodes ipsilateral to the resection. The patient with scalp telemetry without foramen ovale electrodes showed a right anterior temporal focal onset.

PATHOLOGY

Pathology reports were available from 12 operated patients and confirmed the diagnosis of mesial temporal sclerosis. Four patients are waiting for surgery or have withdrawn from the surgery program after being offered a temporal lobectomy. All four had clearly lateralized mesial temporal sclerosis on conventional structural MRI. In addition to mesial temporal sclerosis, one patient had a white matter hamartoma and another patient showed a degree of more widespread neocortical sclerosis involving the ipsilateral subiculum and subtemporal cortex.

INTRACAROTID AMOBARBITAL TEST (WADA TEST)

Three parallel versions of the memory test were developed: two to be shown when the patient was under the effects of left or right internal carotid injections and 10

minutes after recovery from injections to test recognition and one to serve as a control procedure administered subsequently. Each version consisted of six written words, six line drawings of objects, and six faces that were presented to patients on 25 x 12-cm file cards, arranged in pseudo-random order. Although different material was used for each test, the same general order was preserved (face, word, drawing, drawing, face, word, word, drawing, face, drawing, word, face, word, face, drawing, face, drawing, word). For the yes/no recognition memory phase of the experiment, these were mixed with an equivalent number of distractor items (foils) and presented in a further pseudo-random sequence (in total, there were 36 items). The words were of medium or high frequency [Kuzera et al., 1982]. The line drawings were all of common objects taken from the Snodgrass and Vanderwart standardized set of 260 pictures [Snodgrass et al., 1980]. The faces were of young or middle-aged adult men, printed in black and white.

Intracarotid amobarbital testing for the left and right hemisphere was conducted on the same day, with the right intracarotid amobarbital injection carried out first. At the end of right and left testing, there was a further control test of memory functioning using the same language and memory testing but without injection of sodium amobarbital.

The patients were fitted with a set of scalp silver cup EEG electrodes following the "Maudsley" electrode placement system for monitoring throughout the test. A catheter was placed in the right femoral artery and threaded up into the right or left internal carotid artery. Angiography was conducted before intracarotid injections of amobarbital to visualize the formation and flow patterns of the cerebral arteries, using radio-opaque contrast agent (Iohexol, Nycomed Imaging AS, Oslo, Norway) injected into the artery at a constant flow of 6 mL/s. This angiography was used to check that the distribution of the medium was unilateral and confined to the territories supplied by the anterior and middle cerebral arteries. The patients were then instructed to hold both arms up, flexed at the elbow, and make rapid sequential bilateral movements of thumb to the tip of the fingers. Simultaneously, they were required to count forward starting from 1. Sodium amobarbital was then injected at a rate of 25 mL/5 s until hemiparesis of the contralateral arm was observed, thus titrating the amount administered, usually ranging from 75 to 125

mg. They were then instructed to stop counting, and their arms were placed at their sides.

For subsequent memory testing, patients were presented with a series of 18 stimulus items, with concurrent language testing. These comprised six abstract words, six line drawings of objects, and six faces as described above. The patients viewed each item for (approx) five seconds each and were required to respond. For words, the instruction was "Read this word," for drawings "Name this object," and for faces "Do you like this face, yes or no?" As the test progressed, the instructions were repeated, when necessary, as prompts. The reading, naming, and face preference judgments were recorded. A response to words was scored as correct only if the exact word was produced. Similarly, only the name of the object or a suitable synonym was scored as correct for line drawings. For the faces, the response was scored correct only if the patient responded "yes" or "no." Language dominance was assessed clinically on the basis of observation of positive signs of dysphasia and an inability to read words and name the line drawings presented. In addition, residual language function such as preserved counting was noted, because this can reveal cases of mixed dominance. The presentation of the memory items took place over approximately a three minute period, allowing time for the orientation of the patients and for establishing eye contact with the material.

Recovery was monitored using the scalp EEG and through testing grip strength in the contralateral hand. When both of these returned to normal, the recovery time was noted. In all patients, the memory items had been presented before EEG and motor recovery and within approximately three minutes after injection of the sodium amobarbital. After a further 10-minute delay, the patient was tested for recognition memory of the memory items. In the yes/no recognition memory procedure, the patient was instructed to respond "yes" if the item had been seen earlier and "no" if it had not. The 18 stimulus items were presented intermingled with 18 distractor items (foils) that had not been shown before. A false recognition occurred when the patient answered "yes" to a distractor item. If the patient was not sure of the response, (s)he was required to guess rather than not respond.

For the control condition, conducted approximately five minutes after the last intracarotid amobarbital test, the patient was immediately shown the 18 items that

were to be remembered without injection of amobarbital. After a 10-minute delay, recognition memory was tested as indicated above.

For each hemisphere and each category, true and false recognitions were counted. Consequently, a score for each category and each hemisphere was calculated by subtracting the false from the true recognitions. In addition, for each hemisphere, a total memory score was calculated by adding all the scores in each category (in this way, a score of 0 is obtained when a patient answers "yes" on all the items shown). Thus, for each hemisphere, four memory categories are obtained in this way, namely, a total memory score and material-specific memory scores for faces, pictures, and words. A patient failed the test on a side if the total score of the tested hemisphere (contralateral to injection side) was less than five. Asymmetries in the amobarbital test were calculated as the score achieved when injecting the right carotid artery minus the score obtained when injecting the left (score achieved by the left hemisphere minus that obtained by the right). Throughout this article, right and left amobarbital scores refer to the side of the functioning hemisphere (i.e., contralateral to the injection side). Thus, the right score corresponds to that obtained when injecting the left carotid artery and vice versa.

Asymmetry indexes were calculated between memory scores for both hemispheres as the difference between scores for the left minus the right hemispheres.

MRI AND MRS

In a single examination, conventional qualitative proton density, T1-, and T2-weighted brain images and ^{1}H MR spectra were acquired from the medial structures of the temporal lobes using a 1.5 T General Electric Signa Advantage running a 5.4 operating system (General Electric Medical Systems, Milwaukee, WI) with a quadrature transmit-and-receive high-pass birdcage head coil. Data acquisition, shimming, and water suppression were as reported previously [Simmons et al., 1998].

Patients were positioned in the head coil relative to nasion and radiographic baseline landmarks. Foam padding and a forehead restraining strap were used to limit head motion, and patients were advised of the importance of remaining still during the procedure. Sagittal T1-weighted fast spoiled gradient recalled

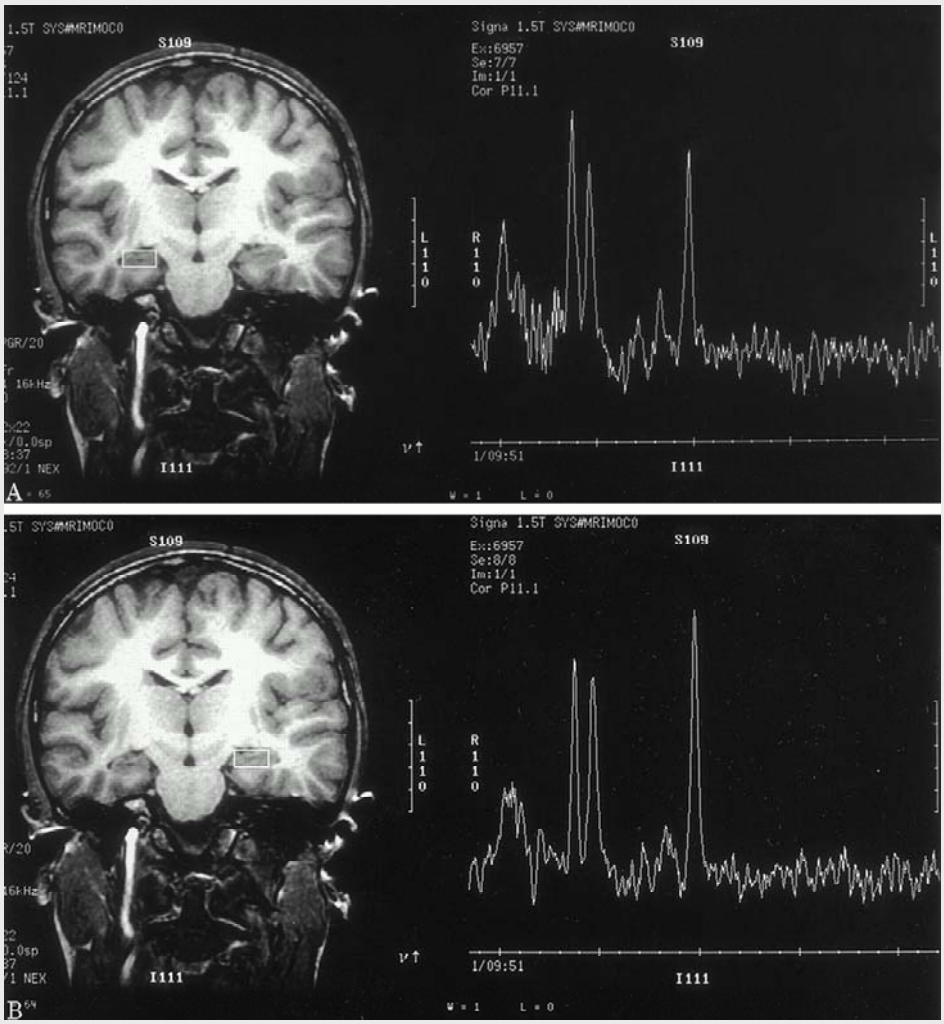
acquisition in the steady state (GRASS) localizer images (repetition time [TR] = 150 ms, echo time [TE] = 4.2 ms, {theta} = 90°, field of view = 22 cm) were initially acquired. Axial dual-echo fast spin echo images were prescribed parallel to the anterior commissure–posterior commissure line (TR = 3,200 ms, TE1 = 20 ms, TE2 = 80 ms, (theta) = 90°, field of view = 22 x 22 cm, matrix = 256 x 256, slice thickness = 5 mm, slice gap = 2 mm) followed by a coronal inversion recovery prepared fast 3D spoiled GRASS dataset (TR = 35 ms, TE = 2.8 ms, inversion time = 450 ms, {theta} = 35°, field of view = 22 x 18 cm, matrix = 256 x 192, slice thickness = 1.5 mm, slice gap = 0 mm). In the medial aspect of each temporal lobe, a 1.5(lateral) x 0.7(vertical) x 2 (anteroposterior) -cm voxel was prescribed, including the amygdalohippocampal complex one third of the distance between the anterior boundary of the amygdala and the aqueduct of Sylvius. The voxel was positioned to avoid the ventricles and cerebral sulci. This region will generally include the amygdala, anterior half of the hippocampus proper and gyrus dentatus, and subfields of the underlying subiculum (Figure 1). The MRS pulse sequence was used in two modes: a "water-imaging mode" to delineate the position and extent of the voxel and to confirm there was no contribution of signal from subcutaneous fat and a "spectroscopy mode" as described above. The ^{1}H MRS analysis was performed as described previously [Simmons et al., 1998].

