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Prognostic Value of Electrocorticography and Surface EEG in Epilepsy Patients with Unilateral Hippocampal Sclerosis Undergoing Selective Amygdalohippocampectomy

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Für meine Eltern und Yan

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1 ABSTRACT

Purpose:

To evaluate the predictive value of intraoperative electrocorticography (ECoG) and surface electroencephalography (EEG) in patients with unilateral hippocampal sclerosis (HS) undergoing transsylvian selective amygdalohippocampectomy (sAHE).

Methods:

ECoG was recorded before and after resection in 22 patients with medication resistant mesial temporal lobe epilepsy. The sAHE was performed, regardless of ECoG findings. ECoG findings recorded from the mesial temporal lobe (MTL) and lateral temporal lobe (LTL) before and after the sAHE were correlated with seizure outcome 12 months later. The preoperative surface EEG findings as well as their correlation with seizure outcome were also discussed. According to pre-resection ECoG findings, patients were divided into the following subgroups: 1) Pre-resection spikes restricted to the MTL; 2) Pre-resection spikes both in MTL and LTL); 3) Pre-resection spikes restricted to the LTL; 4) No pre-resection spikes recorded. According to the distribution of interictal epileptiform discharges (IEDs), the surface EEG findings were divided into four groups: 1) ipsilateral anterior temporal IEDs; 2) ipsilateral lateral temporal IEDs; 3) ipsilateral extratemporal IEDs; 4) contralateral IEDs. Based on seizure occurrence after sAHE, patients were divided into two groups: Group 1 included only patients completely free of any seizures (Engel Classification Ia); Group 2 included patients with post-operative occurrence of any types of seizure and aura only.

Results:

Ten patients (45%) had a right sided and 12 (55%) left sided hippocampal sclerosis. Average age was 37.1 years (between 10 and 57 years). Fifteen patients (68%) remained completely seizure free and 19 (86%) were in Engel class I post-operatively. In 21 of 22 patients (95%), interictal epileptiform discharges were recorded on preoperative surface EEG., thirteen patients (13/21, 62%) had unilateral temporal IEDs ipsilateral to the hippocampal sclerosis, one patients (1/21, 5%) had ipsilateral extratemporal IEDs and seven patients (7/21, 33%) had bilateral IEDs. In 10 of 14 patients (71%) with unilateral IEDs ipsilateral to the HS, IEDs were restricted to the

anterior temporal lobe (ATL). In the remaining one patient (1/22, 5%), no IEDs but temporal intermittent rhythmic delta activity (TIRDA) was recorded.

The patients with unilateral temporal IEDs ipsilateral to the HS remained seizure free more frequently (92%) as compared to those patients with bilateral and / or ipsilateral extratemporal IEDs (25%) (P = 0.003).The patients with restricted IEDs in the ATL ipsilateral to the HS became more often seizure free (90%) than those with IEDs in the ipsilateral LTL, extratemporal lobe, and with bilateral IEDs (45%). This difference was not statistically different (P = 0.06).

Pre-resection spikes were restricted to the MTL in 11 patients (50%) and to the LTL in one (4%). In three patients (14%) spikes were recorded from MTL and LTL and in seven (32%) no spikes were recorded before the resection. Patients with pre-resection spikes restricted to the MTL (n = 11) remained seizure free more frequently (9/11, 82%) as compared to other patients (6/11, 55%) (P = 0.36). Two of four patients with LTL-spikes and four of seven patients without pre-resection spikes remained seizure free. A trend was found that patients with pre-resection spikes of lower frequency (<5 spikes/10s) tended to have a better outcome (6/6, 100%) than those with higher frequency (> 5 spikes/10s) pre-resection spikes (5/9, 56%) (P = 0.1). The persistence of pre-resection spikes on post-resection ECoG was not significantly related to seizure outcome.

In 9 patients with both preoperative IEDs restricted to the temporal lobe (TL) and pre-resection ECoG spikes restricted to the MTL, eight patients (89%) remained seizure free, while 7 of the remainder of the patients (54%) became seizure free (P = 0.16). In 7 patients with preoperative IEDs restricted to the ATL and pre-resection ECoG spikes restricted to the MTL, six patients (86%) became seizure free after operation, while 9 of the remainder of the patients (60%) became seizure free (P = 0.35).

Conclusions:

Pre-resection ECoG may be helpful in the prediction of seizure outcome in patients undergoing sAHE for mesial temporal lobe epilepsy. Patients with ECoG spikes restricted to the mesial temporal lobe remained seizure free more often than others. Pre-resection spikes of lower frequency tended to be associated with a better postoperative seizure outcome than those of higher frequency. Post-resection ECoG had no predictive value regarding seizure outcome although these differences were

not statistically significant. Patients with unilateral temporal IEDs on preoperative surface EEG became seizure free more frequently than those with bilateral and / or extratemporal IEDs. Patients with both preoperative IEDs restricted to the LTL or ATL and pre-resection ECoG spikes restricted to the MTL remained more frequently seizure free than other patients however, the difference was not statistically significant. A combination of the results of preoperative surface EEG and the findings of intraoperative ECoG especially pre-resection ECoG may be more reliable to predict postoperative seizure outcome in patients with hippocampal sclerosis. A larger study including more than 102 patients is needed to determine the predictive value of ECoG in patients with mesial temporal lobe epilepsy.

2 INTRODUCTION

2.1 Epilepsy

2.1.1 Epidemiology

Epilepsy is one of the most common neurological diseases. According to data from the Epilepsy Foundation of America, the prevalence of this disease is nearly 1% of the population (Wieser 2001). The incidence of the newly diagnosed epilepsy reaches 40 – 50 / 100 000 inhabitants per year. In Germany, about 30 000 new patients are diagnosed with epilepsy each year. In industrialized countries, the age-specific incidence of epilepsy is consistently high in the youngest age groups, with highest incidence occurring during the first few months of life. Incidence falls dramatically after the first year of life, seems relatively stable through the first decade of life, and falls again during adolescence, with a nadir during the adult years. In the elderly, the incidence increases again (Camfield and Camfield 1994; Hauser et al. 1993). In most total-population studies, males seem to be at higher risk than females for unprovoked seizures and epilepsy, however, the sex-specific differences for most incidence studies are not statistically significant.

About 40% of epilepsy patients suffer from generalized seizures and 60% suffer from focal seizures (Hauser and Kurland 1975; Sander et al. 1990; Siegel 2001). Among the patients with focal epilepsies, about 55% of seizures arise from the temporal lobe, and 45% are from the frontal, parietal and occipital lobes together. In most cases, epileptic seizures can be suppressed by antiepileptic drugs (AEDs) or at least a satisfying seizure control can be reached. However, some 30-40% of patients with focal epilepsy become medically resistant, regardless of the application of new AEDs (Siegel 2001). For these patients with refractory focal epilepsy, surgical treatment can be considered.

2.1.2 Epileptic seizures

Seizures occur in patients with and without epilepsy. An epileptic seizure is a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena which may include alterations of consciousness, motor, sensory,

autonomic, or psychic events, perceived by the patient or an observer (Commission on Epidemiology and Prognosis 1993). In patients without epilepsy, provoked seizures may arise from an underlying systemic disorder or be caused by direct cerebral insult. These provoked seizures are called acute symptomatic seizures (Hauser and Kurland 1975) or situation- related seizures. Epilepsy is defined as a condition characterized by recurrent (two or more) seizures, unprovoked by any immediate identified cause (Commission on Epidemiology and Prognosis 1993), however, it has long been recognized that even if most seizures appear to occur spontaneously, they may be provoked by a variety of environmental phenomena or specific functional alterations of the body, e.g. sleep deprivation (Janz 1985), alcohol (Mattson 1983), missed antiepileptic medication (Schmidt and Leppik 1988), hyperventilation (Feldman 1983), etc.

2.1.3 Classification of epileptic seizures

In 1981, a seizure classification was introduced by the international League Against Epilepsy (ILAE), based on clinical semiology, interictal EEG findings and also ictal EEG patterns (Commission on Classification and Terminology 1981). However, in many cases, EEG is unavailable or impractical and detailed analysis of clinical semiology and EEG findings frequently shows that no one-to-one correspondence exists between clinical ictal semiology and interictal/ictal EEG findings (Manford et al. 1996). Later, a new seizure classification, the “semiological seizure classification”, was suggested in 1998, which is based only on ictal clinical semiology (Luders et al. 1998) (Table 1). This seizure classification has been applied in our center. To define the epileptic syndrome, all available clinical information of patients including seizure types, clinical history, neurological examination, neurophysiological examination (particularly electroencephalography (EEG)), as well as anatomical and functional neuroimaging such as magnetic resonance imaging (MRI), functional MRI (fMRI), functional transcranial doppler-sonography (fTCD), single-photon emission computed tomography (SPECT), positron-emission tomography (PET), magnetoencephalography (MEG) should be analyzed and integrated.

Table 1 Semiological seizure classification (Luders et al. 1998)

Epileptic seizure	
Aura	
● Somatosensory aura[a]	● Visual aura[a]
● Auditory aura[a]	● Gustatory aura
● Olfactory aura	● Autonomic aura[a]
Abdominal aura	● Psychic aura
Autonomic seizure[a]	
Dialeptic seizure[b]	
● Typical dialeptic seizure[b]	
Motor seizure[a]	
● Simple motor seizure[a]	
Myoclonic seizure[a]	Tonic seizure[a]
Epileptic spasm[a]	Clonic seizure[a]
Tonic-clonic seizure	Versive seizure[a]
● Complex motor seizure[b]	
Hypermotor seizure[b]	Gelastic seizure
Automotor seizure[b]	
Special seizure	
● Atonic seizure[a]	● Astatic seizure
● Hypomotor seizure[b]	● Akinetic seizure[a]
● Negative myoclonic seizures[a]	● Aphasic seizure[b]
Paroxysmal event	

[a] Left/right/axial/generalized/bilateral asymmetric.

[b] Left hemisphere/right hemisphere.

2.1.4 Mesial temporal lobe epilepsy with hippocampal sclerosis

Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) is the most common epilepsy treated by surgery in adolescents and adults. About 90% of TLE surgical treatments refer to the hypothesis that the epileptogenic zone, which is defined as the area of cortex indispensable for the generation of clinical seizures and can not be measured directly (Luders and Awad 1992; Rosenow and Luders 2001), is located in the mesial temporal cortex, i.e. the amygdala-hippocampal complex (Cascino 1997; Stefan 1999; Steinhoff 2004). Therefore, hippocampal sclerosis is the most common lesion associated with medically intractable and surgically treatable MTLE (Babb and Brown 1987; Steinhoff 2004). Recently it has even been proposed

that MTLE associated with hippocampal sclerosis might be considered as a subtype of a broader syndrome of MTLE, with other subtypes being cryptogenic and those due to foreign tissue lesions, developmental or dysplastic lesions, and traumatic lesions (Wieser 2004). Pathologically, hippocampal sclerosis is characterized by marked neuronal loss in the CA1 subfield of the hippocampal formation, a moderate loss of neurons in the endfolium (CA3/CA4), and a relative sparing of the CA2 region (Babb and Brown 1987). Such a specific pattern of cell loss has been described for various cell types in the fascia dentate and hippocampus. The subiculum, entorhinal cortex and other temporal gyri are relatively resistant to cell loss (Najm et al. 2001) (Figure 1). Studies of autopsy and surgically resected specimens indicate bilateral damage in patients with hippocampal sclerosis that is asymmetrical (more severe on the epileptic side) (Palmer et al. 1993). HS coexists with cortical dysplasia or tumor ("dual pathology") in up to 30% of cases (Babb and Brown 1987). Neuroradiologically, the typical MRI-changes of hippocampal sclerosis include hippocampal atrophy on T1-weighted images and increased signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Jack, Jr. et al. 1996; Jackson et al. 1990; Najm et al. 2001) (Figure 2).

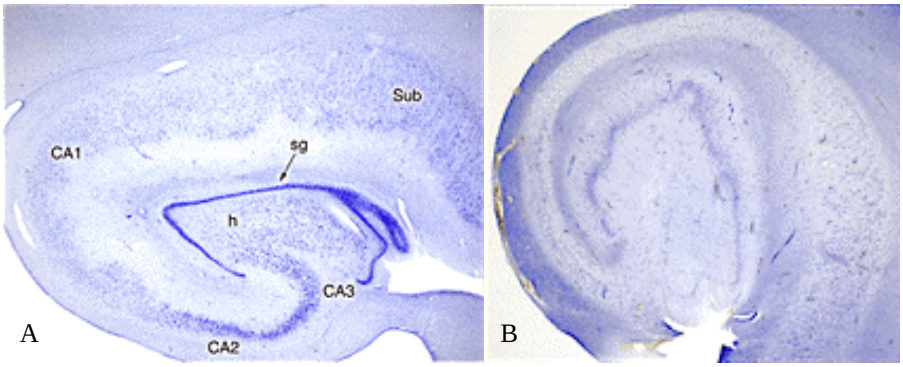

Figure 1 Sections of (A) an autopsy control hippocampus and (B) a hippocampus resected from a patient with HS. *Showing that CA1 is very heavily depleted (Sloviter 2005).*

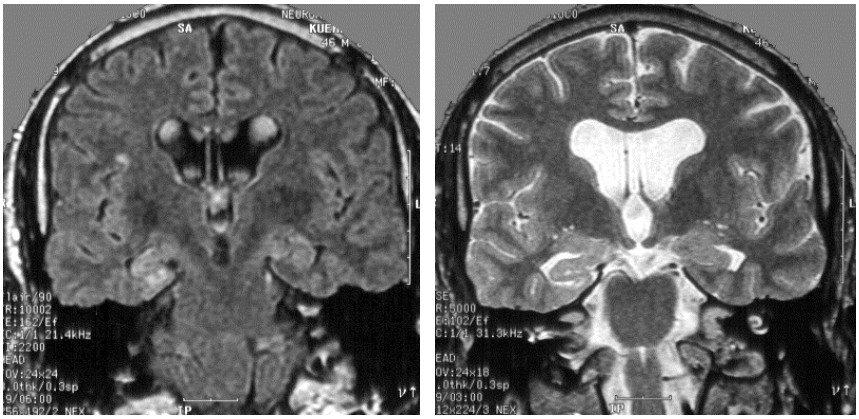

Figure 2 Typical MRI-changes of HS. *Hippocampal atrophy and increased signal intensity on coronal T2-weighted (right) and FLAIR images (left).*

2.2 Selective amygdalohippocampectomy

The most common treatment option for medically intractable MTLE is the surgical resection of the amygdala-hippocampal complex. For many years, the standard surgical technique was the anterior temporal lobectomy, in which the anterior part of the temporal lobe, including the mesiobasal temporal structures, was resected. Considering the potentially functional temporal neocortex, a more limited surgery, namely selective amygdalohippocampectomy (sAHE) was introduced, which could spare unaffected brain tissue from resection. Although it was originally developed by Niemeyer in the 1950s (Niemeyer 1958) and modified and popularized by Yasargil in the 1980s (Wieser and Yasargil 1982), the sAHE did not attain widespread popularity until the 1990s, following the general use of MR imaging and the advent of intraoperative neuronavigation (Abosch et al. 2002). Different from the transcortical approach used by Niemeyer, Yasargil adopted a transsylvian approach, which allowed generous resection of amygdala, hippocampus, and to a lesser extent of parahippocampal gyrus, and permits en bloc hippocampal removal (Figure 8). The Procedure is technically demanding because the approach through the temporal stem provides few orienting landmarks toward the hippocampus and the exposure of the sylvian vessels raises the risk of injury or spasm of these vessels, especially in the case of variations. Early studies have reported approximate seizure control rates between sAHE and standard temporal lobectomy (Engel et al. 1993), however the short-term and long-term neurocognitive benefits of these two different operations

still remain in discussion (Gleissner et al. 2002; Gleissner et al. 2004; Helmstaedter et al. 1996).

2.3 Electrophysiology

Abundant evidence supports that the generator source for EEG waves reside within the cerebral cortex and that surface and scalp-recorded electrical activity results from extracellular current flow associated with summated excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) (Pedley and Traub 1990). Since the EEG reflects summated postsynaptic potentials (PSPs) occurring in thousands or millions of cortical neurons (mostly pyramidal cells), it represents the "average" behaviour of large neuronal aggregates (Figure 3). When EEG waves are rhythmic, it is likely that most cells within a given neuronal pool are behaving similarly. Therefore, synchronous EEG activity such as evoked potentials, sleep spindles and epileptiform discharges show a good correlation with PSPs and reflect well the electrical activity of most neurons within the detected field, although individual variations from the average behaviour of neurons exist. When EEG waves are nonrhythmic, the correlation between activity of any individual cell and nonrhythmic EEG might be poor (Pedley and Traub 1990). Besides synaptic electrogenesis, two types of active dendritic response have been described, which may contribute to current sources of EEG activity: low-threshold Hodgkin-Huxley sodium and potassium conductance changes and regenerative, high-threshold calcium permeability changes. Another type of long-duration potential is the afterhyperpolarization potential (AHP) produced by a calcium-activated potassium current (Barrett and Barret 1976; Hotson and Prince 1980; Pedley and Traub 1990). However, the extent to which these intrinsic nonsynaptic mechanisms contribute to surface or scalp-recorded activity remains unknown.