Metabolite peak areas from NAA (2.0 ppm), (Cr+PCr) (3.0 ppm), and Cho (3.2 ppm) were obtained by a Levenberg–Marquardt fit to Lorentzian line shapes using software provided by the manufacturer (SAGE/IDL, General Electric Medical Systems, Milwaukee, WI). For both sides, the following ratios were calculated independently: NAA/(Cr+PCr), NAA/Cho, NAA/(Cr+PCr+Cho), and Cho/(Cr+PCr). For each ratio, an asymmetry index was calculated as:

[100 x (LHV – RHV)] / [0.5 x (LHV + RHV)] (where LHV = left hemisphere value; RHV = right hemisphere value).

Throughout the article, the terms "ipsilateral" and "contralateral" refer to the operated side.

Figure 1. Coronal MRI shows the location of the voxel defined for spectroscopy measurements and an example of ^{1}H MR spectra (A, right hemisphere; B, left hemisphere) in a patient with right hippocampal atrophy.



ANALYSIS AND STATISTICAL METHODS

Metabolite peak area ratios for NAA/(Cr+PCr), NAA/Cho, NAA/(Cho+Cr+PCr), and Cho/(Cr+PCr) obtained from medial temporal structures were correlated with material-specific (words, faces, and pictures of objects) and total memory scores estimated by the intracarotid amobarbital test. Asymmetry indexes for metabolite ratios and each modality of memory scores were also correlated. Spearman's rank correlation coefficient (rho) was calculated and was considered statistically significant if $p < 0.05$.

Left versus right and ipsilateral versus contralateral comparisons were made for memory scores and metabolite ratios using the nonparametric paired Wilcoxon test. Differences were considered statistically significant if $p < 0.05$.

Results

INTRACAROTID AMOBARBITAL TEST

No patient showed cerebral cross-flow in the angiogram. In all patients, appropriately lateralized EEG changes were present after amobarbital injection and outlasted the period of psychologic testing. The left hemisphere was dominant for language in 13 patients, the right was dominant in one, and both hemispheres shared dominance in two. Four patients failed the test on injection of amobarbital contralateral to the operation side. All patients passed the test on injection of amobarbital ipsilateral to the resection side. Memory scores during the amobarbital test and asymmetries are summarized in Table 1. No significant differences were found between memory scores achieved by the right or left hemispheres. Mean memory scores from ipsilateral hemispheres were lower than those obtained when testing the side contralateral to the operation for all memory modalities, and differences were found significant for total memory ($p = 0.006$), memory for faces ($p = 0.032$), and memory for objects ($p = 0.016$). Separate analysis of the 13 patients with left hemisphere language dominance yielded equivalent results.

^{1}H MRS

^{1}H MRS metabolite peak area ratios and asymmetries are summarized in Table 1. There were no statistically significant differences between mean values from left and right hemispheres. When comparing values from ipsilateral and contralateral hemispheres, differences were found significant only for NAA/(Cr+PCr) ($p = 0.044$).

CORRELATION BETWEEN INTRACAROTID AMOBARBITAL TEST AND ^{1}H MRS METABOLITE PEAK AREA RATIOS

To establish whether there is a relationship between unilateral memory performance and the integrity of neuronal population in medial temporal regions, statistical correlations were calculated between each metabolite peak area ratio and memory scores on the intracarotid amobarbital test for faces, pictures, words, and total items. Correlations were carried out between unilateral memory scores and the corresponding unilateral metabolite peak area ratios and between asymmetry indexes for memory and for metabolite peak area ratios.

Table 2 shows Spearman's rank correlation coefficients for correlations between the different memory modalities and metabolite ratios for asymmetry indexes and for values corresponding to left, right, ipsilateral, contralateral, and all hemispheres. All significant positive correlations involved NAA/(Cr+PCr). Within each correlation type, memory for words was the memory modality that showed the highest correlation coefficients when compared with the corresponding NAA/(Cr+PCr) values, and correlations were significant for the asymmetry indexes ($rho = 0.82$, $p = 0.0001$; Figure 2B), right hemispheres ($rho = 0.51$, $p = 0.045$), contralateral hemispheres ($rho = 0.58$, $p = 0.019$; Figure 3A), and all 32 hemispheres ($rho = 0.45$, $p = 0.009$; figure 4). The most robust correlations were observed between NAA/(Cr+PCr) asymmetry index and (1) memory asymmetry of total memory scores ($rho = 0.72$, $p = 0.002$; figure 2A) and (2) memory asymmetry for words ($rho = 0.82$, $p = 0.0001$; figure 2B). Significant correlations were also found between NAA/(Cr+PCr) from all 32 hemispheres and their corresponding memory scores for words ($rho = 0.45$, $p = 0.009$; figure 4).

Table 1. Mean (SD) left-sided, right-sided, ipsilateral, and contralateral values for memory scores achieved in intracarotid amobarbital test and for ^{1}H MRS metabolite peak area ratios

	Memory				^{1}H MRS Metabolite ratios			
	total	words	Picutres	Faces	NAA/ (Cr+PCr)	NAA/ Cho	NAA/ (Cho+Cr+PCr)	Cho/ (Cr+PCr)
Left	7.44	2.19	4.06	1.19	1.47	0.99	0.55	1.91
	(4.59)	(1.60)	(2.46)	(2.07)	(0.55)	(0.35)	(0.11)	(1.69)
Right	7.50	1.94	4.25	1.31	1.44	0.91	0.55	1.60
	(3.39)	(2.08)	(1.39)	(1.20)	(0.37)	(0.16)	(0.10)	(0.34)
Mean difference	0.06	0.25	-0.19	-0.13	0.03	0.08	0.005	0.32
Z	-0.42	-0.37	-0.28	-0.22	-0.78	-0.41	-0.26	-0.98
P	0.67	0.71	0.78	0.82	0.44	0.68	0.80	0.33
Ipsilateral	6.00	1.88	3.44	0.69	1.28	0.92	0.53	1.45
	(4.01)	(1.75)	(2.34)	(1.74)	(0.23)	(0.25)	(0.10)	(0.35)
Contralateral	8.94	2.25	4.88	1.81	1.63	0.97	0.57	2.06
	(3.43)	(1.95)	(1.20)	(1.42)	(0.56)	(0.30)	(0.11)	(1.65)
Mean difference	-2.94	-0.38	-1.44	-1.13	-0.35	-0.05	-0.04	-0.61
Z	-2.73	-0.77	-2.15	-2.15	-2.02	-0.47	-0.98	-0.93
P	0.006*	0.44	0.016*	0.032*	0.044*	0.64	0.33	0.35

*Ipsilateral and contralateral refer to the operated side. * Significant differences found by the paired Wilcoxon test between right and left hemispheres or between ipsilateral and contralateral hemispheres.*

In addition, there were strong but nonsignificant trends between NAA/(Cr + PCr) and (1) memory for words in the left hemispheres (rho = 0.48, p = 0.06) and (2) total memory scores in all hemispheres (rho = 0.32, p = 0.078).

A negative correlation was found in ipsilateral hemispheres between memory for faces and NAA/Cho (rho = -0.59, $p < 0.05$) or NAA/(Cho + Cr + PCr) (rho = -0.64, $p < 0.01$).

Table 2. Spearman rank correlation coefficient between ^{1}H MRS metabolite peak area ratios and memory scores in intracarotid amobarbital test, and all hemispheres.

	NAA/(Cr+PCr)	NAA/Cho	NAA/(Cho+Cr+PCr)	Cho/(Cr+PCr)
Asymmetry (n = 16)				
Total	0.72[1]	-0.06	0.21	0.30
Words	0.82[1]	0.16	0.45	0.26
Picture	0.39	-0.20	-0.04	0.13
Faces	0.18	-0.16	-0.11	0.23
Right (n = 16)				
Total	0.25	-0.21	-0.25	0.17
Words	0.48	-0.16	-0.04	0.20
Picture	0.25	0.06	0.04	-0.08
Faces	-0.030	-0.34	-0.42	0.20
Left (n = 16)				
Total	0.40	0.31	0.35	0.16
Words	0.51[2]	0.25	0.34	0.26
Picture	0.15	0.34	0.29	-0.12
Faces	0.084	-0.05	0.06	0.17
Ipsilateral (n = 16)				
Total	0.03	-0.14	-0.13	-0.05
Words	0.26	0.26	0.28	-0.27
Picture	0.19	0.05	0.07	-0.19
Faces	-0.32	-0.59[2]	-0.64[1]	0.35
Contralateral (n = 16)				
Total	0.33	-0.11	0.02	0.16
Words	0.58[2]	-0.24	-0.02	0.43
Picture	0.06	0.03	0.02	-0.07
Faces	0.04	-0.05	-0.06	-0.03
All (n = 32)				
Total	0.32	-0.05	0.01	0.21
Words	0.45[1]	0.03	0.14	0.22
Picture	0.19	0.13	0.12	-0.06
Faces	0.04	-0.26	-0.25	0.23

Separate correlations between metabolite ratios and memory modalities have been carried out for asymmetry indexes, left, right, ipsilateral, contralateral. [1]$p < 0.01$, [2]$p < 0.05$, significant correlations.

Figure 2. Correlation and regression line between asymmetry indexes (left versus right) for N-acetylaspartate/(creatine + phosphocreatine) [NAA/(Cr + PCr)] and total memory score (rho = 0.72, p = 0.002) (A) and memory for words (rho = 0.82, p = 0.0001) (B).

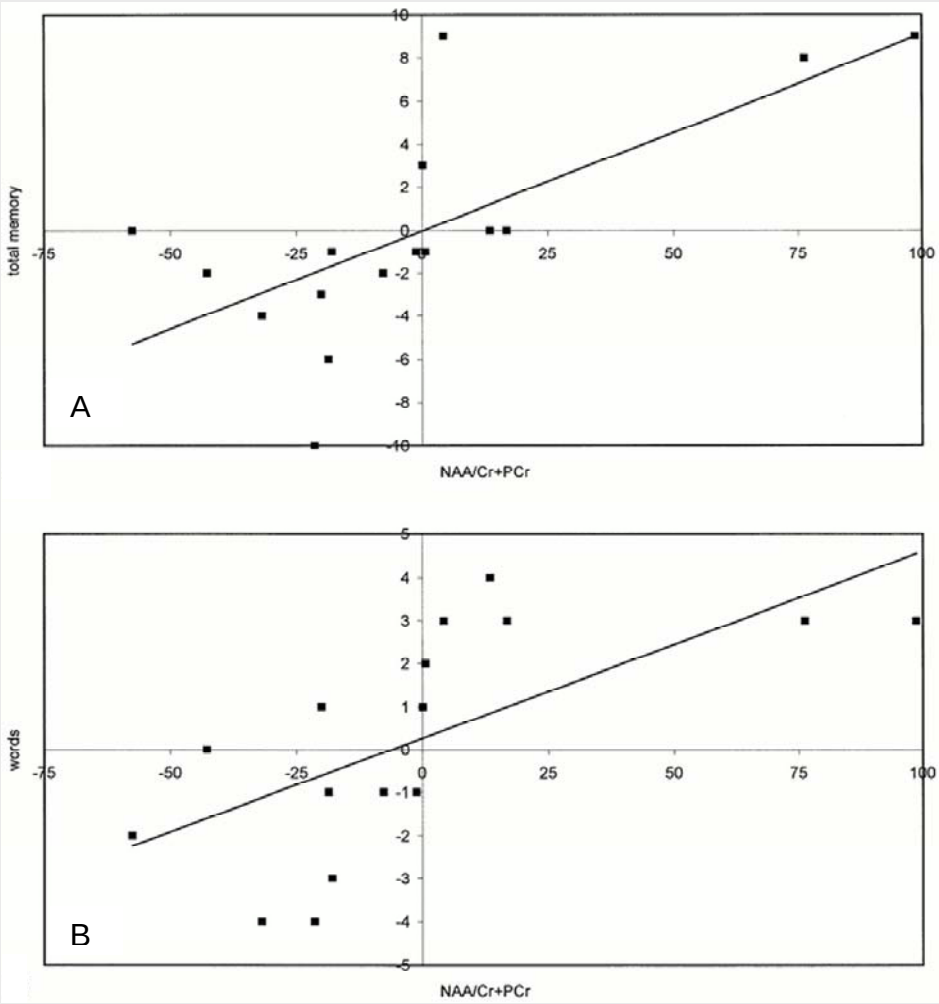


Figure 3. Correlation and regression line between memory for words and NAA/(Cr+PCr) in the nonoperated hemispheres (A) and the operated hemispheres (B).

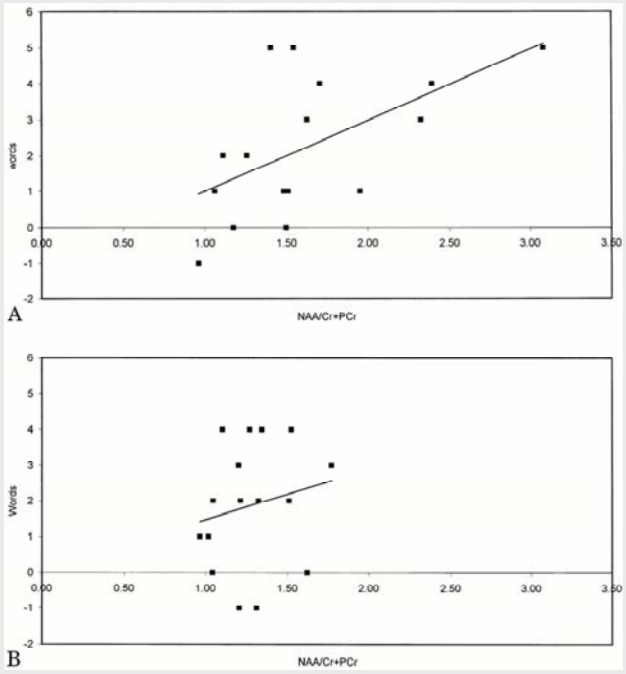
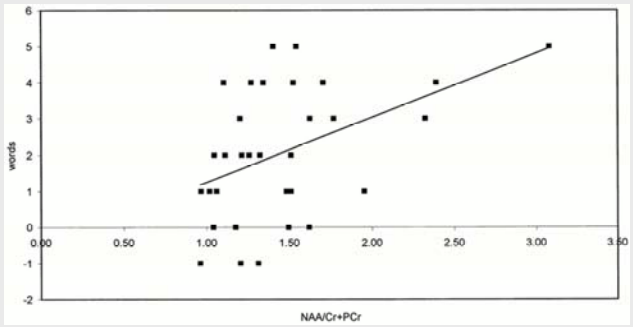


Figure 4. Correlation and regression line between memory for words and NAA/(Cr + PCr) in all 32 hemispheres studied (rho = 0.45, p = 0.009).



Discussion

To our knowledge, this is the first study that shows a significant correlation between unilateral memory function estimated by the intracarotid amobarbital test and in vivo cerebral metabolite levels (or their ratios) in humans. In essence, we have observed correlations between NAA/(Cr+PCr) peak area ratios in medial temporal structures and unilateral memory scores, particularly for words. A correlation between memory scores and NAA/(Cr+PCr) levels in medial temporal structures does not necessarily imply a specific involvement of NAA or (Cr+PCr) in memory function, as the presence of a correlation does not imply a causal relationship. More probably, as NAA levels appear to depend on neuronal integrity [Urenjak et al., 1992; Urenjak et al., 1993; Miller 1991; Birken et al., 1989], the correlation between memory and NAA/(Cr+PCr) ratios is due to the fact that the latter reflects the degree of neuronal loss or damage. Thus, our results suggest a correlation between recognition memory for words and neuronal integrity in medial temporal structures. This interpretation is consistent with previous reports of correlations between unilateral memory during the amobarbital test and neuronal counts in CA3 [Sass et al., 1991], in the hilar region, and in the granular layer of the dentate gyrus [O'Rourke et al., 1993]. Similarly, a correlation between memory asymmetries during the amobarbital test and hippocampal volume asymmetries has been reported [Loring et al., 1993].

Correlations between NAA/(Cr+PCr) and recognition memory were more robust for words, whereas no correlation has been found between NAA/(Cr+PCr) and memory for faces or objects. Verbal memory scores of the Wechsler Memory Scales have been shown to be related to the degree of hippocampal cell loss in patients who underwent temporal lobe surgery, but no relation was found for visual memory [Rausch et al., 1993]. Similarly, a correlation between logical memory asymmetries on the intracarotid amobarbital test and hippocampal volume asymmetries has been reported, whereas no correlation was found for visuospatial memory [Loring et al., 1993]. As mentioned in the introductory section, percent retention scores of the Wechsler Logical Memory Test correlated with left hippocampal volumes estimated by volumetric MRI in candidates for a left temporal

lobectomy [Lencz et al., 1992]. As in most series, the majority of our patients showed left hemisphere language dominance, and this may have contributed to the stronger correlation for verbal memory. Nevertheless, although impairment in verbal memory has been repeatedly reported after a left temporal lobectomy [Rausch et al., 1993; Morris et al., 1995; Rausch et al., 1989; Hermann et al., 1992; Saykin et al., 1992; Rausch et al., 1996], learning and memory complaints following a right temporal lobe resection are not as frequent or severe. On formal testing, cognitive changes following right temporal lobe resections appear to consist of variable declines in visuospatial memory and learning [Milner, 1968; Jones-Gotman, 1986], but changes appear to be less clear-cut and have not been so consistently reported as declines in verbal memory after left temporal surgery [Rausch et al., 1996; Elger et al., 1995]. Accordingly, the negative correlations between NAA ratios and memory for faces found in the present study are less consistent than those seen for memory for words and appear restricted to the ipsilateral hemispheres. As 96 correlations have been carried out in the current study, we can expect nearly five statistical type I errors at $p < 0.05$ and one at $p < 0.01$. Thus, it appears likely that the three significant results obtained for $p < 0.05$ correspond to statistical type I errors and may not be biologically significant. The same could apply to the statistical correlation seen between ipsilateral facial memory and NAA/(Cho+Cr+PCr), as this appears to be a sporadic result, inconsistent with the rest of the findings in Table 2.