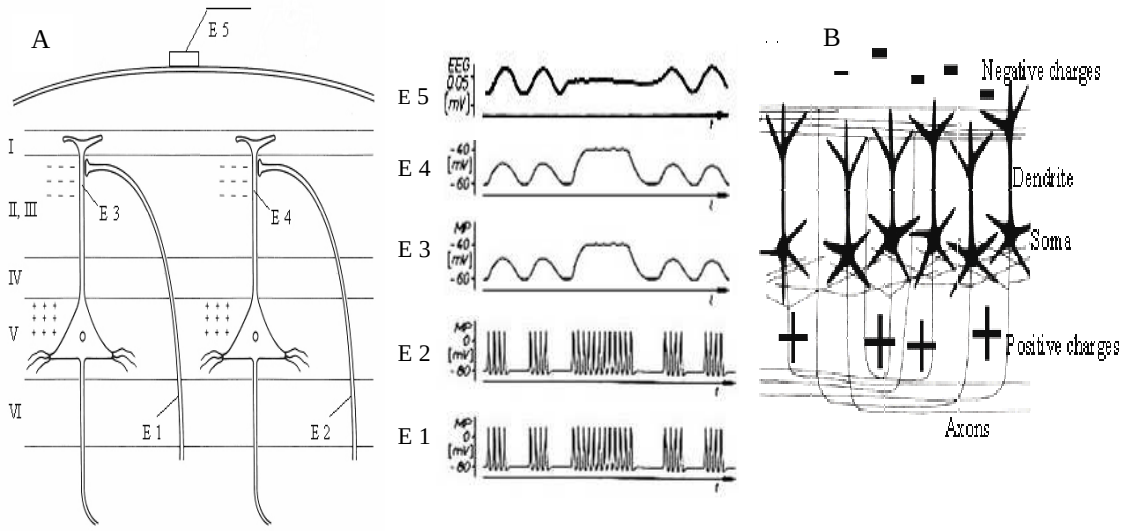

Figure 3 Principles of EEG wave generation. ***A:*** *The excitatory synapses of two afferent fibers contact the superficial dendritic arborisation of two longitudinal neuronal elements. Synchronized groups of action potentials in the afferent fibers (E_1, E_2) generate wavelike EPSPs in the dendritic area (E_3, E_4) and corresponding field potentials in the EEG. EPSP: excitatory postsynaptic potential (Pedley and Traub 1990; Speckmann and Elger 1991);* ***B:*** *Thousands of parallelly oriented neighboring dendrites have to be active synchronously to produce a measurable signal (Hauk 2003) (Copyright UK Medical Research Council (2003) used by kind permission).*

Epileptiform discharges are the electrical markers of an individual's susceptibility to seizures. The term "interictal epileptiform discharges" (IEDs) includes spikes with duration of less than 80ms and sharp waves with duration of 80-200 ms, which are waveforms distinguishable from background activity (Figure 4). Both spikes and sharp waves have a pointed peak and are usually of negative polarity because of their generation by depolarization of vertically oriented neurons (Hamer and Katsarou 2004). Unilateral or bilateral temporal slowing, spikes or sharp waves are the main interictal EEG characteristics of MTLE caused by hippocampal sclerosis. It has been reported that HS is associated with axon/synaptic reorganization of the remaining neurons, which may contribute to the chronic seizures (Babb 1992).

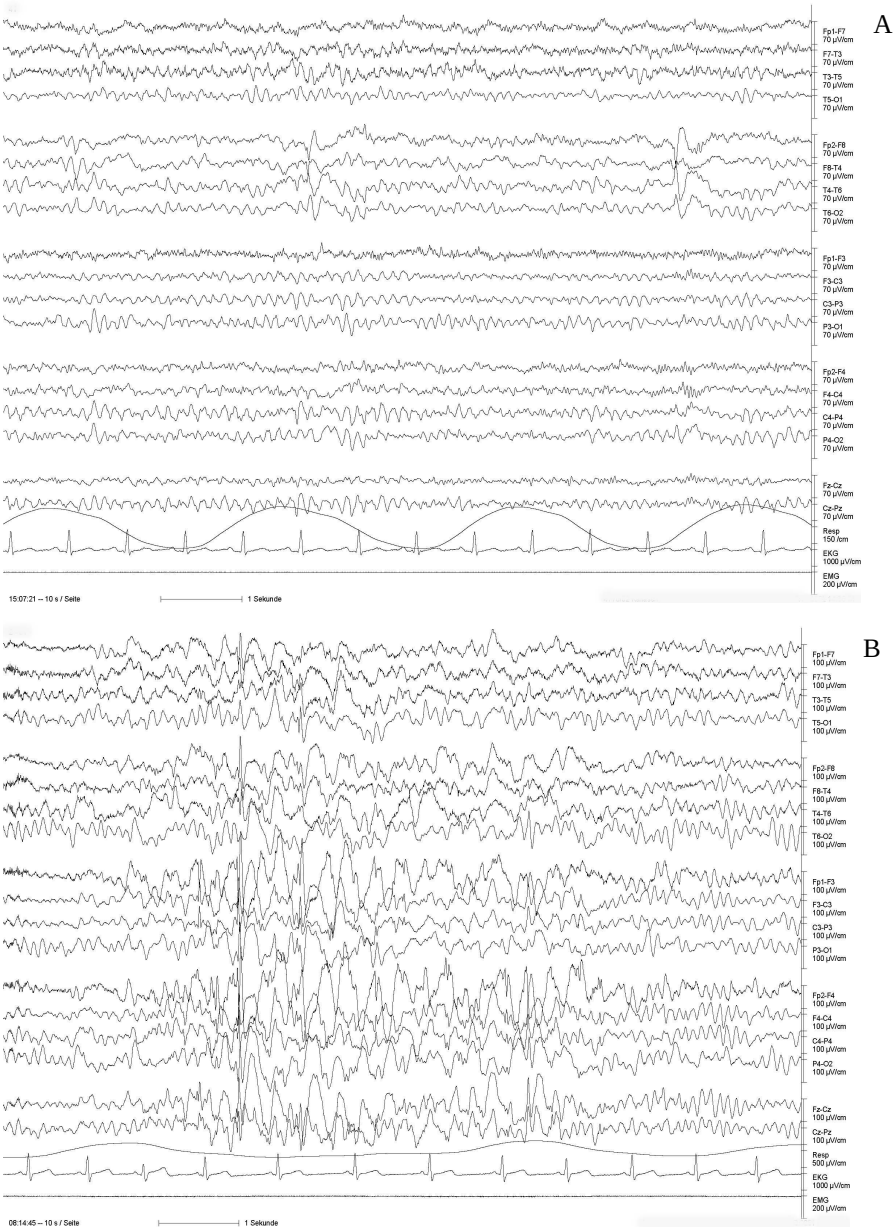

Figure 4 Interictal epileptiform discharges. ***A:*** *Right temporal sharp wave;* ***B:*** *Generalized spike.*

2.4 EEG monitoring and the temporal lobe epilepsy surgery

Epilepsy surgery is based on the principle that resection of an epileptogenic focus can result in seizure freedom (Engel et al. 1997; Luders and Awad 1992; Wyllie et al. 1987). If surgery fails, the resected area was incorrectly or incompletely removed or was only one of several epileptogenic zones (Spencer et al. 1997; Wyllie 1992). In the surgical treatment of TLE, extensive resection of the mesial temporal cortex, in which the epileptogenic zone is mostly hypothesized to be located, is required for satisfying

prognosis of TLE. However, concerning the postoperative functional deficits, especially in dominant temporal lobe resections, the debate on how much of the hippocampus should be removed is still ongoing. Furthermore, the mesial temporal cortex does not always include the complete epileptogenic zone, in spite of hippocampal sclerosis. Therefore, comprehensive presurgical assessment for accurate localization of the epileptogenic zone is crucial for the success of TLE surgery.

2.4.1 Noninvasive and chronic invasive EEG monitoring

A variety of diagnostic tools such as analysis of seizure semiology, noninvasive Video-EEG monitoring, structural and functional neuroimaging can be used to indirectly define the location and boundaries of the epileptogenic zone (Rosenow and Luders 2001) (Table 2). Video-EEG monitoring is a technique recording the behavior and the scalp EEG of a patient simultaneously. It is performed to generate a good hypothesis regarding the localization of the epileptogenic zone and delineate its relation to the symptomatogenic zone and eloquent cortical areas. The primary parameters assessed during long-term monitoring are 1) interictal EEG during both wakefulness and sleep, 2) ictal EEG and 3) clinical signs and symptoms during the seizures (Van Emde and Parra 2001). To enhance the sensitivity for interictal and ictal epileptiform discharges in TLE, additional electrodes such as sphenoidal electrodes are often used. It has been confirmed that sphenoidal electrodes can help differentiate between mesial and lateral neocortical temporal lobe seizure onset (Pacia et al. 1998; Sperling and Guina 2003).

When data from surface EEG recordings agree with the location of an epileptogenic lesion or the area of abnormality detected by neuroimaging as well as with complementary information provided by other different non-invasive tests, it may be sufficient to establish an indication for epilepsy surgery (Spencer 1996; Wyllie 1992). However, in other situations, when diverging evidence appears from neuroimaging and surface EEG, or surface EEG and other noninvasive evaluations fail to define unequivocally the irritative zone, the seizure onset zone and the margin of the neighboring eloquent cortex, it may be impossible to exactly plan a resection and then invasive electrodes may aid in the localization of the ictal onset zone.

Table 2 Descriptions of zones and lesions of the cortex (Luders and Awad 1992)

Epileptogenic zone	Region of cortex that can generate epileptic seizures. By definition, total removal or disconnection of the epileptogenic zone is necessary and sufficient for seizure-freedom
Irritative zone	Region of cortex that generates interictal epileptiform discharges in the EEG or MEG
Seizure onset zone	Region where the clinical seizures originate
Epileptogenic lesion	Structural lesion that is causally related to the epilepsy
Ictal symptomatogenic zone	Region of cortex that generates the initial seizure symptoms
Functional deficit zone	Region of cortex that in the interictal period is functionally abnormal, as indicated by neurological examination, neuropsychological testing and functional imaging or non-epileptiform EEG or MEG abnormalities
Eloquent cortex	Region of cortex that is indispensable for defined cortical functions

Invasive electrodes record cortically generated activity with eight- to 20-fold higher amplitude as compared to scalp electrodes (Cooper et al. 1965; Rosenow 2004). This allows recording of spikes generated in very small cortical areas, which are undetectable by scalp electrodes. Only synchronous discharges involving ≥ 6 cm^2 of cortex are detectable on scalp EEG (Cooper et al. 1965). Therefore, invasive electrodes provide a much superior spatial resolution, which is of particular importance when irritative and seizure-onset zones are near or overlapping with the eloquent cortex (Rosenow 2004). Chronic invasive monitoring can be done using depth electrodes, subdural strip or grid electrodes, epidural electrodes, foramen ovale (FO) electrodes or a combination of different types of electrodes, intracranially implanted with days' or weeks' duration of monitoring (Figure 5). For example, the combination of strip and grid electrodes is frequently used. It takes an average of approximately 5 days for the monitoring. Subdural strip and / or grid electrodes can provide a wider coverage of the cortex and are thus better able to define the spatial boundaries of the cortical zones (Ebner and Luders 2001; Hamer and Morris, III 2001). One or more strips can be inserted through one burr hole with different planted trajectories through the subdural spaces; the insertion of grid electrodes requires open craniotomy (Luders et al. 1989).

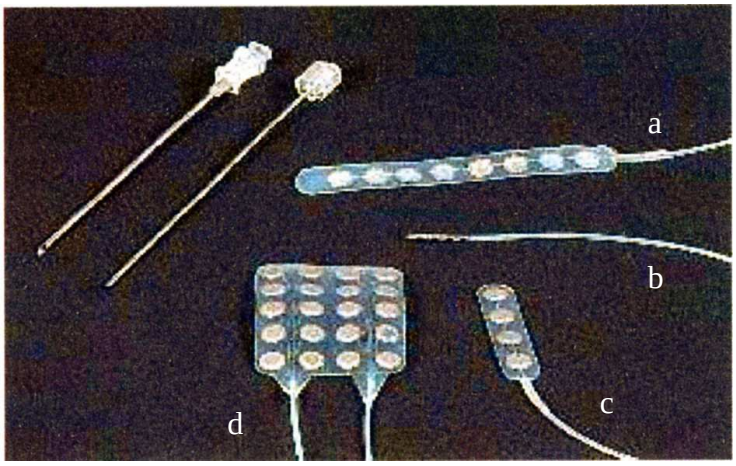

Figure 5 Different types of depth and subdural strip and grid electrodes. *(a) 1x8 strip electrode array; (b) multicontact depth electrode; (c) 1x4 strip electrode array; (d) 4x5 grid electrode array (permitted by PMI® Corporation).*

The selection of invasive electrodes depends mainly on the locations of the target and different circumstances. Because invasive electrodes cover only a very limited part of the brain, they can not provide a global overview of cortical activity as obtained by scalp EEG (Rosenow 2004). In addition, chronic invasive monitoring has significant costs and complications such as mass effect, hemorrhage and infection. Therefore, invasive electrodes should be used mostly when there is reasonable evidence that patient has a respectable epileptogenic focus and the extent of resection needs to be defined clearly to avoid the damage to eloquent cortex (Hamer and Morris, III 2001; Rosenow 2004). Invasive EEG monitoring should not be performed as an exploratory procedure (Jayakar 1999). Despite of its inherent disadvantages, chronic invasive recording still remains beneficial to some patients, especially when exact definition of the margins of the eloquent cortex versus the irritative zone and seizure onset zone is needed (Rosenow and Luders 2001).

2.4.2 Acute intraoperative Electrocorticography

Electrocorticography (ECoG) is a neurophysiological technique used to record cortical potentials from the exposed brain by intracranial electrodes in the operating

room. It has been in common use for nearly seven decades in the surgical treatment of people with medically intractable epilepsy, since it was introduced by Foester in the 1930s (Foerster 1935) and later developed by Penfield in the 1950s (Penfield and Jasper 1954). The main uses of ECoG in epilepsy surgery are: 1) to localize the epileptogenic tissue; 2) map out cortical functions; and 3) predict the success of the surgery (Keene et al. 2000).

During the ECoG, electrodes need to be able to sit on the leptomeninges and move with the pulsations of the brain (Keene et al. 2000). Either flexible ball electrodes mounted on a fixed headset or series of electrodes implanted in a soft flexible silastic strip or grid can be used.

ECoG headsets consist of a horseshoe frame fixed at the craniotomy margin. Various reusable cortical electrodes attach to pivoting metal arms by springs. In TLE, the ECoG-recording with a headset and ball electrodes is mostly used to explore temporal and suprasylvian convexities (MacDonald and Pillay 2000).

To record from the mesial temporal regions, the flexible strip or grid electrodes can be used. Strip electrodes are made from a single row of 4 to 11 nichrome or platinum electrode contacts, approximately 2 to 4 mm in diameter, embedded in flexible material such as silastic at fixed interelectrode distances, typically 10 mm. Grid electrodes are expanded subdural strips with parallel rows of up to 64 electrodes (Ebner and Luders 2001; Hamer and Morris, III 2001; Luders et al. 1989). Strip or grid electrodes can also be applied on the lateral temporal neocortex and thus avoid a relatively clumsy headset (MacDonald and Pillay 2000; Tran et al. 1995). Both strip and grid electrodes have also been frequently used in chronic invasive EEG monitoring (Figure 5).

Because intracranial electrodes have the advantage to be able to be placed flexibly and to record signals from relatively small areas of cortex that are not detectable by scalp recordings and artifacts from muscles and electrode movement are rare and impedances tend to remain stable, the ECoG should allow for better localization of the tissue generating epileptiform potentials. Moreover, during intraoperative ECoG monitoring, the electrodes can be placed under direct visualization and, after the initial resection, further recordings can be made to detect persisting epileptiform activity. In addition, it allows direct electrical stimulation of the brain so that the regions involved in functions that must be spared from the resection (e.g. eloquent cortex) can be delineated with a high degree of confidence (Kuruvilla and Flink 2003;

Zumsteg and Wieser 2000). The advantages of intraoperative ECoG over chronic invasive monitoring with implanted electrodes are that ECoG is less invasive and less expensive, has a lower risk of complications, gives no burden to the patient and allows post-resection recordings. Limitations are the short recording time available for ECoG, that electrode placement depends on surgical exposure and the influence of the anesthetics and narcotic analgesics on the background activity and epileptiform discharges (Zumsteg and Wieser 2000). The probability to record ictal activity is very limited. Therefore, meticulous preoperative planning is required to assure that ECoG can detect IED in the selected position successfully. For example, the clinical history, ictal and interictal scalp EEG and neuroimaging studies need to be carefully reviewed to define the area of exposure needed for adequate ECoG recording prior to the operation (Keene et al. 2000).

2.4.3 Electrocorticography and the temporal lobe epilepsy surgery

About 80% of the epilepsy surgery centers around the world still perform ECoG in some or all of their patients with partial epilepsy (Engel and Ojemann 1993). Intraoperative ECoG is frequently used to tailor resections, i.e. to modify the exact extent of a resection according to the ECoG findings (Rosenow and Luders 2001). However, the role of ECoG in TLE surgery still remains controversial. Some authors have emphasized the importance of pre- and postoperative ECoG in guiding the extent of both mesial and lateral temporal lobe resections (Bengzon et al. 1968; Fiol et al. 1991; Jasper et al. 1961; McBride et al. 1991; Rasmussen 1983; So et al. 1989; Wyllie et al. 1987), others have advanced a standard operation regardless of ECoG findings (Cascino et al. 1995; Devinsky et al. 1992; Falconer and Serafetinides 1963; Kanazawa et al. 1996; Palmini et al. 2004). In most reports, the extent of the resection was influenced by the ECoG findings and / or patients with both, lesional and nonlesional (Bengzon et al. 1968; Cascino et al. 1995; Devinsky et al. 1992; Falconer and Serafetinides 1963; Fiol et al. 1991; Jasper et al. 1961; Kanazawa et al. 1996; Niemeyer 1958; So et al. 1989; Wyllie et al. 1987) , epilepsy were included. Even though sAHE has been widely accepted and applied to the treatment of medically intractable TLE for a long time, only few studies have addressed the role of ECoG in sAHE (Cendes et al. 1993; McBride et al. 1991; Niemeyer 1958). However the

predictive value of pre-resection ECoG findings was not investigated in these studies. SAHE has been found as effective as the more extensive anterior temporal lobectomy (Palmini et al. 2004), although the resection of sAHE is more limited. To definite the mesial temporal site of the epileptogenic zone is very important in the decision of the resection field in sAHE. ECoG can be used to localize of the irritative zone. SAHE can frequently remove the the epileptogenic zone in MTLE. The complete removal of the epileptogenic zone is predictive of seizure-free outcome. Therefore, it is interest to investigate the predictive value of intraoperative ECoG in sAHE regarding the postoperative seizure outcome.