Two hypotheses can, in principle, explain the poorer correlation between the integrity of medial temporal structures and memory for faces and objects: Either the medial regions of the temporal lobe are not as relevant for visuospatial memory as for verbal memory, or the neuropsychological protocols used were not appropriate to show a significant correlation for visuospatial memory. Verbal memory may decline after a right temporal lobectomy, but only if there is contralateral damage, as suggested by ^{1}H MRS and T2 relaxometry [Incisa della Rocchetta et al., 1995]. Others have stated that the right hippocampus is of major importance for visual memory but failed to show a decline in visual memory after right amygdalohippocampectomy [Gleißner et al., 1998]. In our series, memory scores for faces were lower and for objects higher than memory scores for words during

the intracarotid amobarbital test (Table 1). This suggests that face recognition may have presented greater difficulty than the other tasks and consequently was less sensitive to memory deficits, thus decreasing the likelihood of demonstrating a correlation with ^{1}H MRS ratios. Possibly, the problem arises from the test procedure: As pictures of objects can be remembered via verbal and/or nonverbal strategies, memory for objects might have been maintained after anesthetizing one hemisphere if the contralateral side was able to use one of these strategies, a phenomenon that may have obscured a correlation between ^{1}H MRS peak area ratios and amobarbital scores for objects.

No correlation between ^{1}H MRS peak area ratios and memory was found within the operated side. Correlations have previously been reported between unilateral memory and neuronal cell counts that are necessarily restricted to the resected temporal lobe [Sass et al., 1991; O'Rourke et al., 1993]. Cell counts are likely to be more sensitive than ^{1}H MRS in showing neuronal loss and may show a stronger correlation with function when available. It is difficult to explain the lack of correlation on the operated hemispheres solely on the basis of lower memory scores for words on this side, as differences in memory scores for words between ipsi- and contralateral hemispheres were not statistically significant (Table 1). Memory scores appear more scattered around the correlation line for values of NAA/(Cr+PCr) below 1.8, for ipsilateral as well as contralateral hemispheres (Figure 3). A similar relationship has been found between unilateral memory and neuronal density in the hilar region, and memory measures were more scattered for patients with lower neuronal densities in the hilar region, a result that is consistent with ours [O'Rourke et al., 1993]. These findings imply that patients with higher NAA/(Cr+PCr) tend to show high memory scores, whereas those with lower NAA/(Cr+PCr) ratios can show high as well as low memory scores for words. Two interpretations can explain the higher scatter at low NAA/(Cr+PCr) ratios. First, extrahippocampal structures in the same hemispheres can also be involved in memory processing. Indeed, the dorsolateral frontal cortex appears to be activated during performance of verbal working memory tasks in normal volunteers studied with PET [Petrides et al., 1993]. The temporal neocortex may also be involved, as hypometabolism of the left lateral temporal lobes correlates with verbal memory in

epileptic patients considered for surgery [Rausch et al., 1994]. Second, when hippocampal structures are damaged, memory function may be undertaken by other structures in the same hemisphere. In patients who underwent temporal lobectomy, verbal memory declined with surgery mainly in those with a relatively healthy hippocampus in the operated side [Hermann et al., 1992] and in those with a more recent onset of epilepsy [Saykin et al., 1992], further suggesting that in these patients, hippocampal functions may not have been assumed by other cortical structures preoperatively. This interpretation is also consistent with the findings shown in Figure 3B, where no significant correlation can be observed between NAA/(Cr+PCr) ratios and memory in the operated hemispheres. This may be a floor effect, as all NAA/(Cr+PCr) values in the operated side are clustered at the lower end of their distribution.

Further evidence that extrahippocampal structures might be involved in memory arises from reports that patients with temporal lobe epilepsy have less memory decline after selective amygdalohippocampectomy than those who undergo a standard en bloc temporal lobectomy, suggesting that nonhippocampal structures may play an important role in memory [Wieser et al., 1982; Goldstein et al., 1993]. Indeed, a correlation has been shown between the verbal Selective Reminding Test and left temporal lobe volume but not with hippocampal volumes [Lencz et al., 1992]. Converging information from human patients and nonhuman primates seems to suggest that the deficit in declarative memory associated with temporal lesions is related to the degree of extrahippocampal damage induced. Neither patient R.B., who had bilateral ischemic lesions restricted to area CA1 of the hippocampus as demonstrated by postmortem examination [Zola-Morgan et al., 1986], nor the four patients with bilateral lesions strictly restricted to the hippocampus on structural MRI [Squire, 1990] were as severely impaired as the well-known patient H.M., who underwent bilateral surgical removal of medial temporal structures [Scoville et al., 1957], presumably not restricted to the hippocampus proper. Similarly, the degree of memory deficits after temporal lesions seen in monkeys trained in a variety of object discrimination tasks appears to depend on whether neocortical regions around medial temporal structures are also damaged (for review, see Squire [Squire, 1992]).

The most significant results were obtained when using asymmetry indexes rather than unilateral measurements. A similar effect has also been found between hippocampal volumes and memory scores obtained in the intracarotid amobarbital test [Loring et al., 1993]. This effect may have been enhanced by the sample selection, as the study was restricted to candidates for temporal lobectomy where memory scores from the operated sides tend to be lower than from the nonoperated hemispheres (Table 1), presumably reflecting preoperative asymmetries in memory function due to epileptiform discharges or to underlying neuronal damage.

The existence of a correlation between memory function and metabolite levels appears to provide a sensitive tool to identify subtle neuronal damage and help localization of cognitive functions in the human brain in vivo. Metabolite peak area ratio for NAA/(Cr+PCr) seems to be particularly sensitive. In contrast to volumetric techniques, ^{1}H MRS is not restricted to the study of anatomically defined regions. Our results suggest that the hippocampal formation may play a significant role in recognition memory for words. It is likely that memory can also be processed by extrahippocampal cortices, which may take over memory functions in the presence of a damaged hippocampus, and ^{1}H MRS could be useful in identifying neuronal damage and delimiting proposed surgical interventions. This could be important for epilepsy surgery, as ^{1}H MRS is a noninvasive method that may be useful in identifying the epileptogenic hemisphere and in localizing memory functions to prevent postsurgical neuropsychologic deficits. Further studies must be undertaken to establish these issues; in particular, chemical shift imaging may prove helpful to study larger cortical areas.

CHAPTER 7

Discussion

The objective of resective epilepsy surgery is the complete resection or disconnection of the epileptogenic zone with preservation of the eloquent cortex [Rosenow & Lüders, 2001]. To minimize language and memory deficits after surgery, patients who are at risk of postoperative cognitive decline should be identified during the presurgical evaluation; however, the tests used in such an evaluation may themselves cause complications. The Wada test is used to assess the hemispheric contribution to language and, in temporal lobe epilepsy, the memory compensation provided by the contralateral hemisphere. Because of the invasive character of the Wada test, there is a need for non-invasive alternatives. Although functional MRI can assess hemispheric language-dominance reliably in some patients [Rutten et al., 2002; Rutten et al., 2002], it cannot establish the hemispheric contribution to declarative memory. We are the first to establish a positive correlation between unilateral memory function and the neuronal integrity of the mesial temporal areas of both hemispheres, as expressed by in vivo measurement of metabolite levels (or ratios) of N-acetylaspartate- and creatine-containing compounds (chapter 6). This is an important finding because the direct correlations between these in vivo measurements, especially in the temporal lobe contralateral to the seizure onset, suggest that memory function can be established preoperatively on the basis of ^{1}H MRS metabolite levels (or ratios) in the mesial temporal areas. Further studies involving more patients should explore the possibility of predicting postsurgical memory outcome with non-invasive 1H MRS, an investigation that can be carried out in combination with routine MRI and does not require the patient's cooperation beyond that he/she lies still.

To achieve seizure control, the epileptogenic zone should be included in the resection and this zone is estimated by identifying the cortical areas responsible for ictal semiology (symptomatogenic zone), interictal epileptiform abnormalities (irritative zone), and transformation into ictal activity (ictal-onset zone), and the lesion as detected by MRI [Carreño & Lüders, 2001]. In general, surgical results are best when there is congruence between the results of different tests performed in the presurgical evaluation of patients.

With regard to prognosis, medial temporal lobe epilepsy has an excellent surgical outcome in terms of seizure control when the epilepsy is caused by mesiotemporal

sclerosis [Kim & Spencer, 2000]. The preoperative identification of other syndromes with underlying pathology is important for optimal neurophysiological tailoring of the surgical approach and for postoperative outcome. Advances in neuroimaging, especially structural MRI, mean that more surgical candidates with pharmacoresistant lesional epilepsy will be identified. A significant number of them will be children with neurodevelopmental lesions that often involve extratemporal areas, particularly the frontal lobes [Wyllie, 2001]. The size and distribution of these lesions may vary from subtle or extensive focal, to widespread and multifocal. Outcome with regard to seizure control in such patients lags behind that achieved in mesiotemporal lobe epilepsy with sclerosis [Sisodiya, 2000].

In this thesis we studied several questions aimed at improving the outcome of epilepsy surgery. In chapter 2 we investigated a series of consecutive patients who were operated on for pharmacoresistant frontal lobe epilepsy. In this series, half of the patients had focal cortical dysplasia, but only a third of them became seizure-free after resection. Thus, the abnormalities of ‘focal’ cortical dysplasia may have been more widespread than previously thought. This underscores the significance of syndromal classification and the need to identify predictors of a favourable outcome. We found that a focal abnormality on neuroimaging was associated with a favourable surgical outcome. Unfortunately, this was the only factor predictive of a good surgical result. Conversely, ictal head version, eye deviation, and autonomic features were associated with a poor outcome in terms of postoperative seizure control. The most robust negative predictor was unilateral head version. This was surprising because head version is usually thought to be contralateral to seizure onset. However, the localizing and lateralizing value of ictal semiology may be overestimated by fast seizure propagation. Early symptoms of seizures can arise from areas located far from, or even contralateral to, the initial functional abnormality, and the association between such findings and outcome may not be obvious. Contralateral head version as an ictal phenomenon in frontal lobe epilepsy may be the result of fast seizure propagation or it may arise from areas outside the frontal lobe [Penfield & Jasper, 1954; Ochs et al., 1984; Williamson, 1992]. This should serve as a warning that a good surgical outcome in frontal lobe

epilepsy cannot be guaranteed even when ictal semiology seems to provide a straightforward source localization.

In contrast to some ictal clinical signs, the interictal scalp EEG abnormalities were not predictive of a good surgical outcome. Interestingly, rapidly generalized or bilateral synchronous discharges were not associated with a poor surgical outcome. These discharges may represent secondary spread from localized areas within (most likely) the frontal lobes [Williamson, 1992] that can be controlled if they are included in the resection. On the other hand, a multifocal ictal onset did seem to be associated with a poor surgical outcome. Thus, whereas a multifocal ictal onset should alert clinicians, the observation of interictal generalized discharges in frontal lobe epilepsy should not be a reason per se to withdraw patients from an epilepsy surgery programme.

With a possible exception of vascular malformations (good outcome), Rasmussen encephalitis (poor outcome), and the absence of a lesion (poor outcome), the histopathology was not predictive of the surgical outcome. This may be explained by the topography, distribution, and histological properties of the lesion. When widespread or multifocal lesions are identified on neuroimaging, complete resection may not be achieved, either because of involvement of the eloquent areas or because the histological abnormalities extend beyond the boundaries determined by neuroimaging. The question then arises as to whether the extent of surgery should be guided by the location and extent of (intraoperative) ECoG abnormalities or by the histological nature of the lesion (chapter 3).

With respect to ECoG findings, the presence of interictal discharge patterns appeared relevant. The presence or abolition of sporadic spikes in the post-resection ECoG did not correlate with outcome, whereas the abolition of dense epileptiform discharge patterns was associated with a good surgical outcome in terms of seizure control. It thus appears that residual ECoG discharge patterns after resection are a negative predictor of outcome. It was surprising that incomplete removal of the histological abnormalities was not associated with a poor outcome. This indicates that not all structural abnormalities are equally epileptogenic, and that the ECoG may aid the identification of the most

epileptogenic regions, in addition to revealing more extensive pathology than that predicted by MRI.

Our finding (chapter 3) that some ECoG discharge patterns (with a dense spiking appearance) are associated with (focal) cortical dysplasia has important implications because this enables the detection of the underlying pathology before resection and thus influences the procedure. Another major implication is that even if a lesion involves the eloquent cortex, effective epilepsy surgery may still be feasible if (intraoperative) ECoG reveals dense epileptiform discharge patterns indicative of epileptogenic areas outside these areas, especially in patients with cortical dysplasia.

It thus seems that some types of ECoG discharge patterns are associated with a histological diagnosis of focal cortical dysplasia. In the studies described in chapters 4 and 5 we investigated whether these patterns also occur in other types of congenital lesions. In the study described in chapter 5, we determined the specificity of dense epileptiform discharge patterns by comparing findings in patients with neurodevelopmental lesions (i.e. focal cortical dysplasia or glioneuronal tumours) with those in cavernoma patients. We found that dense epileptiform discharge patterns also occurred in patients with cavernomas, to a similar degree as in the patients with neurodevelopmental lesions. Thus, although the literature on these ECoG patterns suggests that dense epileptiform discharge patterns are specific for cortical dysplasia, or other neurodevelopmental lesions [Rosenow et al., 1998; Binnie et al., 2000; Chassoux et al, 2000; Seo et al, 2003; Boonyapisit et al., 2003], our results do not support this idea.

Interestingly, a younger age at epilepsy onset was associated with continuous spiking, especially when there were neurodevelopmental lesions, but also, although statistically less evident, when there were cavernomas (chapter 5). It is likely that such an early debut of seizures is the consequence of an early insult (vascular, genetic, toxic, metabolic) to the developing brain, leading to structural and functional changes and the formation of secondary cortical dysplasia (see illustrative case)[Marin-Padilla, 2000]. In the case of cavernomas, early (micro)bleeding with subsequent iron deposition at a crucial stage of brain development can result in functional changes similar to those seen in

neurodevelopmental lesions. Cavernomas and their surrounding cortex lack the typical structural changes of cortical dysplasia, perhaps as a result of a later insult to the brain when compared with neurodevelopmental lesions. A later debut of epilepsy in patients with cavernomas supports this notion. We consider the expression of continuous neocortical spiking in the ECoG to be a marker of early disruption of functional systems in the developing brain.

In the study reported in chapter 4, we found that in the patients with a neurodevelopmental lesion, the dense epileptiform patterns on intraoperative ECoG were present in both patients with focal cortical dysplasia and patients with a glioneuronal tumour. The continuous spiking pattern was associated with a diagnosis of focal cortical dysplasia, but, more importantly, it was predictive of the presence of a disorganized cortical architecture, as seen in surgical specimens. This hallmark of cortical dysplasia thus serves as a histopathological substrate for at least one of the dense epileptiform discharge patterns, i.e. continuous spiking.

Another interesting finding is that the occurrence of the continuous spiking pattern in the hippocampus was associated with a longer duration of epilepsy (chapter 5). This association suggests secondary or perhaps even end-stage epileptogenesis that is, most likely, irrespective of the underlying pathology. If this is the case, it is a strong argument to perform neocortical resection early in the course of temporal lobe epilepsy, when the hippocampus is possibly not yet involved and can be spared.

The presence of continuous spiking on the intraoperative ECoG in the patients with a neurodevelopmental lesion was predictive of (associated) cortical dysplasia in the form of a disorganized cortical architecture. In these patients there is a reasonable chance that neuroimaging (MRI) will fail to detect any pathology, showing only non-specific abnormalities, and may even lead to a wrong diagnosis (see case vignette, chapter 1). Thus, in some clinical settings (especially in young patients and patients with non-specific MRI abnormalities), when MRI does not point to a certain diagnosis, the presence of dense ECoG discharge patterns, especially neocortical continuous spiking, helps to identify areas of cortical dysplasia which should be included in the resection in order to achieve good seizure control.

The case vignette (chapter 1) showed that intraoperative ECoG is able to identify a highly epileptogenic and dysplastic cortex in the absence of clear abnormalities on MRI. The poor surgical outcome in the patient described in chapter 1 was due to the presence of another epileptogenic focus, as evidenced by the residual continuous spiking after the resection. The resection strategy and ECoG tailoring was not optimal. ECoG tailoring can be improved if the localization of discharge patterns can be predicted from scalp EEG findings during the presurgical assessment. However, there are no methods to extrapolate the findings obtained with scalp EEG to those obtained with ECoG with regard to dense epileptiform discharge patterns. Thus, to improve the outcome in such patients, especially when there are ‘red flags’, subdural electrodes should be implanted for chronic ECoG recordings in order to define the epileptogenic zone. Preoperative EEG findings (source localization, magnetoencephalography, functional MRI) can help to determine the site of electrode placement.

FUTURE RESEARCH

The occurrence of ECoG discharge patterns

We found that dense epileptiform discharge patterns are common in at least three types of congenital lesions in patients with pharmacoresistant epilepsy, i.e. focal cortical dysplasia, glioneuronal tumours, and cavernomas. We also observed such patterns in patients with refractory epilepsy due to tuberous sclerosis. The topography of these patterns should be compared with histopathological findings from epileptogenic and non-epileptogenic tubers and with neurophysiological recordings from the inside of the tuber. Furthermore, it remains to be determined whether dense patterns also occur in other types of (non-congenital) pathology.