2.5 Aims of this study

We retrospectively studied the prognostic value of intraoperative ECoG findings as well as the preoperative surface EEG findings in patients with unilateral hippocampal sclerosis, who underwent a standard sAHE, regardless of the ECoG findings. We hypothesized that pre-resection spikes restricted to the mesiobasal temporal lobe (MTL) may indicate a restricted mesial temporal epileptogenic zone and, therefore, a good outcome, whereas pre-resection lateral temporal lobe (LTL) spikes may indicate a more extensive epileptogenic zone, e.g. dual pathology (e.g. HS and MR-negative cortical dysgenesis), an entity known to be associated with poorer seizure outcome (Sisodiya et al. 1997) and possibly not adequately treated by sAHE. Furthermore, we investigated the question, whether the disappearance of pre-resection spikes following the resection predicts a better seizure outcome.

3 PATIENTS AND METHODS

3.1 Inclusion and exclusion criteria

In our center, ECoG were routinely performed in all patients undergoing epilepsy surgery to confirm preoperative noninvasive EEG findings. In this retrospective study, only patients with medication resistant unilateral mesial temporal lobe epilepsy and MRI-evidence of mesial temporal sclerosis without other lesions, who underwent sAHE by a transsylvian approach at the Interdisciplinary Epilepsy-Center Marburg between 2000 and 2003, and when the resection procedure was not influenced by ECoG findings, were included. Patients with evidence of bilateral seizure onset were excluded. 22 patients met these criteria and underwent intraoperative ECoG and sAHE. Preoperatively, all patients had a detailed clinical history and received noninvasive presurgical evaluation including long-term video-EEG monitoring with sphenoidal electrodes, neuropsychological testing and a MRI of the head including coronal T1, T2 and FLAIR images perpendicular to the axis of the hippocampus. An intracarotid amobarbital test (n=17) and functional transcranial Doppler sonography (fTCD, n=11) were used when necessary.

3.2 Methods

3.2.1 Intraoperative electrocorticography recording

Pre-resection recordings were made unilaterally as a standard procedure, using a strip electrode (1×8- or 1×6- contact with 1-cm spacing, AD-TECH® medical instrument corporation, Racine, WI, USA) sequentially positioned over the lateral temporal surface and, following the preparation of the sylvian fissure, over the mesial-basal temporal region (Figure 6, 7). Post-resection recordings were made with the same strip electrode from the same positions, especially where pre-resection spikes had been recorded. If pre-resection spikes were recorded from the mesial temporal structures, which were resected, the margins of the resection were included for the post-resection recordings. Pre- and post-resection ECoG activity was recorded for a minimum of 2 minutes per position. ECoGs were recorded using a 6- or 8-channel-EEG. Referential recordings were made with an electrode on the

contralateral scalp. The sensitivity was set to 300 or 500 µV/cm, the high and low frequency filters were 70 Hz and 0.5 Hz, a 50 Hz notch filter was used when necessary. The ECoG was usually recorded digitally with 200 samples / second using the Brainlab® software (Schwarzer, Munich, Germany). Occasionally paper recordings were used (ED24®, Schwarzer, Munich, Germany).

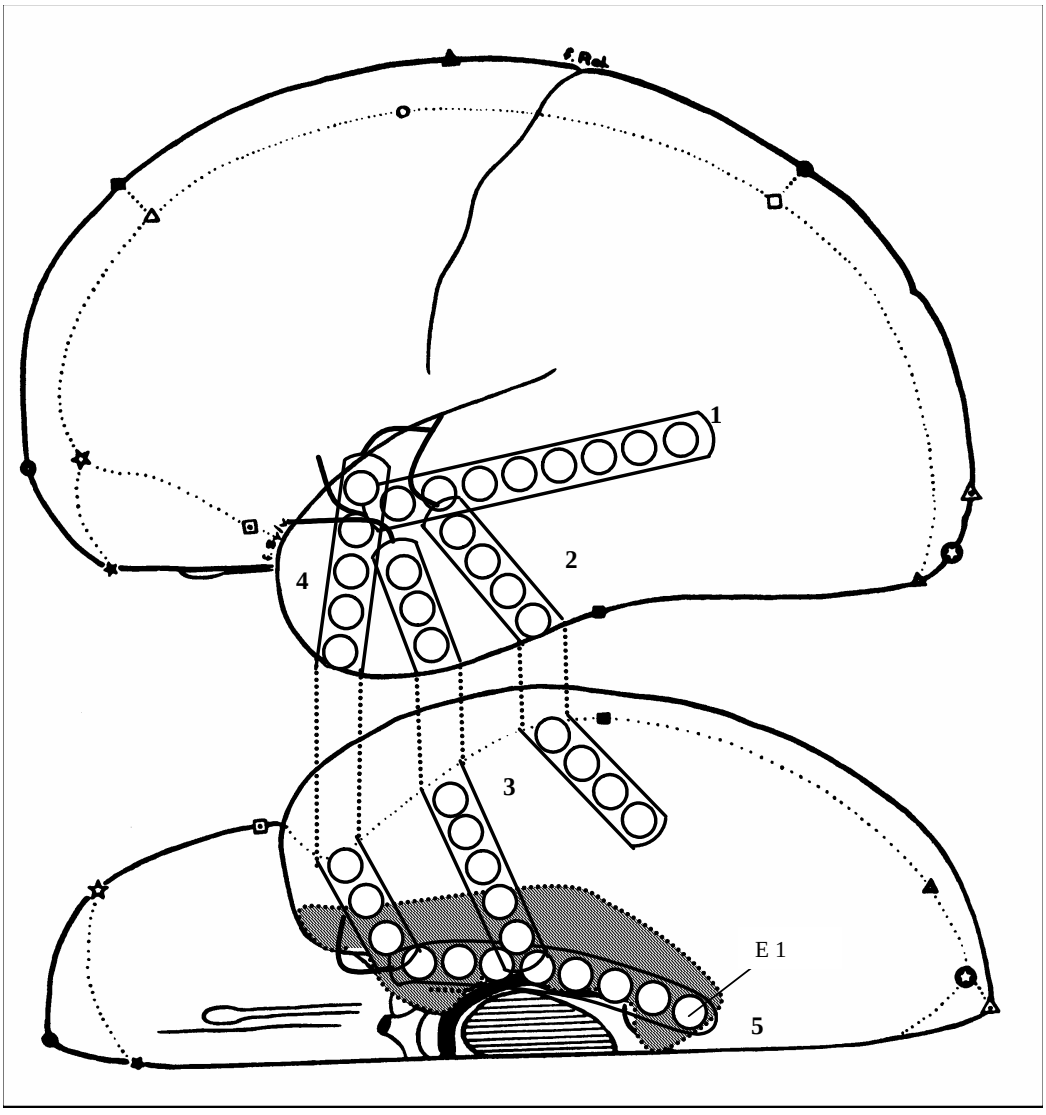

Figure 6 Placement of electrocorticography strip electrodes and definition of the regions of the mesiobasal vs. the lateral temporal lobe (Chen et al. 2005).

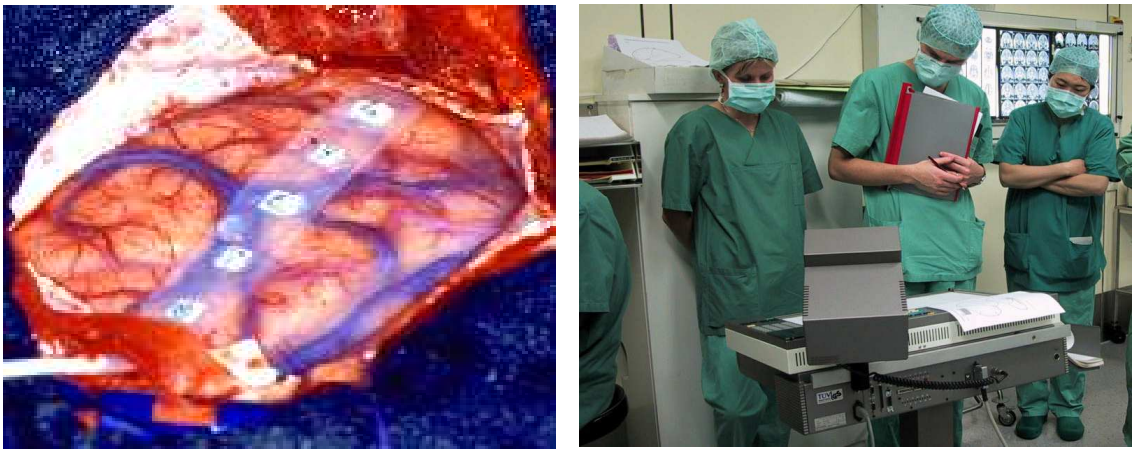

Figure 7 Intraoperative ECoG recording. *Left: A strip electrode positioned over the temporal surface; Right: the intraoperative ECoG recording.*

3.2.2 Surgery and anesthesia

Surgery

All patients were treated by a standardized unilateral sAHE using a transsylvian approach (Wieser and Yasargil 1982; Yasargil et al. 1985) via a routine pterional craniotomy of 4-5 cm in diameter (Figure 8). Before the sylvian fissure is opened microsurgically, the carotid artery, the anterior cerebral artery, the optic nerve, the oculomotor nerve, the posterior cerebral artery and the superior cerebellar artery are freed of the arachnoid in order to avoid injury to these structures through the latter described technique of subpial dissection. The middle cerebral artery (MCA) is then dissected free and veins crossing the sylvian fissure are usually maintained. As an initial step of resection, the temporomesial structures (uncus and amygdala) are removed through a corticotomy below or above the M1 and/or M2 segment of the MCA. The temporomesial pia is maintained and further resection is performed mainly by subpial dissection sometimes aided by cottonoid-supported dissection of the targeted structures. The initial resection cavity is then enlarged laterally up to the margin of the fusiform gyrus and sometime of the parahippocampal gyrus. Accordingly the temporal horn of the lateral ventricle is usually opened. After mesio-lateral enlargement of the temporal horn opening, the head and the anterior body of the hippocampus is visualized and resected usually in a piecemeal fashion (ca 2 cm in length) after visualizing and securing the choroids plexus of the temporal horn

(Figure 9). The extent of the resection was not influenced by the ECoG results. After surgery, routine pathological examination was performed. Hippocampal sclerosis was proven histologically whenever sufficient amounts of tissue were available. The technique of neuronavigation was applied during the operation in the majority patients and guided us especially to define the posterior border of our resection (Figure 10). Perioperatively, including on the day of operation, the antiepileptic medication was continued unchanged.

Anesthesia

Patients were operated under general anesthesia with sevoflurane 0,4-0,7% (Sevorane®) and sufentanil (Sufenta®). During, before and after the ECoG, the general anesthesia with was maintained.

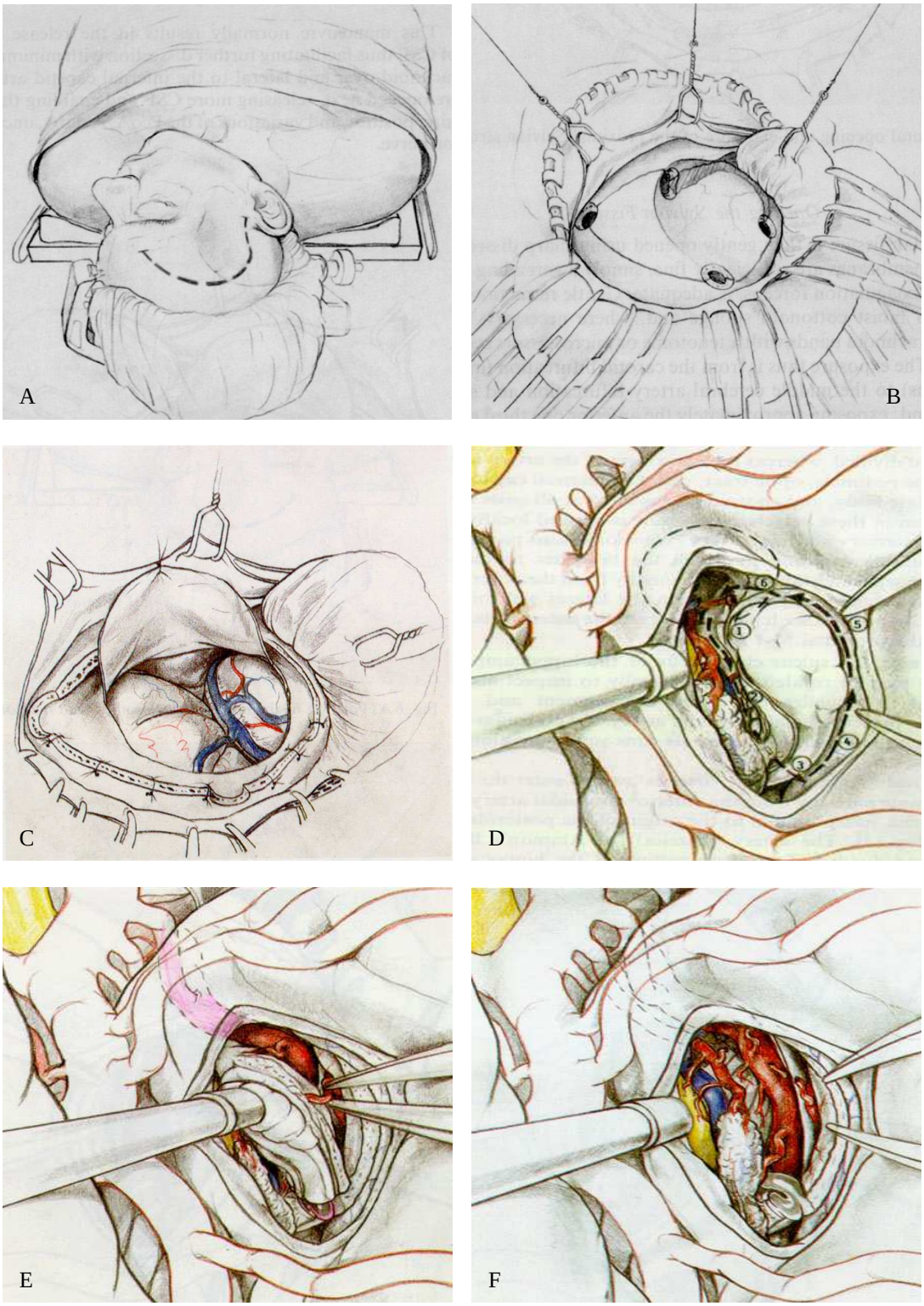

Figure 8 Surgical procedure of sAHE. *A: Position of the head and location of scalp incision; B: enlarged pterional craniotomy; C: Dural opening and exposure of the Sylvian fissure; D: The removal of amygdala (dotted lines). The direction of the arrows indicates the dissection steps around the hippocampus; E: The resection of hippocampus; F: After resection of hippocampus (Yasargil et al. 1985) (with kind permission by Springer Wien NewYork).*

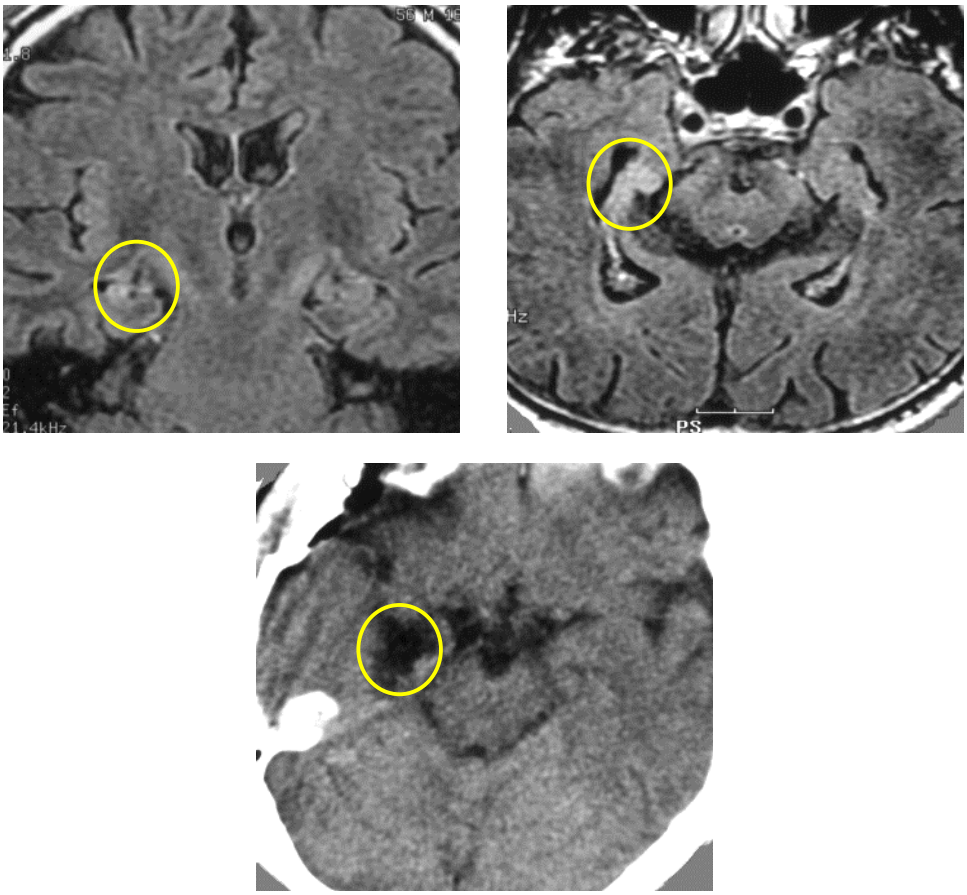

Figure 9 Preoperative MRI and postoperative CT. *Above: The preoperative MRI shows right HS; Below: The postoperative computer tomography shows the resection of the right mesial temporal structures.*