Assessment of unilateral hemispheric memory functioning

New non-invasive tests should be developed to replace the invasive Wada test. Functional methods that depend on activation of specific brain areas that are involved in specific memory tasks, for example functional MRI, MEG, or functional transcranial Doppler sonography, seem promising. Memory-specific test paradigms

may prove to be difficult, although some are currently being developed. Their sensitivity and specificity should be compared with that of the current gold standard, the Wada test. Because it is straightforward, 1H MRS should be studied further for the evaluation of unilateral memory function in temporal lobe epilepsy.

ECoG discharge patterns in non-epileptic patients

It should be investigated whether dense epileptiform ECoG patterns also occur in neurosurgical patients with an indication for resective surgery for benign lesions, but without pharmacoresistant epilepsy (for example, low-grade tumours, meningiomas, cavernomas, vascular malformations). In the future, ECoG may prove useful for tailoring the resection or for detecting those patients at risk of developing pharmacoresistant seizures.

Acute intraoperative ECoG versus chronic ECoG

It remains to be established whether the discharge patterns seen on acute intraoperative ECoG in the anaesthesized patient occur to a similar degree and with a similar distribution in awake and sleeping patients with chronically implanted subdural electrodes. Different types of pathology may respond differently to general anaesthesia, which can both suppress and enhance epileptiform activity. Such knowledge may be used to localize the epileptogenic zone more accurately. These are important issues that need to be addressed to establish the added value of intraoperative ECoG when subdural electrodes are being implanted for prolonged recordings.

Topography of ECoG discharge patterns and neuroanatomical substrates

To gain more insight into the topography and distribution of interictal epileptiform abnormalities and ictal spreading of the discharge, it is worthwhile to establish whether these patterns are correlated with anatomical neuronal pathways (for example, with in vivo diffusion tensor MR imaging). Such associations may explain unexpected ictal semiology (according to the classical localization principles) and multifocality of interictal epileptiform abnormalities.

Cortical stimulation, afterdischarges, and histopathology

Focal afterdischarges may occur during cortical electrostimulation to map the functional cortex. These discharges resemble dense epileptiform discharge patterns and may reveal networks with epileptogenic propensity. Since cortical stimulation is performed routinely in patients with chronically implanted subdural electrodes, and occasionally intraoperatively, the significance and the contribution of these afterdischarges to epileptogenicity should be examined.

Identification of ECoG discharge patterns

Automatic pattern recognition programmes should be developed to detect the occurrence of dense epileptiform discharge patterns. Non-linear methods to recognize deterministic behaviour and coherence analysis can be used to detect synchronized activity between cortical regions showing such patterns. Such advanced methods may contribute to the definition of the irritative zone. And lastly, it needs to be established whether scalp EEG findings can predict the occurrence of dense epileptiform ECoG discharge patterns, in order to select those patients who need to undergo ECoG, to tailor the resection.

CHAPTER 8

Summary

The objective of resective epilepsy surgery is the complete resection or disconnection of the epileptogenic zone under preservation of the eloquent cortex. Outcome depends on exact functional localisation of the epileptogenic focus and critical, eloquent areas. In search for variables that determine outcome, we identified specific combinations of clinical neurophysiological findings with their underlying histopathology. These findings may have important surgical consequences.

Chapter 1 starts with an illustrative case of a patient with pharmacoresistant temporal lobe epilepsy and describes the occurrence and topography of four discrete highly epileptogenic foci on the lateral temporal neocortex that showed a continuous spiking pattern and were associated with cortical dysplasia. The hippocampus showed an ischemic scar. The case is followed by a general introduction and the aims of the individual studies in this thesis.

In chapter 2 we describe 37 patients with pharmacoresistant frontal lobe epilepsy who had undergone epilepsy surgery. In a retrospective analysis we established that focal cortical dysplasia was the histopathological diagnosis in 17/37 (46%) of the patients. We determined predictors in the presurgical evaluation for surgical outcome. Univariate analysis showed that a focal abnormality on neuroimaging was the only variable that was associated with a favourable surgical outcome (Engel I or II) whereas contralateral head version, eye deviation and autonomic manifestations were associated with a poor surgical outcome (Engel III or IV). Multivariate logistic regression showed that a focal abnormality on neuroimaging was associated with a favourable surgical outcome whereas contralateral head version was predictive of a poor surgical outcome.

In chapter 3 we describe the electrocorticographical abnormalities in 35 patients with frontal lobe epilepsy and we estimated the significance of residual ECoG and histopathological abnormalites on seizure control after surgery for frontal lobe epilepsy. In this retrospective analysis the pre- and post-resection ECoG records were reviewed for the presence of sporadic spikes and dense epileptiform ECoG

discharge patterns. Histopathology was reviewed for completeness of resection. We concluded that dense epileptiform ECoG patterns were significantly more common in patients with focal cortical dysplasia, with a sensitivity of 94% and a specificity of 75%, and their abolition on postresection ECoG recordings was associated with a favourable surgical outcome. Persistence of sporadic ECoG spikes and incomplete removal of histopathological abnormalities did not significantly affect outcome.

In chapter 4 we investigated the occurrence of dense epileptiform ECoG discharge patterns in patients with a neurodevelopmental lesion (FCD or a GNT) and associations with specific histopathological features. Continuous spiking was seen significantly more often in FCD and this pattern was highly specific for the presence of a disorganized cortical architecture in FCD or GNT. We concluded that dense epileptiform ECoG discharge patterns occur in patients with FCD and GNT, but the continuous spiking pattern was seen significantly more often in patients with FCD. When continuous spiking is found with GNT it is likely to be associated with dysplastic regions with a high neuronal density.

In chapter 5 we studied whether cavernomas exhibit dense ECoG discharge patterns similar to those occurring in NDLs and whether these patterns are related to pathological and demographic features. We found that dense epileptiform patterns occur in both cavernomas and NDLs but hipppocampal bursts occurred more often in the patients with a cavernoma. In both patients with NDL and cavernoma neocortical continuous spiking seems characteristic of early onset of seizures and such patterns may involve the hippocampus in time. In patients with a cavernoma the degree of iron staining was not associated with any of the discharge patterns. Microglia cells may inhibit the expression of dense epileptiform discharge patterns.

In chapter 6 we investigated the relationship between recognition memory and the neuronal integrity in medial structures of the temporal lobes in the living human brain as expressed by metabolite levels. Metabolite ratios [NAA/(Cr + PCr),

NAA/Cho, and NAA/(Cr + PCr + Cho)] from the mesial temporal regions were correlated with unilateral memory scores estimated by the intracarotid amobarbital test for words, objects, faces, and total score. The total memory score, memory for objects and faces, and NAA/(Cr + PCr) were significantly lower for the hemisphere ipsilateral to the resection. Furthermore, we found positive correlations between unilateral memory for words and the NAA/(Cr + PCr) ratio from medial temporal structures in patients with mesial temporal sclerosis. The findings suggest that medial temporal structures play a significant role in recognition memory in humans, particularly for words and raise the question whether ^{1}H MRS can be used for presurgical memory lateralisation.

In chapter 7 the findings in the preceding chapters are discussed with special attention to associations between the occurrence of dense epileptiform ECoG discharge patterns and histopathological abnormalities. In general, these patterns, were not specific for a certain diagnosis, and the continuous spiking pattern probably results from an early insult to the developing brain. However, the specificity of these patterns for dysplastic or neurodevelopmental lesions may increase when neuroimaging is normal or only shows minimal or non-specific abnormalities. In such instances, the occurrence of a continuous spiking pattern indicates dysplastic changes of cortex that should be included in the resection in order to achieve a good surgical outcome.

Future research should focus on the preoperative detection of dense epileptiform discharge patterns with non-invasive EEG methods. In cases where subdural electrodes are implanted for chronic recordings the added value of acute intraoperative ECoG should be established. The occurrence of dense epileptiform patterns in patients with other types of pathology should be investigated with a possible role for ECoG in tailoring the resection to improve outcome and prevent the development of future (pharmacoresistant) seizures.

Samenvatting

Bij epilepsiechirurgie streeft men naar complete verwijdering of disconnectie van de epileptogene zone met behoud van eloquente hersengebieden. Het doel is immers om de aanvallen te stoppen zonder dat er neurologische uitval optreedt. Het resultaat van de operatie hangt daarom af van een exacte lokalisatie van deze gebieden. In dit proefschrift worden specifieke combinaties van klinisch neurofysiologische bevindingen en onderliggende histopathologische afwijkingen geïdentificeerd. Dergelijke bevindingen kunnen belangrijke chirurgische konsekwenties hebben.

In hoofdstuk 1 wordt een illustratieve casus gepresenteerd van een kind met therapieresistente epilepsie vanuit de temporaalkwab. Tijdens de operatie werden bij intraoperatieve electrocorticografie onverwachts vier discrete, onafhankelijk vurende en zeer lokale epileptische foci gevonden in de laterale temporale neocortex. De epileptiforme afwijkingen werden gekenmerkt door lange reeksen van ritmische piekaktiviteit. Dergelijke electrocorticografische patronen hingen bij deze patiënt samen met corticale dysplasie in de temporale neocortex. In de hippocampus werd een ischemisch litteken gezien. De casus wordt gevolgd door een algemene introductie en doelen van de verschillende individuele studies in dit proefschrift.