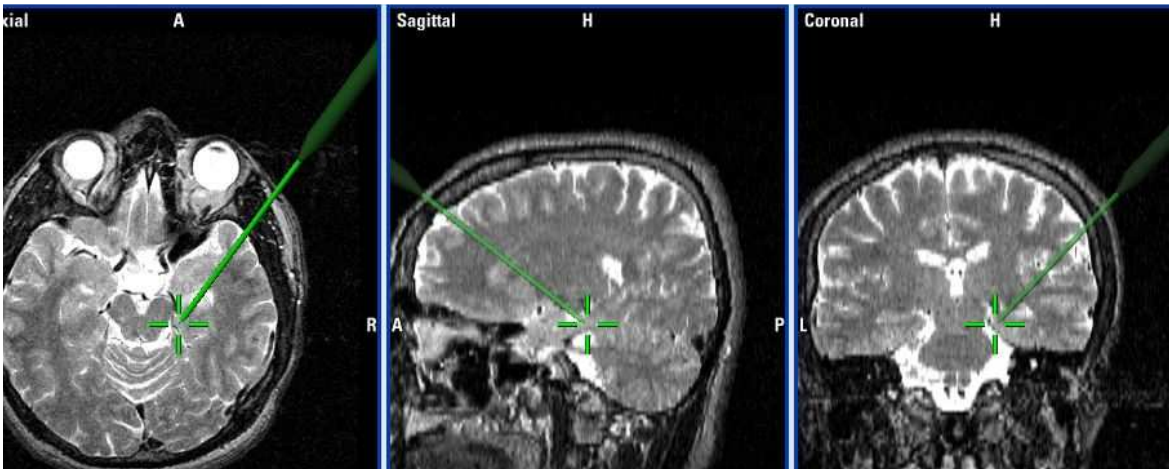

Figure 10 Intraoperative neuronavigation. *During the operation, neuronavigation is used to define the posterior border of the resection of the mesial temporal structures.*

3.2.3 Electrocorticography analysis

All ECoG data were sampled by experienced, board certified (ABCN, DGKN) clinical neurophysiologists (FR, HMH) and were reviewed retrospectively by one electroencephalographer who was blinded to the outcome of the patients (XC). The position of the strip electrode was marked in a drawing during the operation. A spike was defined as a paroxysmal fast transient waveform with a pointed peak and negative polarity with an amplitude of at least twice as high as the background activity and lasting less than 80ms (Rosenow et al. 1998). Polyspikes are multiple (more than 2) repetitive spikes occurring at about 20 Hz (Luders and Noachtar 2000). Sharp waves were considered as spikes assuming similar pathophysiology and epileptogenic relevance. ECoG results were classified by the presence and localization of spikes recorded (see Figure 6). According to pre-resection ECoG findings, patients were divided into the following subgroups: 1) Pre-resection spikes restricted to the MTL; 2) Pre-resection spikes both in MTL and LTL); 3) Pre-resection spikes restricted to the LTL; 4) No pre-resection spikes recorded. For each of the recording sites, the electrode contact with the greatest number of spikes was identified and the spike-pattern was classified as (Rosenow et al. 1998): 1) Infrequent spiking (<5 spikes/10s), 1a) Continuous infrequent spiking (pattern 1 lasting for ≥30s), 2) Frequent spiking (5-20 spikes/10s), 2a) Continuous frequent spiking (pattern 2 lasting for ≥30s), 3) Very frequent spiking (>20 spikes/10s), 3a) Continuous very frequent spiking (pattern 3 lasting for ≥30s).

3.2.4 Electroencephalography analysis

All surface EEG reports from preoperative noninvasive Video-EEG monitoring were reviewed retrospectively by one electroencephalographer who was blinded to the outcome of the patients (XC). According to the distribution of IEDs, the surface EEG findings were divided into four groups: 1) ipsilateral anterior temporal IEDs; 2) ipsilateral lateral temporal IEDs; 3) ipsilateral extratemporal IEDs; 4) contralateral IEDs.

3.2.5 Outcome and follow-up

The follow-up data were obtained by interview in the outpatient epilepsy clinic. The follow-up time of all patients was no less than 12 months and the seizure states at the follow-up time of 12 months after operation were analyzed. Based on seizure occurrence after sAHE, patients were divided into two groups: Group 1 included only patients completely free of any seizures (Engel Classification Ia) (Engel et al. 1993) (Table 3); Group 2 included patients with post-operative occurrence of any types of seizure and aura only.

Table 3 Engel's Classification of Postoperative Outcome (Engel et al. 1993)

Class I: Free of disabling seizures[a]
a: Completely seizure free since surgery
b. Nondisabling simple partial seizures only since surgery
c. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
d. Generalized convulsions with AED discontinuation only
Class II: Rare disabling seizures ("almost seizure free")
a. Initially free of disabling seizures but has rare seizures now
b. Rare disabling seizures since surgery
c. More than rare disabling seizures since surgery, but rare seizures for the last 2 years
d. Nocturnal seizures only
Class III: Worthwhile improvement[b]
a. Worthwhile seizure reduction
b. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 years
Class IV: No worthwhile improvement
a. Significant seizure reduction
b. No appreciable change
c. Seizures worse

[a] Excludes early postoperative seizures (first few weeks).

[b] Determination of "worthwhile improvement" will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function, and quality of life.

3.2.6 Statistical analysis

The main hypothesis tested was whether or not patients with pre-resection spikes restricted to the MTL have a higher seizure free rate than patients with other ECoG findings such as LTL only, MLT+LTL or no spikes.

Furthermore, the influence of the ECoG spike frequency, the persistence of ECoG spikes after the sAHE as well as the preoperative surface EEG findings on seizure outcome was analyzed. Fisher's exact test was used. The results were considered as statistically significant when $P<0.05$. The software Statistical Analysis System (SAS) 8.1 was used for statistical analysis. Based on the results of this study, the number of patients needed to provide statistical evidence of a predictive value of certain spike distributions was calculated.

4 RESULTS

4.1 Study population

Twelve (55%) of 22 patients were women. The age at the time of operation ranged from 10 to 57 years (mean 37.1 years). Twelve patients (55%) underwent a left-sided and 10 a right-sided sAHE. Fifteen of 22 patients (68%) were completely free of seizures and auras (group 1), seven patients (32%) were in group 2 (3 were Ib, 1 was Ic, 2 was IIb, 1 were IIIa). Thus, a total 19 patients (86%) were Engel class I (Table 4).

4.2 Preoperative surface electroencephalography

In 21 of 22 patients (95%), interictal epileptiform discharges were recorded on preoperative surface EEG., thirteen patients (13/21, 62%) had unilateral temporal IEDs ipsilateral to the hippocampal sclerosis, one patients (1/21, 5%) had ipsilateral extratemporal IEDs and seven patients (7/21, 33%) had bilateral IEDs (Table 4). In 10 of 14 patients (71%) with unilateral IEDs ipsilateral to the HS, IEDs were restricted to the anterior temporal lobe (ATL). In the remaining one patient (1/22, 5%), no IEDs but temporal intermittent rhythmic delta activity (TIRDA) was recorded.
The patients with unilateral temporal IEDs ipsilateral to the HS remained seizure free more frequently (92%) as compared to those patients with bilateral and / or ipsilateral extratemporal IEDs (25%) ($P = 0.003$, Table 5).The patients with restricted IEDs in the ATL ipsilateral to the HS became more often seizure free (90%) than those with IEDs in the ipsilateral LTL, extratemporal lobe, and with bilateral IEDs (45%). This difference was not statistically different ($P = 0.06$, Table 6).

4.3 Pre-resection Electrocorticography results

In 11 patients (50%), spikes were restricted to the MTL. In one of the remaining 11 patients spikes were recorded only from the LTL, three had spikes in both MTL and LTL and in seven patients no spikes were recorded (Table 4). Patients with pre-resection spikes restricted to the MTL remained seizure free more frequently

(82%) as compared to the remainder of the patients (55%). This difference was not statistically significant (P = 0.36). Two of four patients with LTL-spikes and four of seven patients without pre-resection spikes remained seizure free (Table 7, Figure 11). Based on these data, it was calculated that a minimum of 102 patients is needed to evaluate such a 27% difference in outcome with a power of 80% and a significance level of 0.05 using a two-sided test. In order to prove a clinically still significant difference of 20% in outcome and assuming a less equal distribution regarding the ECoG groups a study with 220 patients would be necessary.

The patterns of interictal ECoG-spikes observed included frequent spiking (9 patients, 5 in Group1) and infrequent spiking (6 patients, all in Group 1), very frequent spiking was not recorded. Continuous frequent spiking was recorded from MTL in two patients. One remained completely seizure free and the other had seizures during the follow-up. Polyspikes were recorded from LTL in one patient who remained completely seizure free. In the nine patients with frequent spiking (> 5 spikes/10s) a seizure-free outcome was less frequent (56%) than in those six with infrequent spikes who all became seizure-free (100%). The difference was not statistically significant (p = 0.10; Table 8).

4.4 Post-resection Electrocorticography results

In five of the 15 patients with pre-resection spikes these were no longer recorded after the resection and three (66%) of these remained seizure free. Of the ten patients with persistent spikes eight (80%) remained seizure free. There was no correlation between seizure outcome and the presence of persistent spikes recorded on post-operative ECoG (Table 9).

4.5 Presurgical electroencephalography and intraoperative electrocorticography

In 9 patients with both preoperative IEDs restricted to the TL and pre-resection ECoG spikes restricted to the MTL, eight patients (89%) remained seizure free, while 7 of the remainder of the patients (54%) became seizure free (P = 0.16, Table 10). In 7 patients with preoperative IEDs restricted to the ATL and pre-resection ECoG spikes restricted to the MTL, six patients (86%) became seizure free after operation, while 9

of the remainder of the patients (60%) became seizure free (P = 0.35, Table 11).

Table 4 Results of intraoperative ECoG of Patients with sAHE

No.	Age (years)	Sex	Side of HS (MRI)	Localization of interictal EDs max. on surface EEG**				ECoG (pre-resection)		ECoG (post-resection)		Outcome Group (Engel class.)#
				ATL*	LTL*	Extra-temporal*	Contra-lateral	MTL	LTL	MTL	LTL	
1	39	F	L	Sp1 (100%)	-	Fp1 (rarely)	no	++ C.s.	+	++	+	2 (Ib)
2	33	F	R	Sp2 (70%), F8 (10%)	T8 (20%)	no	Sp1 (<2%)	-	-	-	-	2 (Ib)
3	47	M	R	Sp2 (100%)	-	no	no	+	-	++	-	1 (Ia)
4	23	M	L	-	-	no	no	++	-	+	-	1(Ia)
5	38	M	R	Sp2 (100%)	-	no	no	-	-	-	-	1(Ia)
6	19	F	L	Sp1 (94%)	T7 (6%)	no	no	+	-	-	-	1 (Ia)
7	51	M	L	Sp1 (95%),	-	no	Sp2 (5%)	-	-	+	++P.s.	2 (IIIa)
8	44	F	L	FT9 (100%)	-	no	no	-	-	-	-	1 (Ia)
9	10	F	L	gen.	gen.	gen.	gen.	++	+ R.s.	-	-	2 (Ic)
10	45	F	L	Sp1 (80%)	T7 (20%)	no	no	++	-	+	-	1 (Ia)
11	46	M	R	F8 (85%), Sp2 (15%)	T8 (rarely)	no	no	-	+P.s.	+P.s.	++P.s.	1 (Ia)
12	32	F	L	Sp1 (100%)	-	no	no	++	-	-	+ R.s.	1 (Ia)
13	40	F	L	Sp1 (100%)	-	no	no	++	-	-	-	2 (IIb)
14	19	M	R	Sp2 (66%),	T8 (33%)	no	Sp1 (<1%)	++ C.s.	++	+ R.s.	+	1 (Ia)
15	38	M	L	Sp1 (100%)	-	no	no	+	-	+	-	1 (Ia)
16	37	F	R	FT10 (100%)	-	no	no	+	-	+	-	1 (Ia)
17	57	M	R	Sp2 (100%)	-	no	no	+	-	-	-	1 (Ia)
18	41	M	L	Sp1 (100%)	-	no	no	-	-	-	-	1 (Ia)
19	33	F	R	Sp2 (100%)	-	no	no	++	-	++	-	1 (Ia)
20	57	M	L	Sp1 (80%)	T7 (1%)	no	Fp2 (19%)	-	-	-	-	1 (Ia)
21	22	F	R	Sp2 (95%),	-	no	Sp1 (5%)	++	-	+	-	2 (IIb)
22	45	F	R	Sp2 (50%),	T8 (50%)	no	Sp1 (rarely)	-	-	-	-	2 (Ib)

HS: hippocampal sclerosis; EDs: epileptiform discharges; R.: right; L.: left; LTL: lateral temporal lobe; MTL: medial temporal lobe; ATL: anterior temporal lobe; "+": < 5spikes/10s; "++":>5spikes/10s; "-"; no spikes or no sharp waves; Group 1: good outcome; Group 2: poor outcome; P.s.: polyspikes; C.s.: continuous spikes; R.s.: rare spikes; F: female; M: male; gen.: generalized; ATL electrodes: Sp 1 / 2, F 7 / 8, FT 9 / 10; LTL electrodes: T 7 / 8, P 7 / 8; TP 9 / 10; extratemporal electrodes: the rest of scalp electrodes; *: ipsilateral to the HS; **: The scalp electrodes were placed according to the international 10-20 system; #: 12 months after operation.

Table 5 Seizure outcome with regard to the lateralization of preoperative IEDs on surface EEG in 21 patients

Distribution of preoperative IEDs on surface EEG	Group 1	Group 2
Ipsilateral TL only	12 (92%)	1 (8%)
Extratemporal und bilateral	2 (25%)	6 (75%)
Total	14	7
P = 0.003		

Group 1: completely seizure free; Group 2: not completely seizure free; IEDs: interictal epileptiform discharges; TL: temporal lobe.

Table 6 Seizure outcome with regard to the distribution of preoperative IEDs on surface EEG in 21 patients

Distribution of preoperative IEDs on surface EEG	Group 1	Group 2
Ipsilateral ATL IEDs only	9 (90%)	1 (10%)
Ipsilateral LTL, extratemporal and bilateral	5 (45%)	6 (55%)
Total	14	7
P = 0.06		

Group 1: completely seizure free; Group 2: not completely seizure free; IEDs: interictal epileptiform discharges; ATL: anterior temporal lobe

Table 7 Seizure outcome with regard to the distribution of pre-resection spikes (in MTL only vs. others)

Distribution of pre-resection spikes	Group 1	Group 2
MTL spikes only (n = 11)	9 (82%)	2 (18%)
Other groups (n = 11)	6 (55%)	5 (45%)
- MTL and LTL spikes	1	2
- LTL spikes only	1	0
- No spikes recorded	4	3
Total	15 (68%)	7 (32%)
P = 0.36		

Group 1: completely seizure free; Group 2: not completely seizure free; MTL: mesial temporal lobe; LTL: lateral temporal lobe

Table 8 Seizure outcome with regard to the spike frequency on pre-resection ECoG in patients with pre-resection spikes

Frequency of spiking	Group 1	Group 2
Frequent spiking (5-20 spikes/10s)	5 (56%)	4 (44%)
Infrequent spiking (< 5 spikes/10s)	6 (100%)	0 (0%)
Total	11 (73%)	4 (27%)
P = 0.10		

Group 1: completely seizure free; Group 2: not completely seizure free

Table 9 Seizure outcome with regard to the persistence of pre-resection spikes on post-resection ECoG in patients with pre-resection spikes

Pre-resection spikes on post-resection ECoG	Group 1	Group 2
Persisting	8 (80%)	2 (20%)
Disappearing	3 (60%)	2 (40%)
Total	11 (73%)	4 (27%)
P = 0.56		

Group 1: completely seizure free; Group 2: not completely seizure free

Table 10 Seizure outcome with regard to the distribution of preoperative IEDs on surface EEG and pre-resection spikes on intraoperative ECoG (TL only and MTL only vs. others)

Distribution of preoperative IEDs on EEG and pre-resection spikes on ECoG	Group 1	Group 2
Ipsilateral TL IEDs only and MTL spikes only	8 (89%)	1 (11%)
Other distributions	7 (54%)	6 (46%)
Total	15	7
P = 0.16		

Group 1: completely seizure free; Group 2: not completely seizure free; IEDs: interictal epileptiform discharges; TL: temporal lobe; MTL: mesial temporal lobe

Table 11 Seizure outcome with regard to the distribution of preoperative IEDs on surface EEG and pre-resection spikes on intraoperative ECoG (ATL only and MTL only vs. others)

Distribution of preoperative IEDs on EEG and pre-resection spikes on ECoG	Group 1	Group 2
Ipsilateral ATL IEDs only and MTL spikes only	6 (86%)	1 (14%)
Other distributions	9 (60%)	6 (40%)
Total	15	7
P = 0.35		

Group 1: completely seizure free; Group 2: not completely seizure free; IEDs: interictal epileptiform discharges; ATL: anterior temporal lobe; MTL: mesial temporal lobe

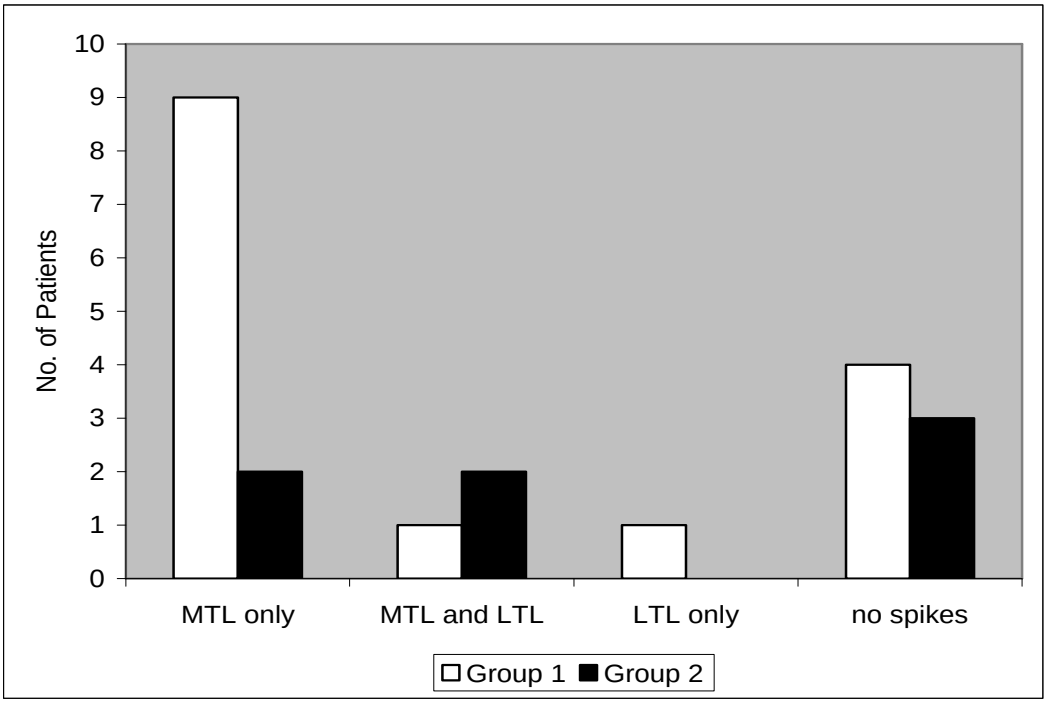

Figure 11 ECoG-Spike-Distribution vs. Outcome. *Number of patients with different spike- distributions in the outcome group 1 (completely seizure free) and group 2 (not completely seizure free). (MTL: mesiobasal temporal lobe; LTL: lateral temporal lobe) (Chen et al. 2005).*

4.6 Case reports

The following are some typical illustrative cases included in this study:

Patient 1:

A 38-year-old woman, right handed, who had the first seizure at the age of two and a half. The frequency of seizures was reported as 4-5 × / month. A family history of epilepsy was present. The seizure semiology: abdominal aura →.left hemisphere automotor seizure → generalized clonic seizure. The video-EEG monitoring showed interictal regional sharp waves predominantly in the left mesial temporal lobe and only once in the left frontal lobe. Ictal onset was recorded from the left temporal lobe. MRI showed left hippocampal sclerosis. PET showed left temporal hypometabolism, max. in mesial temporal region. Wada-test: right language dominance and right memory dominance. Intraoperative ECoG recorded spikes from both mesial temporal lobe and lateral temporal lobe before and after resection. Postoperatively except vertigo (3-8 × / month) no epileptic seizures were reported (Engel Ib) (Figure 12, 13).

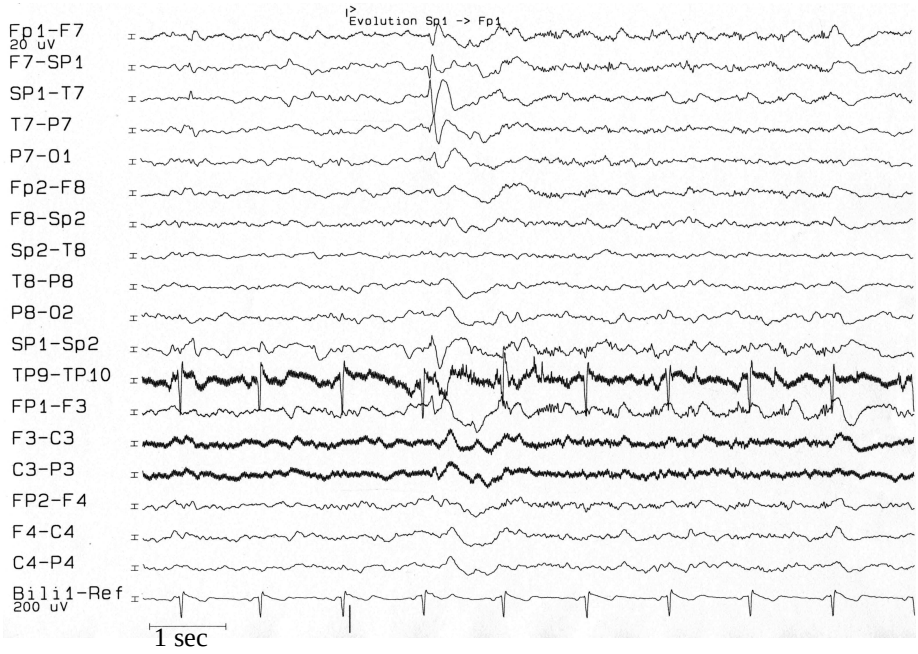

Figure 12 Preoperative Video-EEG monitoring of patient 1. *EEG showed left mesial temporal sharp wave (Sp1).*

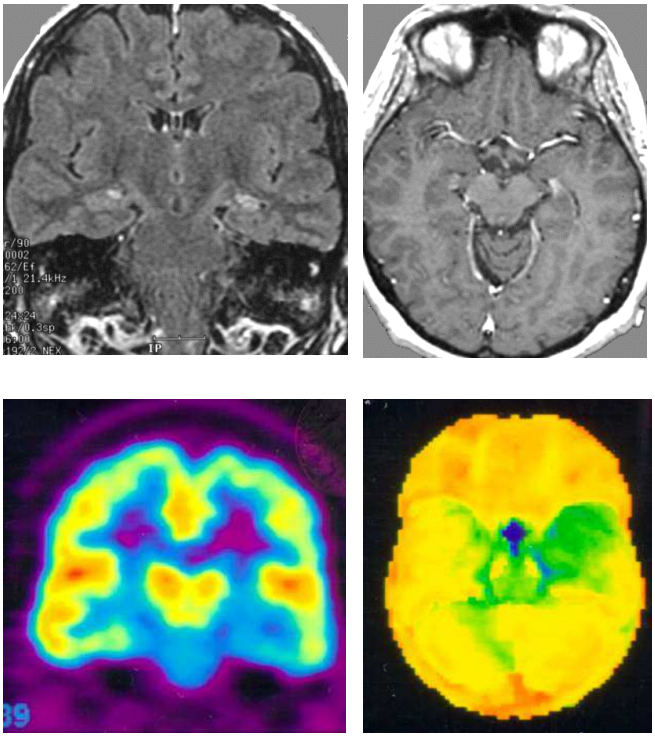

Figure 13 Preoperative MRI and PET of patient 1. *MRI (above) showed the left HS; PET (below) showed mesial temporal hypometabolism ipsilateral to the HS.*

Patient 2:

A 33-year-old female, right handed, who suffered from epilepsy since the age of 13, with the frequency of seizures 5-12 × / month. The seizure semiology: abdominal aura → automotor seizure → generalized tonic-clonic seizure. EEG-monitoring recorded sharp waves mainly from the right temporal lobe (70% from the mesial area) and rarely from the left temporal lobe. Ictal onset was observed from the right temporal lobe. MRI showed right hippocampal sclerosis. FTCD showed a left language dominance. No ECoG spikes were recorded intraoperatively. After operation, she reported only auras at 12 months follow-up (Engel Ib) (Figure 14, 15, 16 A-D).

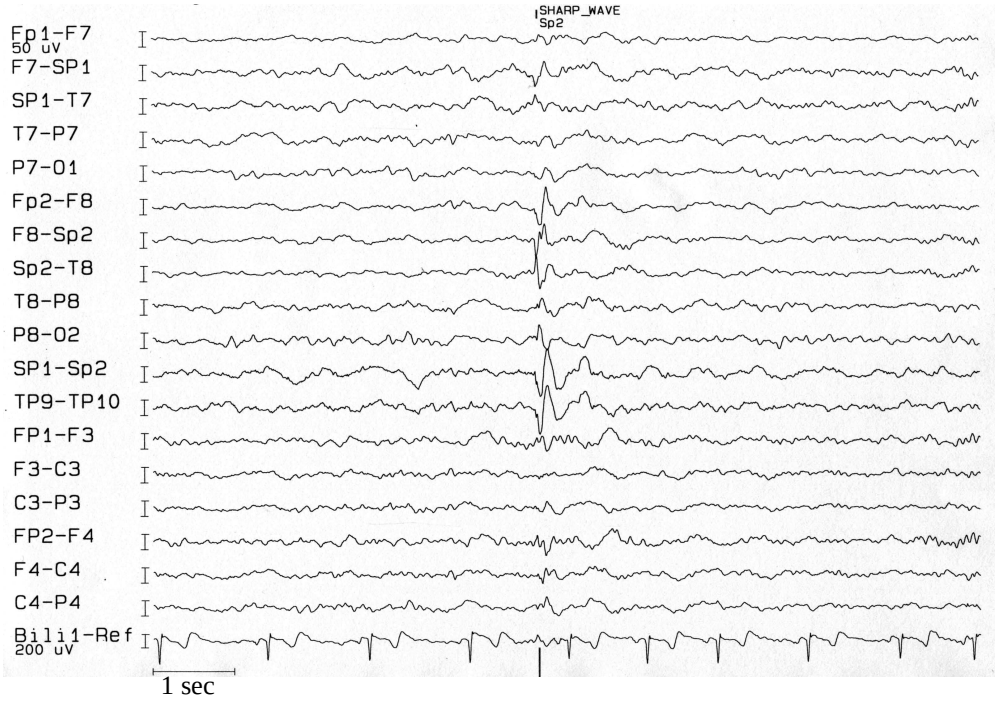

Figure 14 Preoperative Video-EEG monitoring of patient 2. *EEG showed right mesial temporal sharp waves (Sp2).*