In hoofdstuk 2 wordt gezocht naar faktoren die bepalend kunnen zijn voor het chirurgisch resultaat m.b.t. aanvalsvrijheid bij patiënten met therapieresistente epilepsie vanuit de voorhoofdkwab. Ongeveer de helft (46%) van deze groep patiënten heeft een onderliggende diagnose van focale corticale dysplasie. De onderliggende pathologie was niet voorspellend voor het operatie resultaat. Een focale afwijking bij beeldvormend onderzoek van de hersenen hing daarentegen samen met een gunstig resultaat, terwijl een contralaterale hoofddraai, oogdeviatie en autonome verschijnselen als ictale symptomen geassocieerd zijn met een slecht resultaat. Regressie analyse liet zien dat een focale afwijking bij de beeldvorming en een contralaterale hoofddraai onafhankelijke voorspellers waren voor een respectievelijk goed en slecht resultaat.

In hoofdstuk 3 worden epileptiforme afwijkingen, zoals die gezien worden tijdens intraoperatieve electrocorticografie, beschreven bij patiënten met epilepsie vanuit de voorhoofdkwab. Deze epileptiforme afwijkingen worden geclassificeerd als zgn. *'dichte bezette ECoG patronen'* (hier *'ontladingspatronen'* bestaande uit een continu piekpatroon, bursts van pieken of recruterende ontladingen) of *'sporadische pieken'*. In dit retrospectieve onderzoek werd het vóórkomen van dergelijke patronen vóór en na de resectie bestudeerd. Deze patronen werden gerelateerd aan de ondeliggende histopathologische diagnose en het operatie resultaat. *'Dicht bezette ECoG patronen'* komen significant vaker voor bij focale corticale dysplasie (sensitiviteit 94%, specificiteit 75%, positief voorspellende waarde 80%). Het verdwijnen van dergelijke patronen hing samen met een gunstig operatie resultaat terwijl het persisteren van sporadische pieken na de resectie of incomplete verwijdering van de histologische afwijking niet gerelateerd waren aan het operatie resultaat.

In hoofdstuk 4 worden de *'dichte bezette ECoG patronen'* in relatie gebracht met specifieke histopathologische kenmerken bij een groep patiënten met een neuronale ontwikkelingsstoornis zoals focale corticale dysplasie of glioneuronale tumoren (gangliogliooom of dysembryoplastisch neuroepitheliale tumor). Van de *'dichte bezette ECoG patronen'* kwam alleen het continue piekpatroon vaker voor bij een diagnose van focale corticale dysplasie, terwijl de overige epileptiforme patronen even vaak voorkwamen bij beide groepen. Het continue piekpatroon had een hoge specificiteit (96%) en positief voorspellende waarde (91%) voor de aanwezigheid van een gestoorde en ongeorganiseerde corticale architectuur bij alle patiënten met een neuronale ontwikkelingsstoornis. Voorts hingen de continue piekpatronen en recruterende ontladingen samen met een hoge dichtheid van neuronen. We concluderen dat *'dichte bezette ECoG patronen'* voorkomen bij zowel focale corticale dysplasie als glioneuronale tumoren. Wanneer het continue piekpatroon wordt gezien bij glioneuronale tumoren is het waarschijnlijk dat dit samenhangt met dysplasie van de cortex en een relatief hoge neuronale dichtheid.

In hoofdstuk 5 worden de electrocorticografische afwijkingen bestudeerd bij patiënten met therapieresistentie epilepsie en een cavernoom. Deze worden vergeleken met de bevindingen bij patiënten met een neuronale ontwikkelingsstoornis. De *'dichte bezette ECoG patronen'* werden gezien bij zowel de patiënten met een cavernoom als bij die met een neuronale ontwikkelingsstoornis. Dergelijke ECoG patronen kwamen voor in de neocortex en in hippocampus, maar hippocampale bursts werden relatief vaker gezien bij cavernomen. Een continu piekpatroon in de neocortex hing samen met een vroeg debuut van de epilepsie, terwijl een dergelijk piekpatroon in de hippocampus gerelateerd was aan een lange duur van de epilepsie. De mate van ijzer depositie bleek niet geassocieerd met één van de electrografische piekpatronen terwijl microgliacellen mogelijk een inhiberend effect hadden op het vóórkomen van *'dicht bezette patronen'*.

In hoofdstuk 6 wordt de relatie tussen geheugen (i.e. herkenning) en de neuronale integriteit in de mesotemporale structuren van het levende brein zoals gemeten met ^{1}H MRS bestudeerd bij patiënten met mesotemporale sclerose en therapieresistente epilepsie. Metaboliet ratios (NAA/(Cr+PCr), NAA/Cho en NAA/(Cr+PCr+Cho)) van deze structuren worden gecorreleerd met herkenning van woorden, objecten en gezichten. De totale geheugenscore, herkenning van objecten, herkenning van gezichten en de ratio NAA/(Cr+PCr) bleken significant lager in de hemisfeer ipsilateraal van de resectie (epileptisch focus). Unilaterale herkenning van woorden correleerde met de ratio NAA/(Cr+PCr). Deze bevindingen suggereren dat de neuronale integriteit van de mesotemporale structuren belangrijk is voor goed functioneren van het geheugen bij de mens. De resultaten roepen de vraag op of ^{1}H MRS in het prechirurgische traject een bijdrage kan leveren aan lateralisatie van geheugenfuncties.

In hoofdstuk 7 worden de bevindingen van de voorgaande hoofdstukken bediscussiëerd met de nadruk op het vóórkomen van *'dicht bezette patronen'* zoals gezien tijdens intraoperatieve ECoG bij verschillende histopathologisce afwijkingen. Dergelijke ECoG patronen blijken niet specifiek te zijn voor een

bepaalde onderliggende diagnose. Een continu piekpatroon is waarschijnlijk het resultaat van een vroege stoornis in de ontwikkeling van het brein. Echter, de specificiteit van dergelijke ECoG patronen kan toenemen wanneer de MRI normaal is of slechts aspecifieke afwijkingen laat zien. In zulke gevallen wijst het vóórkomen van een continu piekpatroon op aanwezigheid van dysplasie in de cortex, waarvan het niet verwijderen samenhangt met een slecht operatie resultaat.

Toekomstig onderzoek dient zich o.a. te richten op het identificeren van *'dichte bezette patronen'* met non-invasieve EEG methoden. De additieve waarde van het intraoperatieve ECoG dient te worden onderzocht bij patiënten bij wie subdurale electroden worden geimplanteerd voor langdurige registraties. De electrocorticografische afwijkingen bij andere soorten pathologie dienen te worden bestudeerd, met name m.b.t. het vóórkomen van *'dicht bezette patronen'*. De bijdrage van het intraoperatieve ECoG ter vebetering van het operatie resultaat en ter preventie van toekomstige epileptische aanvallen dient te worden bepaald bij patiënten met èn zonder therapieresistente epilepsie.

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&
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List of Publications

&

Curriculum Vitae

PUBLICATIONS

Ferrier CH, Engelsman J, Alarcón G, Binnie CD, Polkey CE. Prognostic factors in presurgical assessment of frontal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 1999;66:350-356.

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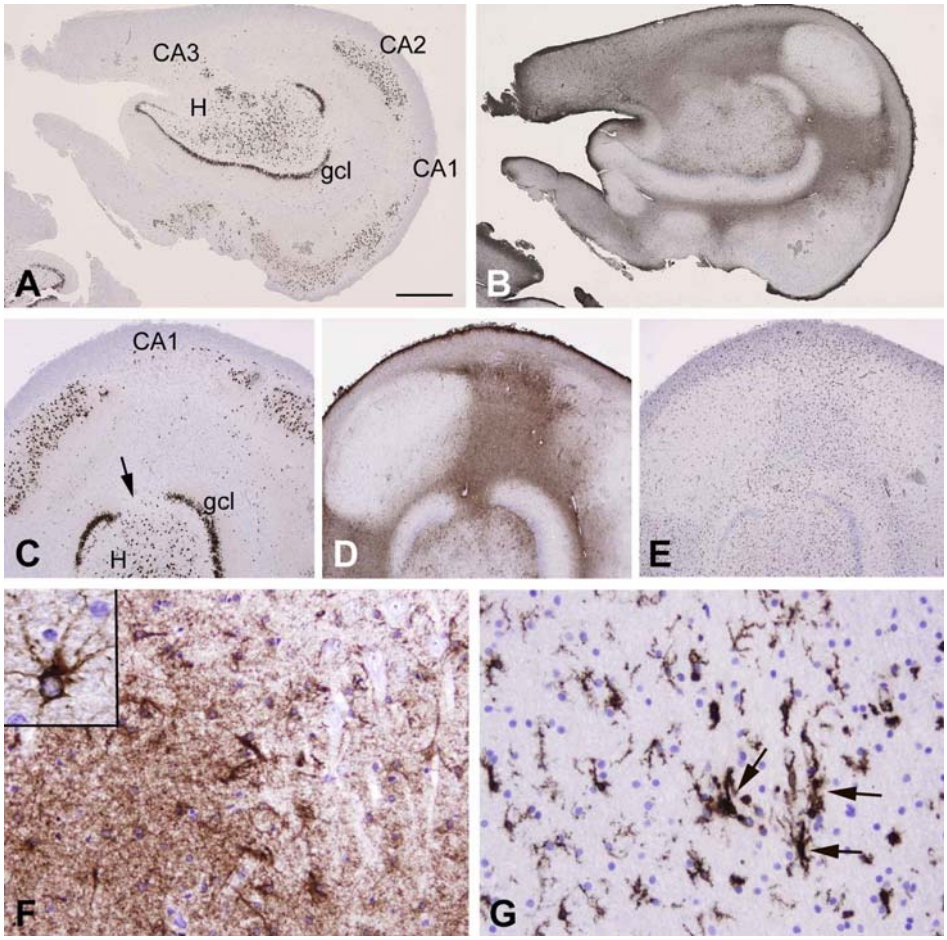
CURRICULUM VITAE