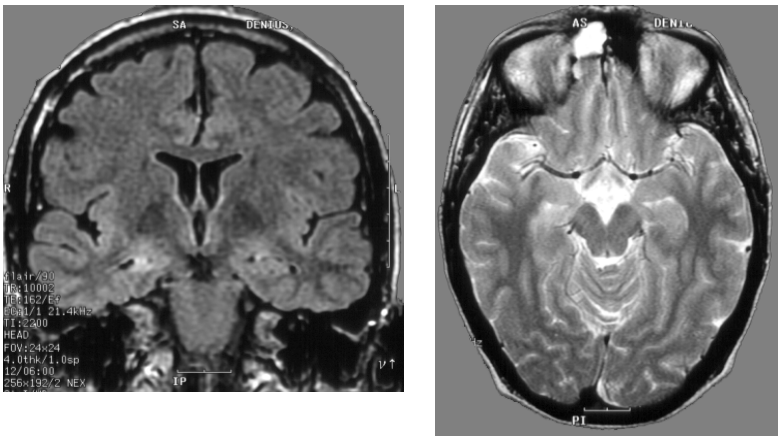

Figure 15 Preoperative MRI of patient 2. *Showing right typical HS.*

Figure 16A. Pre-resection ECoG, MTL

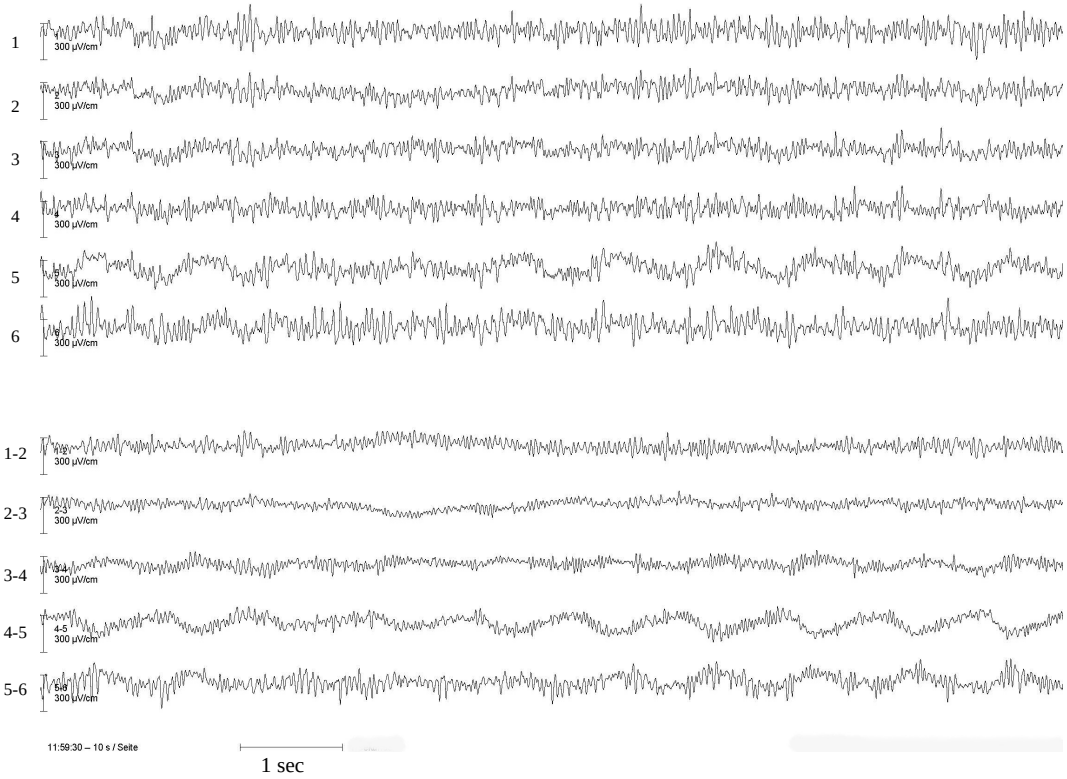

Figure 16B. Pre-resection ECoG, LTL

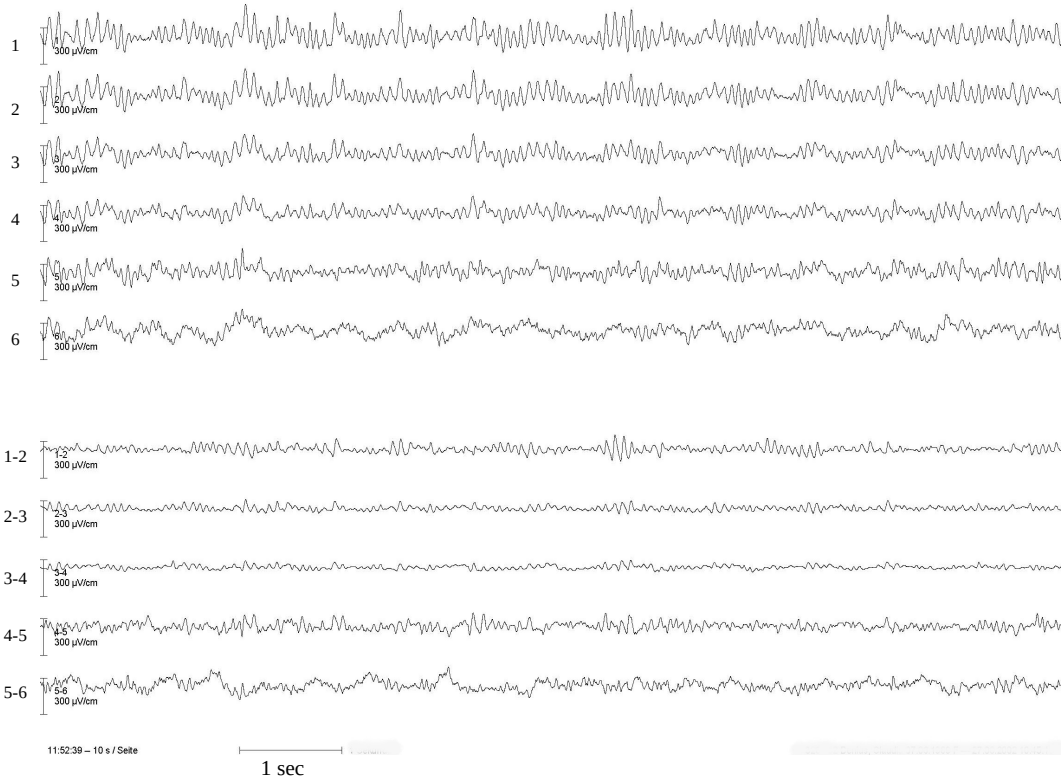

Figure 16C. Post-resection, MTL

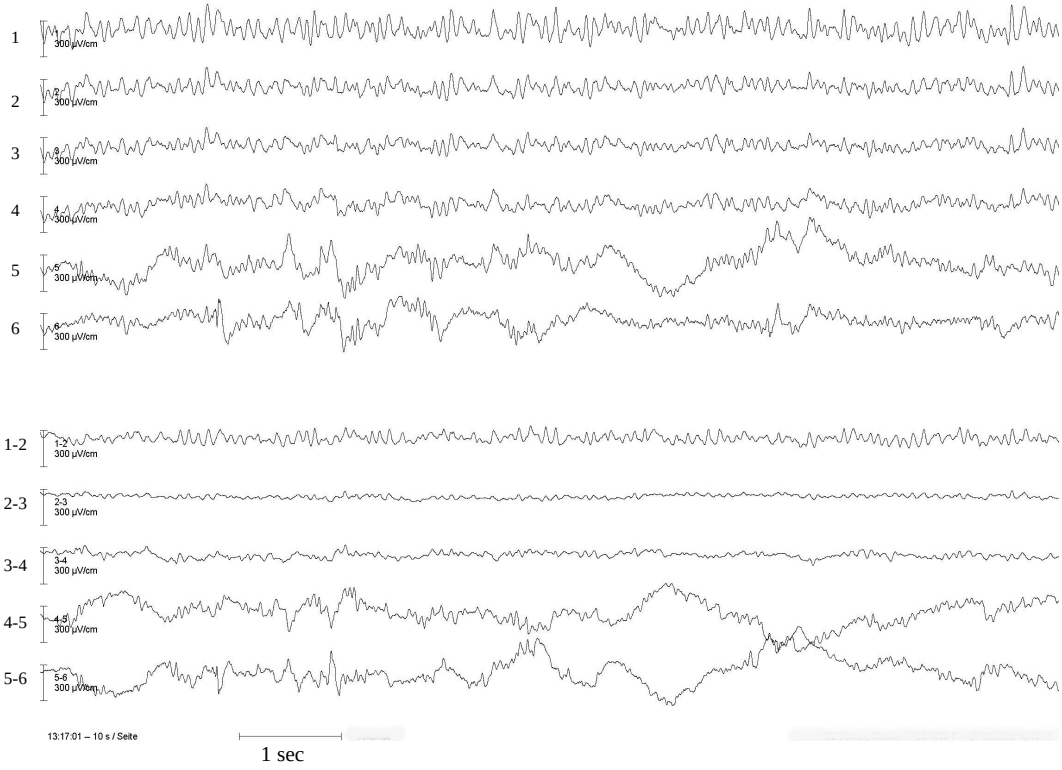

Figure 16D. Post-resection, LTL

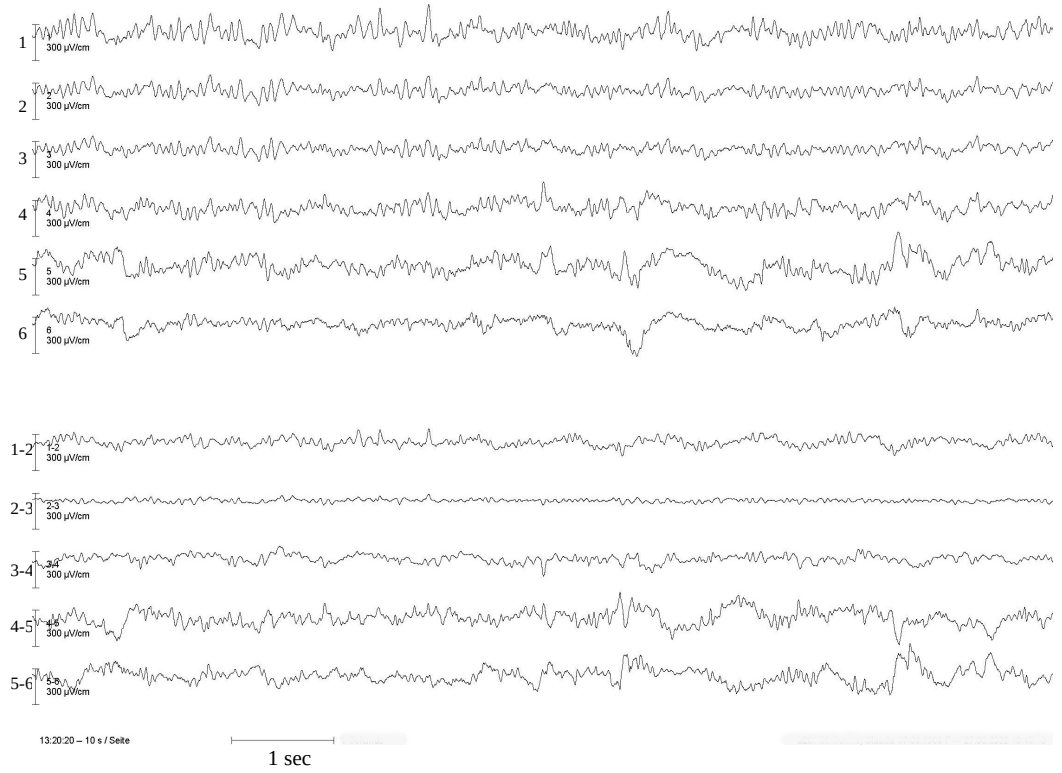

Figure 16 Intraoperative ECoG of patient 2. *Spikes were recorded neither on preresection ECoG (**A:** MTL, **B:** LTL) nor on post-resection ECoG (**C:** MTL, **D:** LTL). The upper 6 channels (or 8 channels in*

some other patients) are referential montage with electrodes referenced against a contralateral scalp electrode; the lower channels are bipolar Montage (E1-2, E2-3, …).

Patient 4:

Male, 21 years old, right handed. Epileptic seizures began at the age of 7, with the frequency of ca 1-6 × / month. The seizure semiology included non-specific aura → automotor seizure → right arm tonic seizure or right versive seizure → generalized clonic seizure. A history of febrile convulsion at the age of 1 year was reported. During the video-EEG monitoring ictal onset was observed from the left temporal lobe. Except temporal intermittent rhythmic delta activity (TIRDA), no IEDs were recorded. Cranial MRI showed left hippocampal sclerosis. Wada-test indicated left hemisphere language dominance and right memory dominance. Intraoperatively, spikes were recorded from the mesial temporal lobe before and after resection. After operation, no seizures recurred during the follow-up period of 12 months (Engel 1a) (Figure 17A, 17B, 18, 19A, 19B).

Figure 17A.

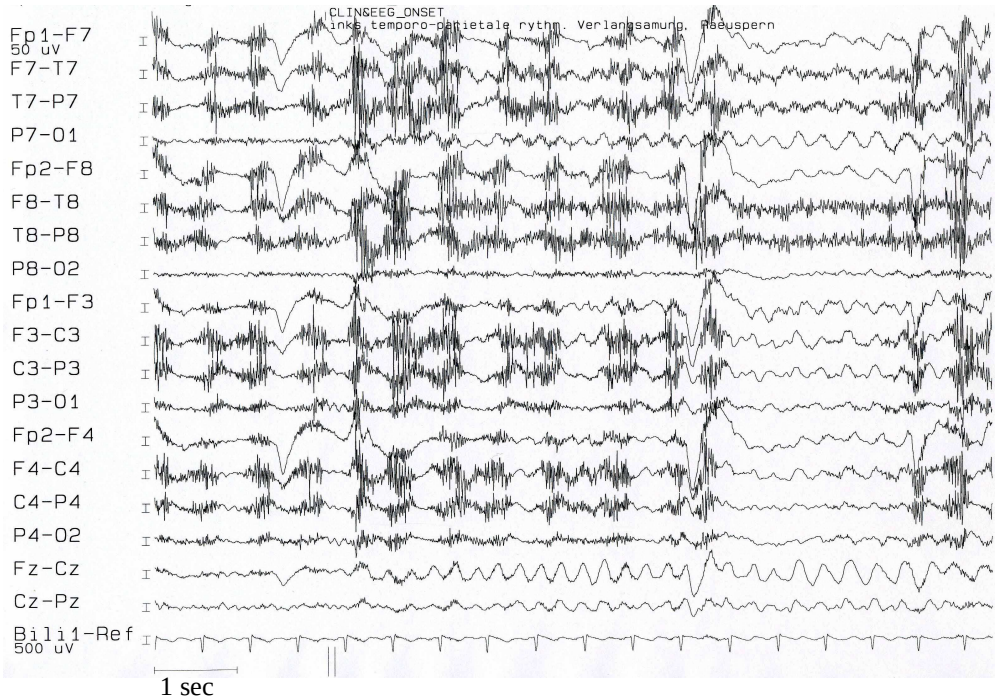

Figure 17B.

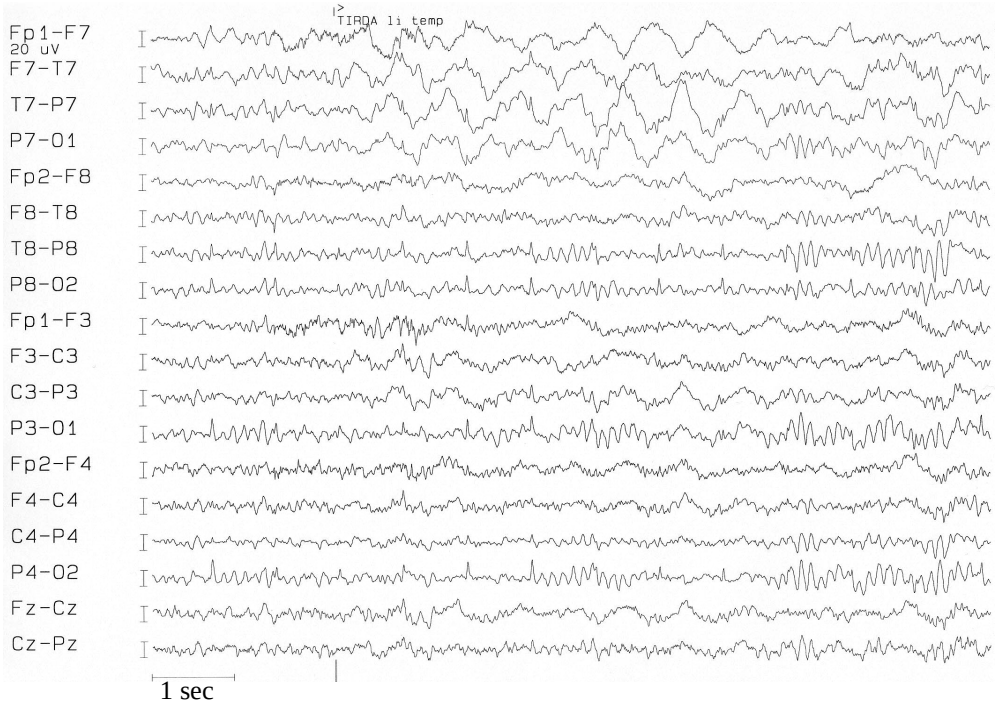

Figure 17 Preoperative Video-EEG monitoring of patient 4. ***A:*** *EEG showed the ictal onset from the left temporal lobe (T7);* ***B:*** *left temporal intermittent rhythmic delta activity (TIRDA).*

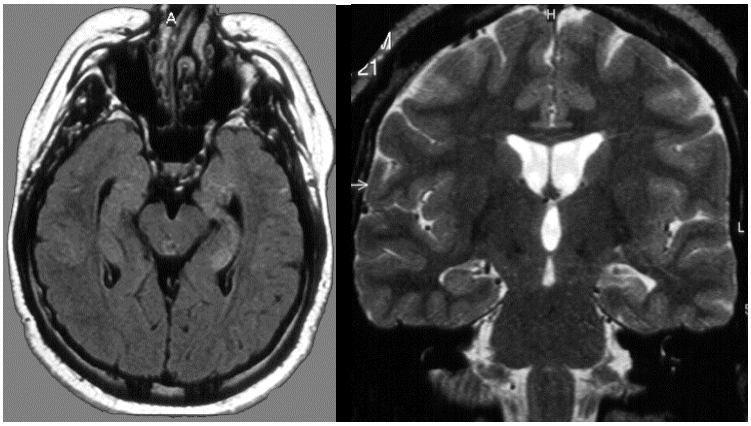

Figure 18 Preoperative MRI of patient 4. *Showing left HS.*

Figure 19A. Pre-resection ECoG, MTL

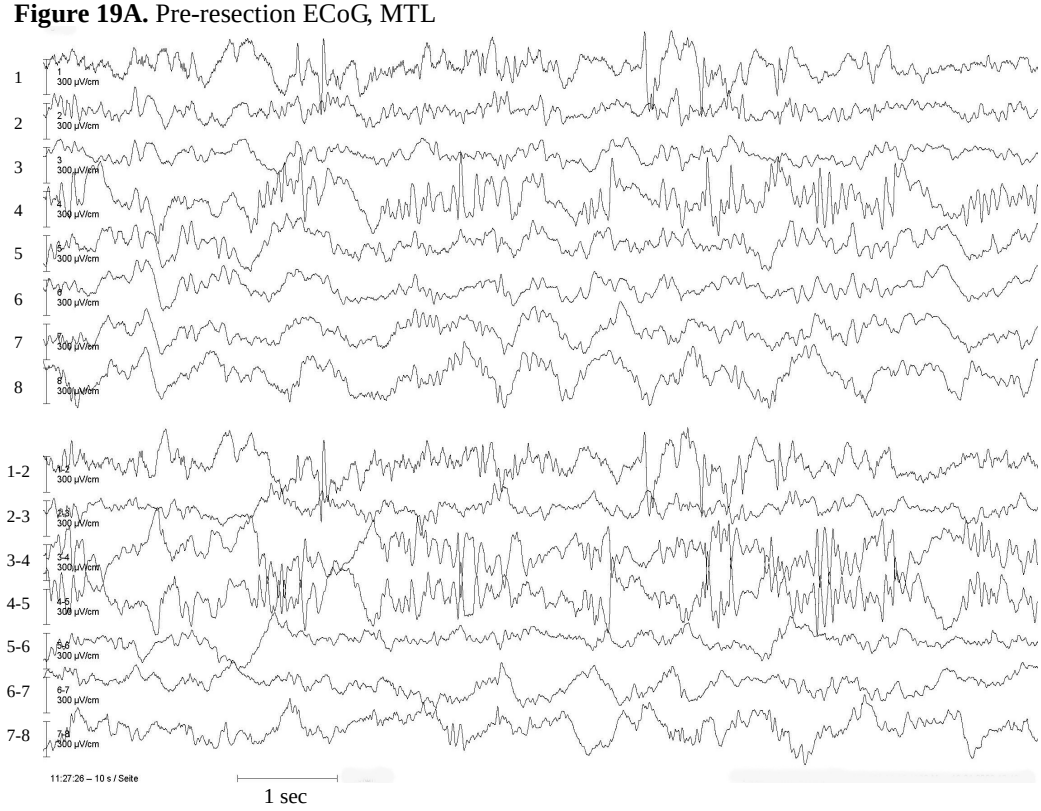

Figure 19B. Post-resection ECoG, MTL

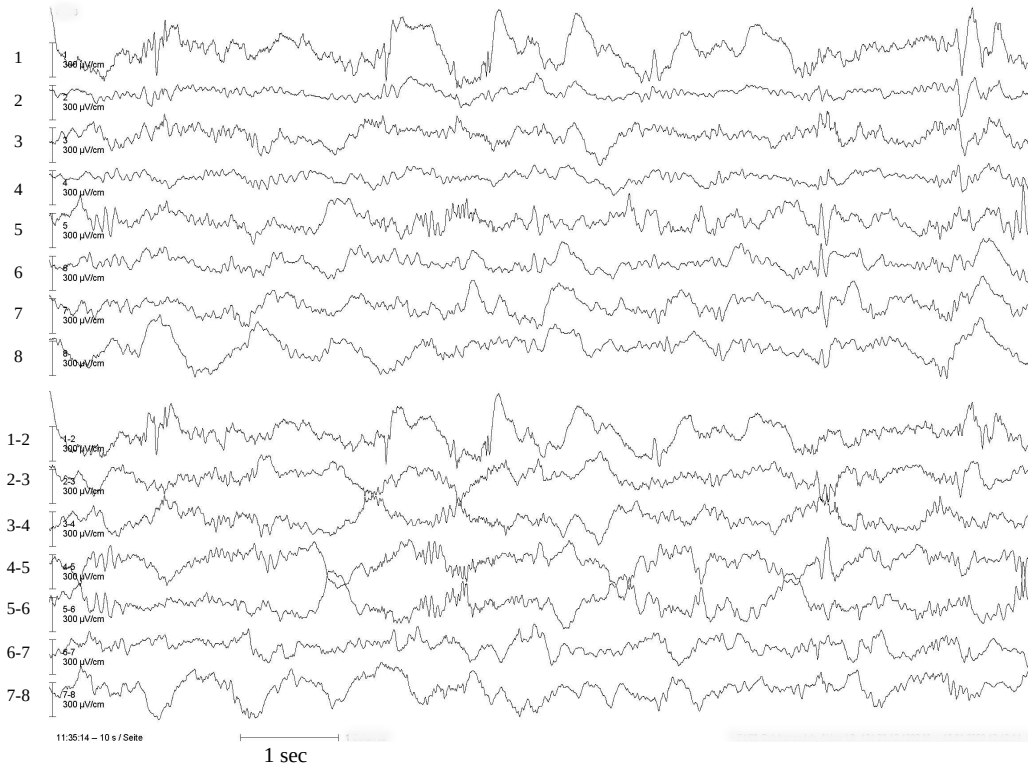

Figure 19 Intraoperative ECoG of patient 4. ***A:*** *Pre-resection ECoG showing frequent spiking (5-20 spikes/10s) recorded from the mesial temporal lobe only (position 5 (Figure 6), electrodes 1-4);* ***B:***

Post-resection ECoG from the same position showing infrequent spiking (< 5 spikes/10s, electrode 1) and a low amplitude background activity (electrodes 5-8).