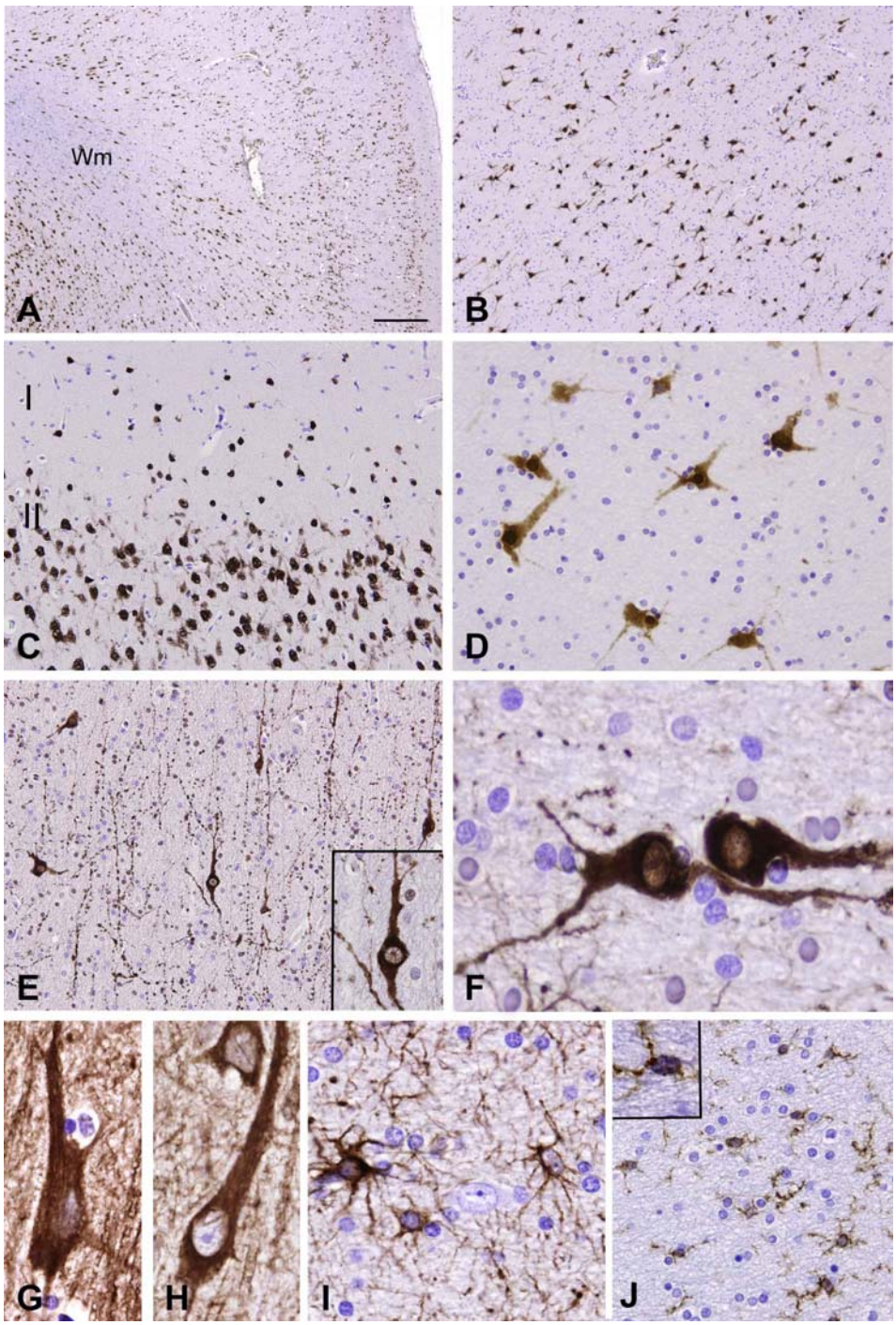
De auteur werd geboren op 9 augustus 1973 te Dordrecht. In 1991 behaalde hij zijn VWO diploma op het Titus Brandsma College te Dordrecht. In 1993 slaagde hij voor de propaedeuse Technische Informatica aan de Technische Universiteit Delft. In 1993 begon hij de studie Geneeskunde aan de Universiteit van Amsterdam. In 1997 en 1998 deed hij als student geneeskunde wetenschappelijk onderzoek dat betrekking had op klinisch neurofysiologische aspecten van epilepsiechirurgie in het King's College Hospital te Londen (prof. C.D. Binnie). In november 2000 behaalde hij zijn artsendiploma en in februari 2001 begon hij met de opleiding neurologie – hoofdvak klinische neurofysiologie in het UMC Utrecht bij prof.dr. A.C. van Huffelen (klinische neurofysiologie) en prof.dr. J. van Gijn (neurologie). De opleiding zal in januari 2007 worden afgerond. Tijdens de opleiding is hij aktief bestuurslid geweest van de VAAN (Vereniging Arts Assitenten in opleiding tot Neuroloog) voor de KNF-gerelateerde zaken en als lid van de visitatiecommissie. Daarnaast heeft hij deel uitgemaakt van de commissie assistentencurus KNF van de Nederlandse Vereniging KNF en was deels verantwoordelijk voor de organisatie van deze cursus in 2004 t/m 2006.

Color Figures

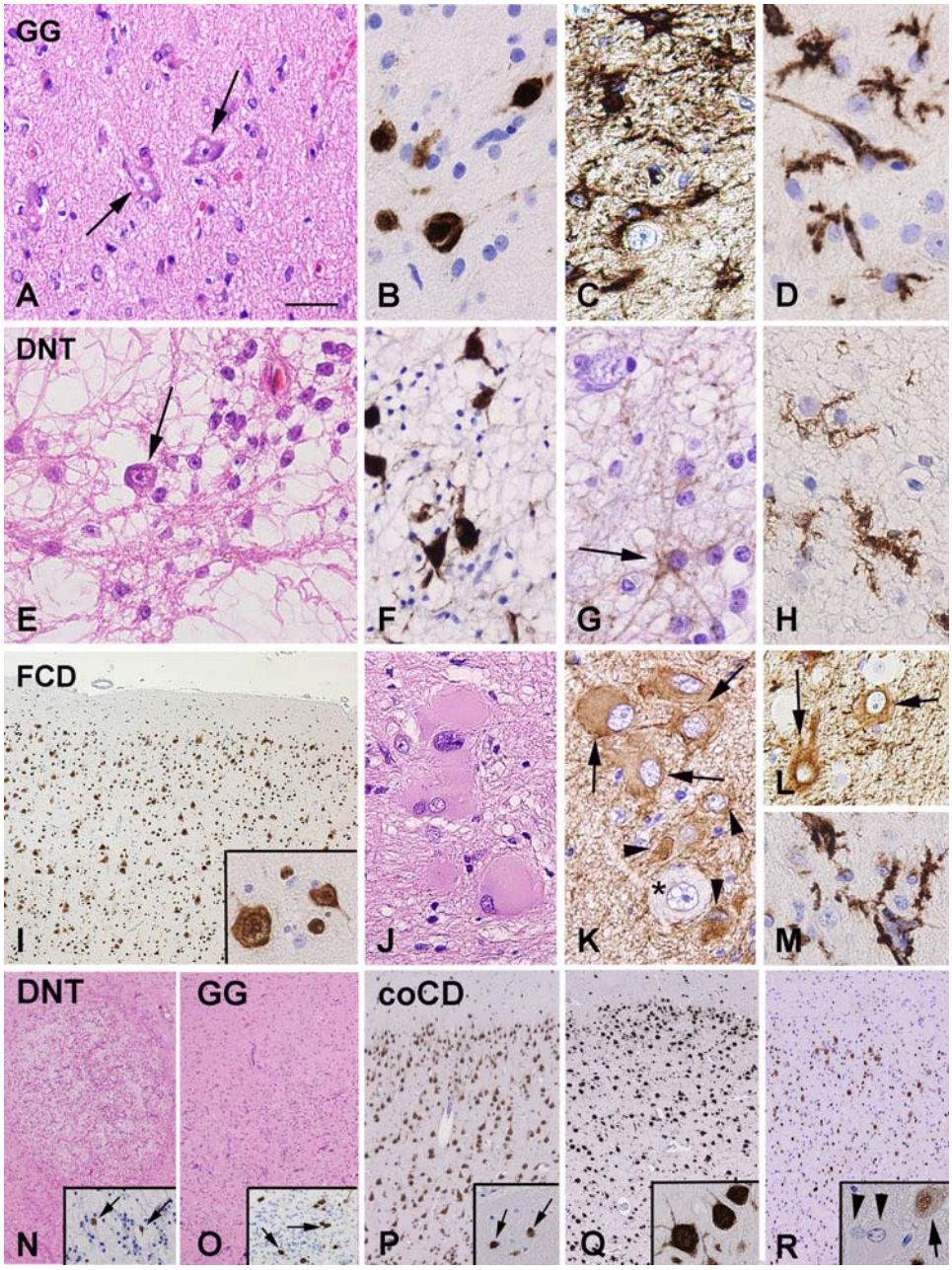
Chapter 1. Figure 5 (see page 16).



Chapter 1. Figure 6 (see page 18).



Chapter 4. Figure 2 (see page 73).



Chapter 5. Figure 1 (see page 92)