Patient 6:

A 19-year-old female, right handed. A febrile convulsion was present when she was 11 months old. Between the age of 6 and 7 years, she had 5 febrile seizures. The seizure semiology: 1) unspecific aura → automotor seizure, which began at the age of 14, with a frequency of 5-30 × / month; 2) left hemispheric motor seizure, which was present between the age of 6 and 14 years, with a frequency of 1-4 × / year; 3) generalized tonic-clonic seizure. EEG-monitoring recorded sharp waves and spikes from the left temporal lobe (mainly mesial area, 94%). Ictal onset was observed from the left temporal lobe. MRI showed left hippocampal sclerosis. Wada-test showed left language dominance and right memory dominance. FTCD confirmed the left language dominance. Intraoperatively, only mesial temporal pre-resection spikes were recorded. After operation, no seizures recurred during the follow-up (Engel Ia) (Figure 20, 21).

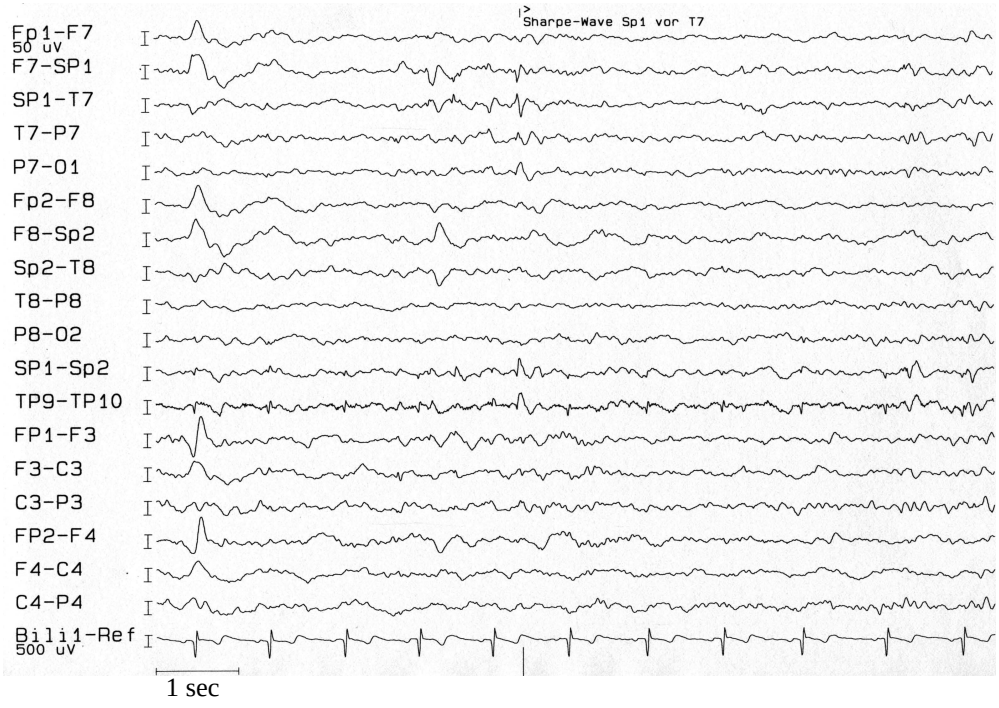

Figure 20 Preoperative Video-EEG monitoring of patient 6. *EEG showed left mesial temporal sharp wave (Sp1>T7).*

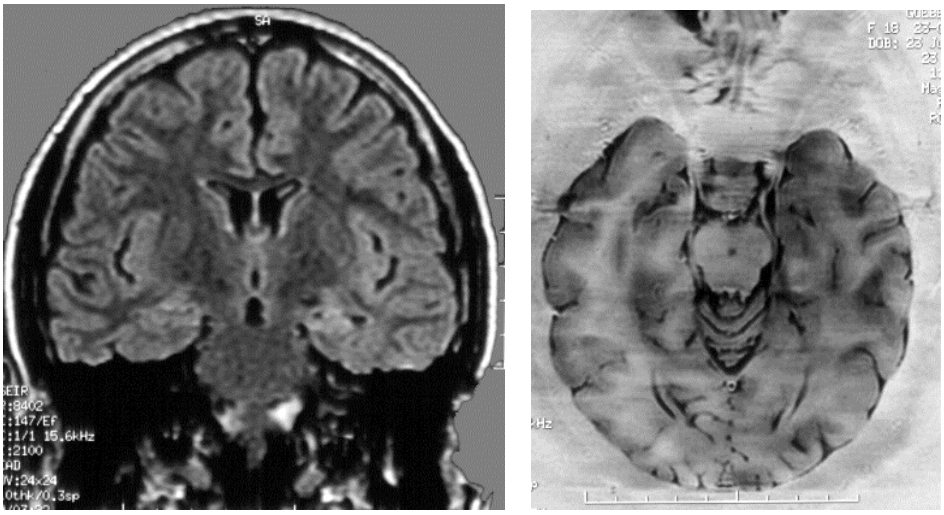

Figure 21 Preoperative MRI of patient 6. *Showing left HS.*

Patient 7:

51-year-old male, right handed; the first epileptic seizure occurred at the age of 31. Five years before EEG monitoring, he was operated on for astrocytoma (WHO grade II). After that he was thought to be seizure free for nearly 2 years. One and a half year later, he suffered a heavy car accident when he drove, but was not hurt. A seizure was possibly responsible for the accident. The seizure semiology: left hemisphere automotor seizure → generalized motor seizure. The EEG-monitoring detected sharp waves mainly from left mesial temporal lobe (90%) and rarely from right mesial temporal lobe. Ictal onset was recorded from left mesial temporal lobe, 37 of 39 recorded seizures were subclinical. MRI: left hippocampal sclerosis and changes after resection of right frontal tumor (no evidence of residual or recurrent tumor). SPECT showed interictal hypoperfusion and ictal hyperperfusion in left mesial temporal lobe. Wada-test indicated left language dominance and bilateral memory representation. Intraoperative ECoG recorded post-resection spikes from both mesial and lateral temporal lobe. After operation, seizures were reduced by > 50% (Engel IIIa) (Figure 22, 23, 24A-C)

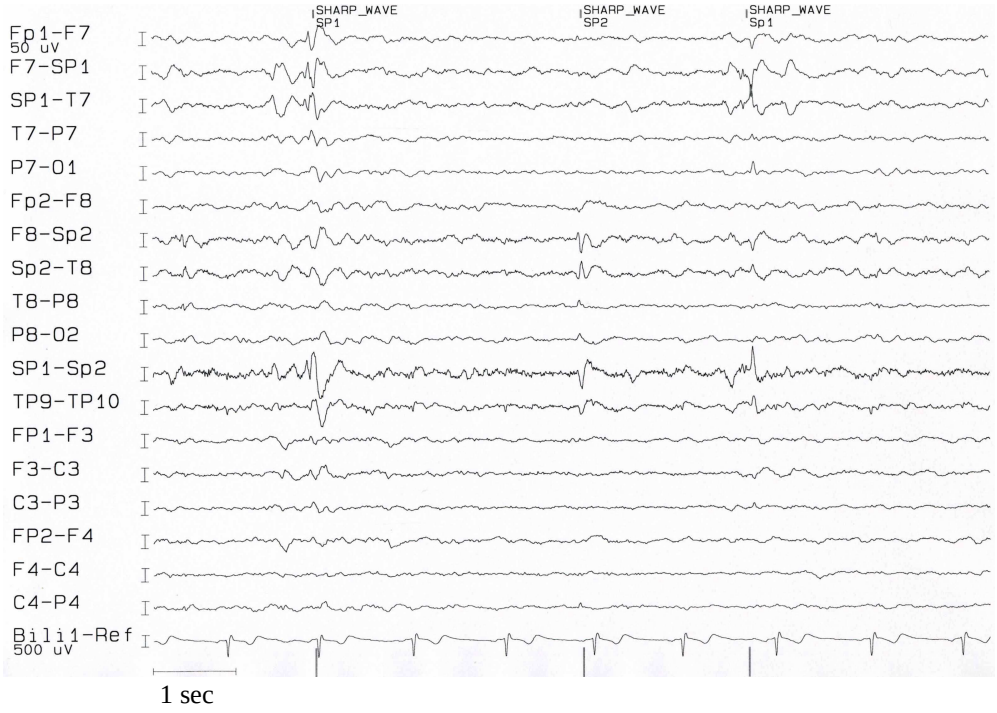

Figure 22 Preoperative Video-EEG monitoring of patient 7. *EEG recorded sharp waved mainly in left MTL (Sp1, 90%) and rarely in right MTL (Sp2, 10%).*

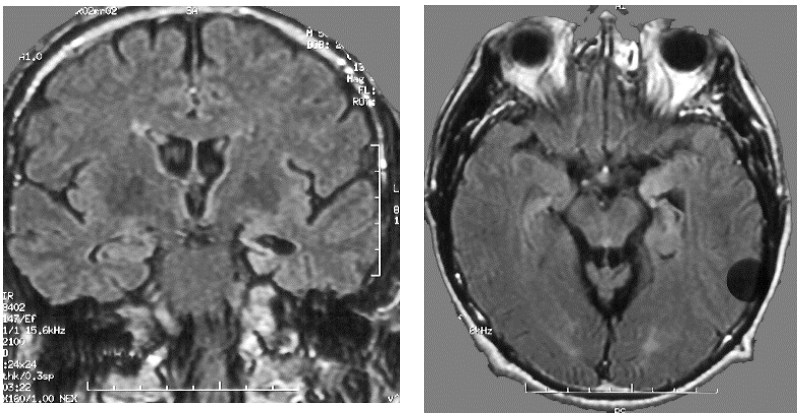

Figure 23 Preoperative MRI of patient 7. *Showing left HS.*

Figure 24A. Pre-resection ECoG, MTL

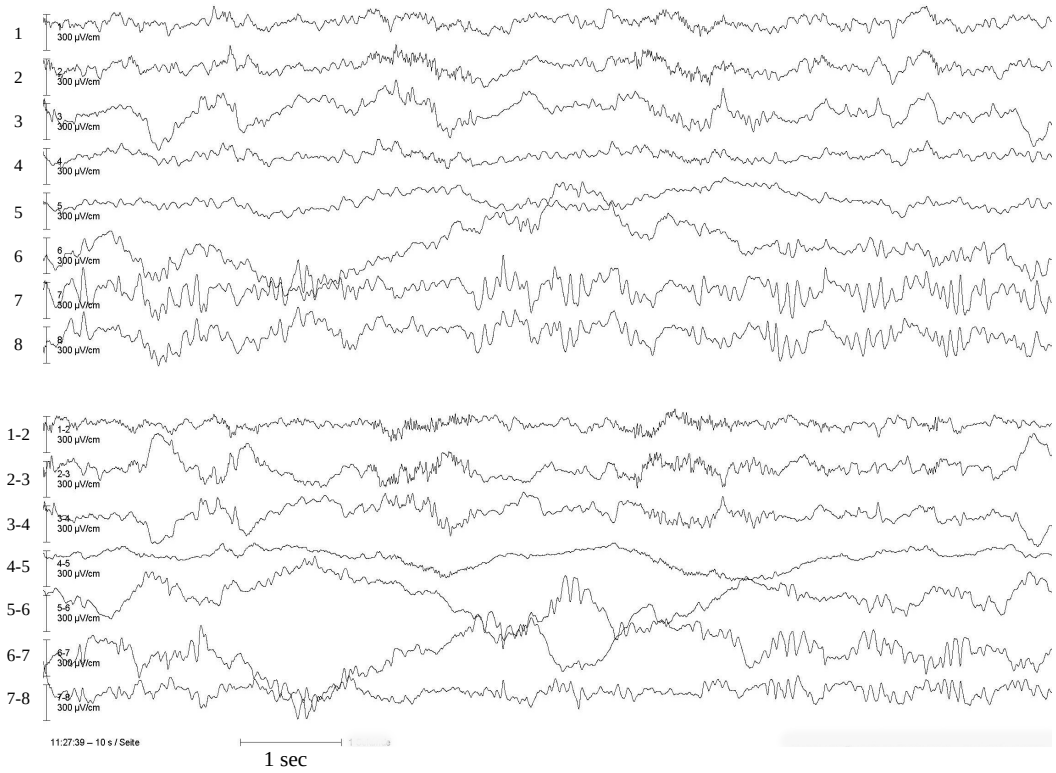

Figure 24B. Post-resection ECoG, MTL

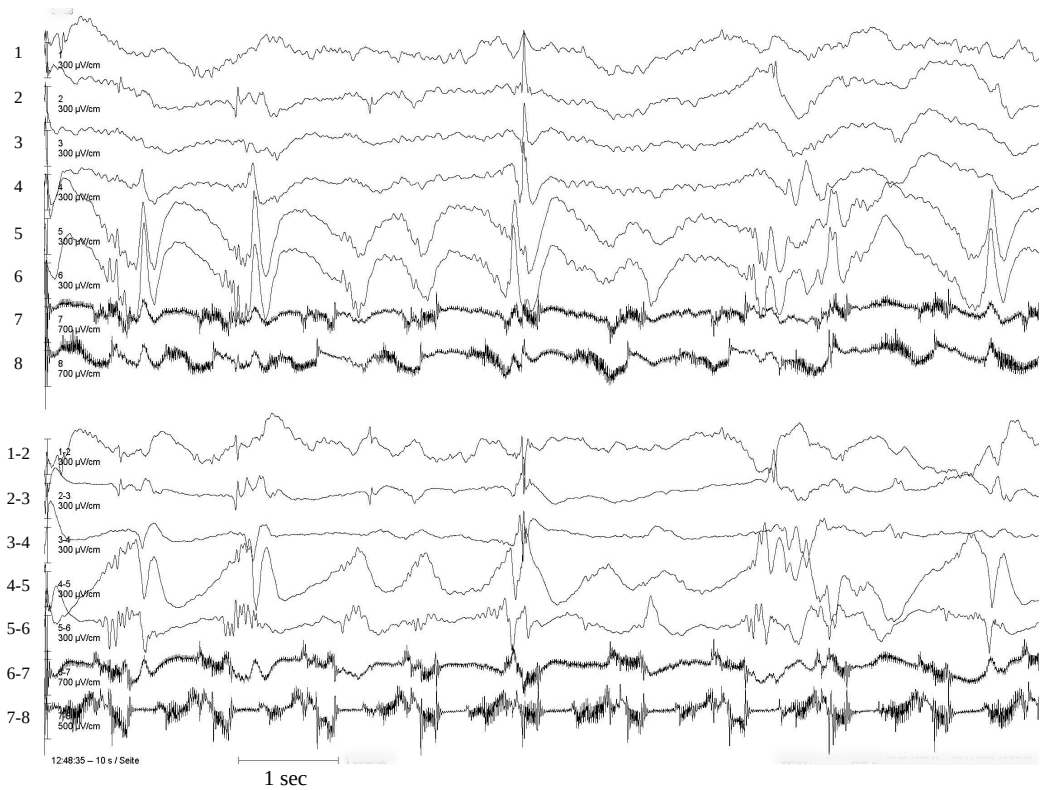

Figure 24C. Post-resection ECoG, LTL

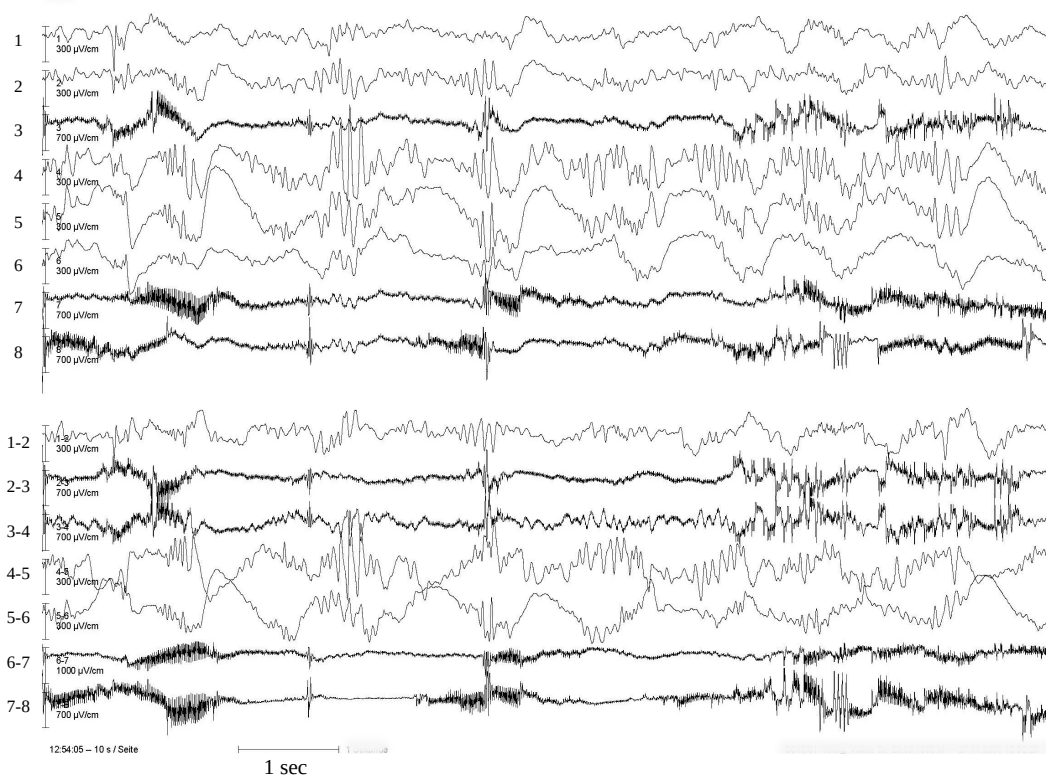

Figure 24 Intraoperative ECoG of patient 7. ***A:*** *No spikes were recorded on pre-resection ECoG;* ***B*** *and* ***C:*** *After resection, spikes and polyspikes were recorded in MTL (B) and LTL (C) respectively.*

Patient 9

A right-handed 9-year-old girl, who suffered from febrile convulsions and status epilepticus at the age of 2. An automotor seizure began 4 years later, with a frequency of 2-3 × / week. No family history of epilepsy. EEG-monitoring showed generalized irregular spike-wave complexes. Ictal onset was observed from left temporal lobe. Left hippocampal sclerosis was confirmed by MRI. FDG-PET showed left lateral and mesial temporal lobe hypometabolism. Wada-test and fTCD indicated left language dominance. Intraoperatively, pre-resection spikes were recorded from both the mesial and lateral temporal lobe. After operation, only one seizure directly after the operation and once febrile convultion (during the fever with 42°C) were reported (Engel Ic) (Figure 25, 26).

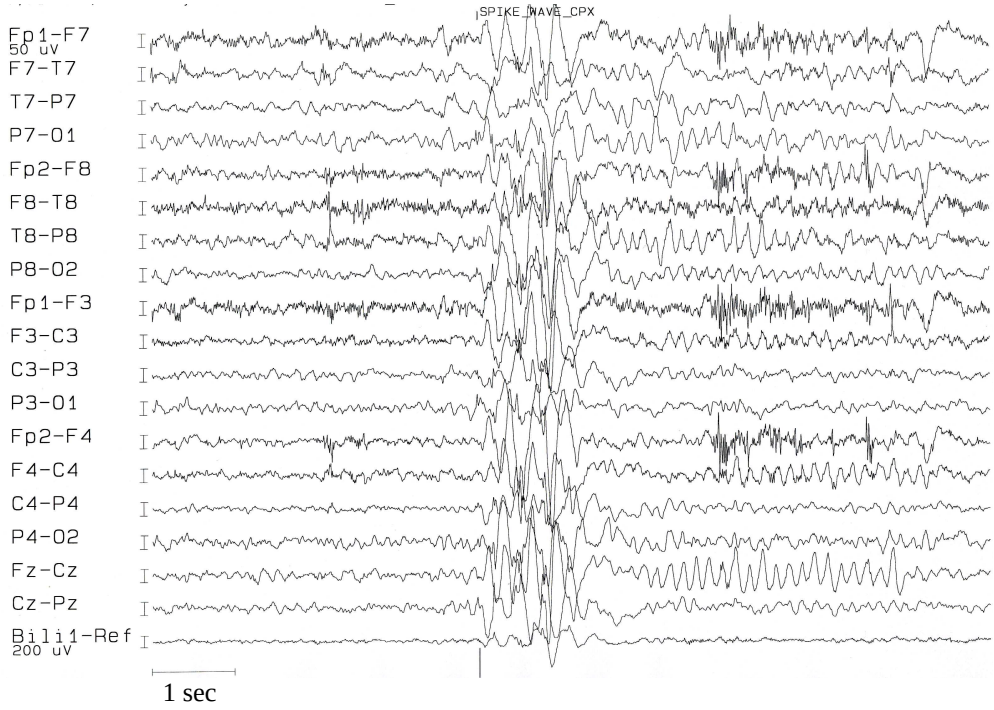

Figure 25 Preoperative Video-EEG monitoring of patient 9. *EEG recorded generalized spike-wave complex.*

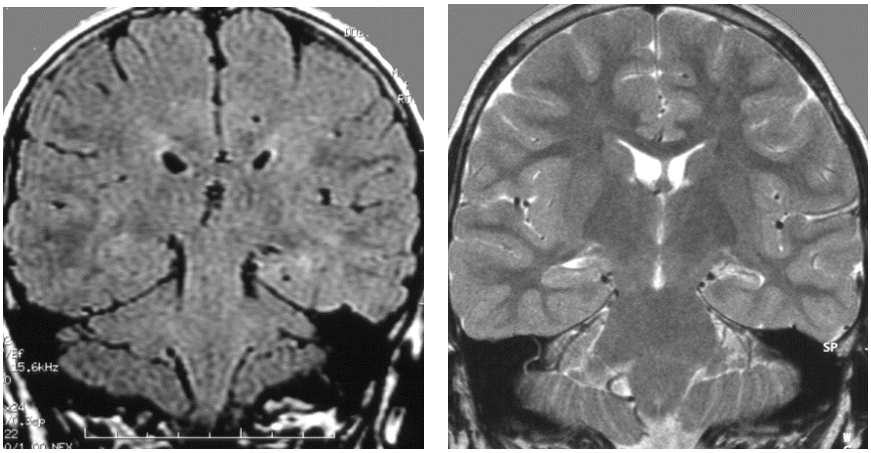

Figure 26 Preoperative MRI of patient 9. *Showing left HS.*

Patient 11

A 46-year-old male, right handed; epileptic seizures began at the age of 10. The frequency of seizures varied from 1 × / 4 months to 2 / week. The seizure semiology: psychic aura → dialeptic seizure → secondary generalized tonic-conic seizure. The EEG-monitoring found right lateral and mesial temporal sharp waves. Ictal onset was observed from the right temporal lobe. MRI showed right hippocampal sclerosis. Wada's test indicated left hemispheric language and memory dominance. Intraoperative ECoG showed lateral temporal pre-resection spikes and both mesial and lateral post–resection spikes. Postoperatively, no seizure recurred at the follow-up of 12 months (Engel Ia) (Figure 27, 28, 29A-D).

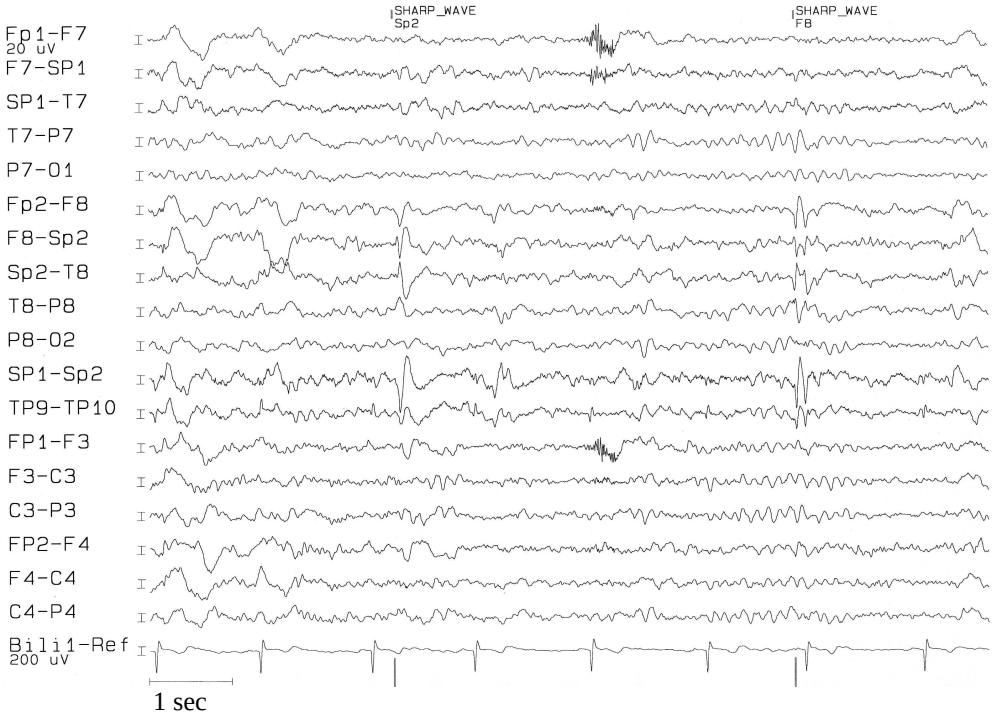

Figure 27 Preoperative Video-EEG monitoring of patient 11. *EEG showed sharp waves in right lateral temporal.(T8) and mesial temporal (Sp2) regions.*

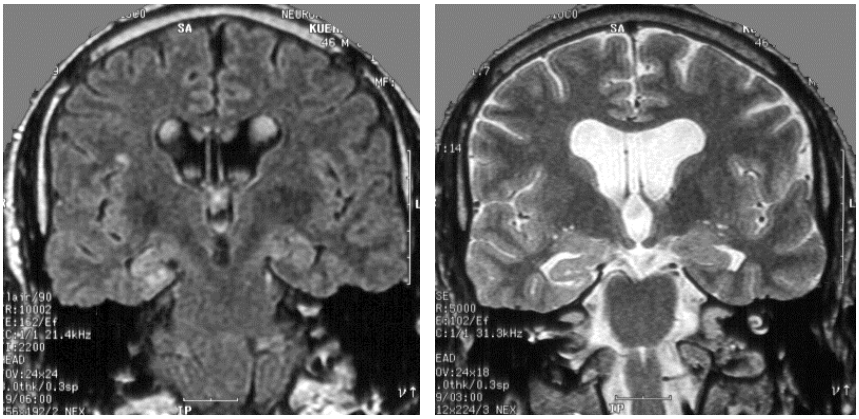

Figure 28 Preoperative MRI of patient 11. *Showing right HS.*

Figure 29A. Pre-resection ECoG, MTL

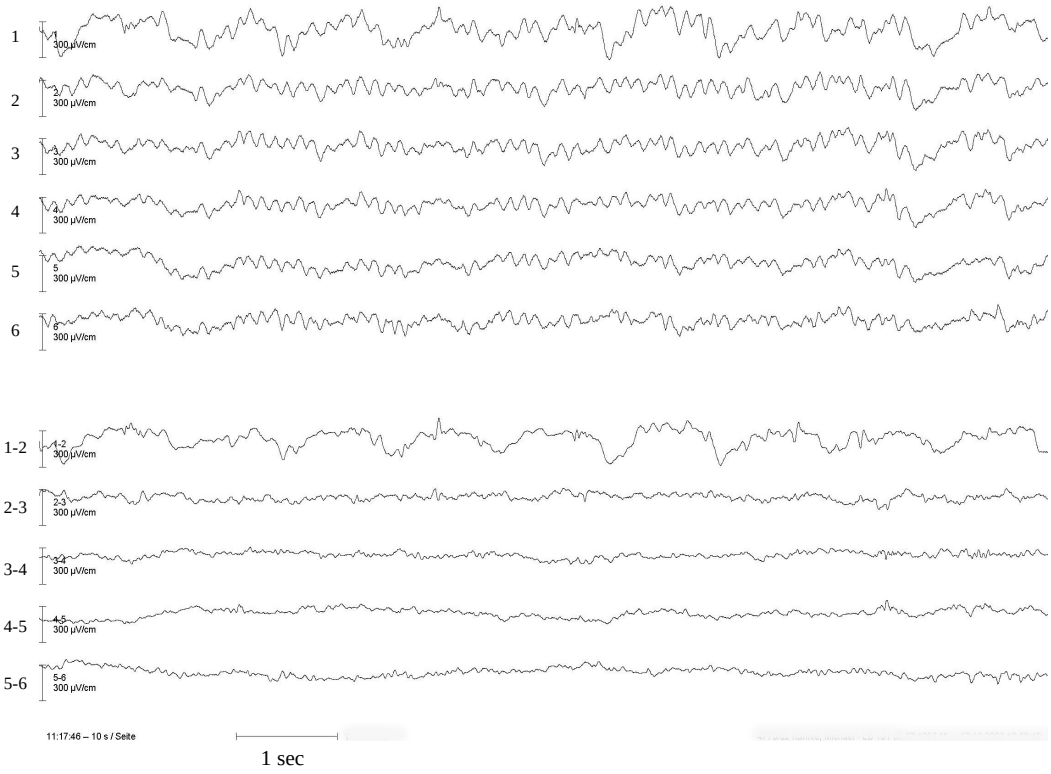

Figure 29B. Pre-resection ECoG, LTL

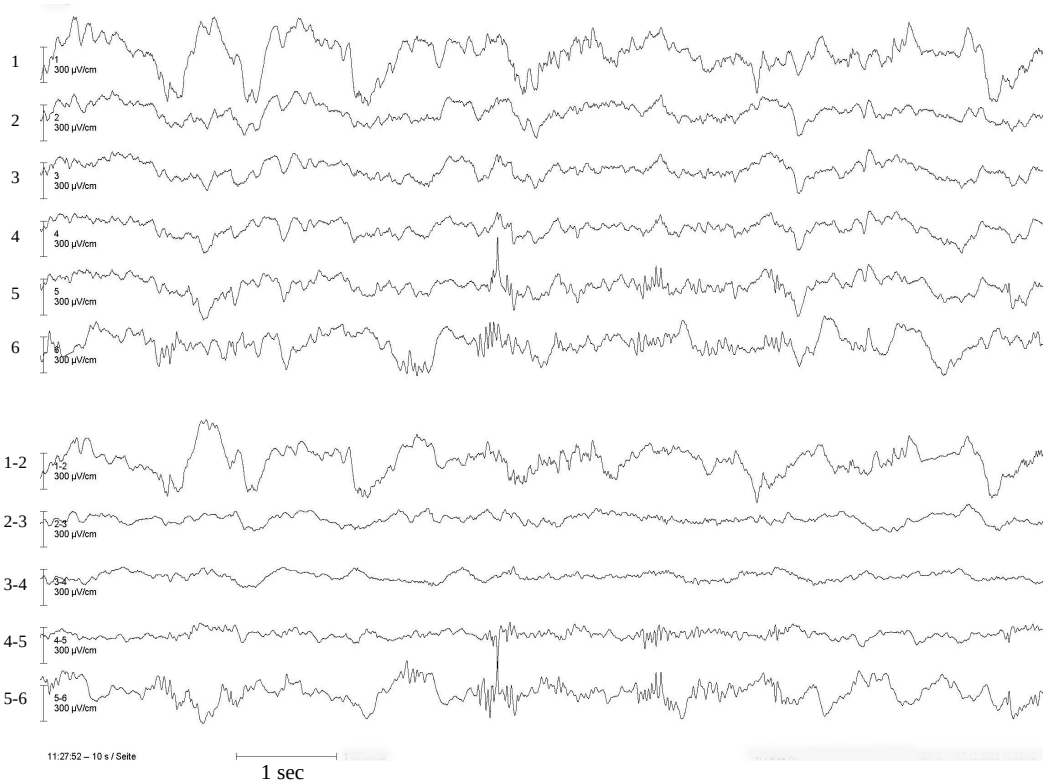

Figure 29C. Post-resection ECoG, MTL

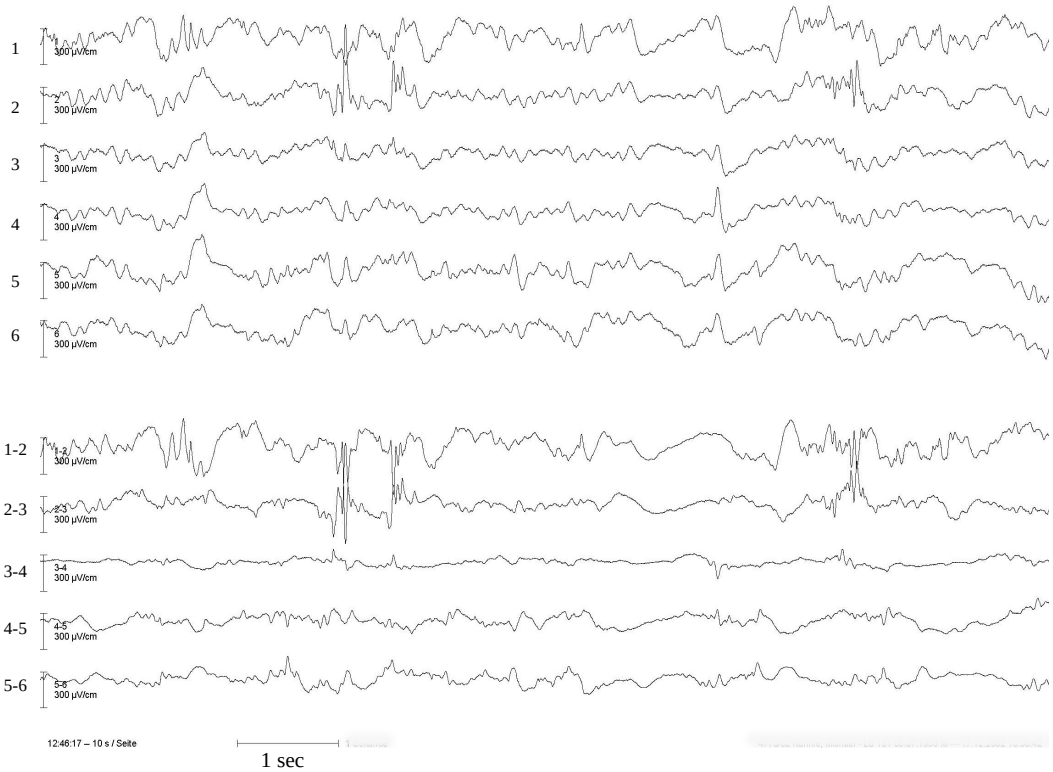

Figure 29D. Post-resection ECoG, LTL

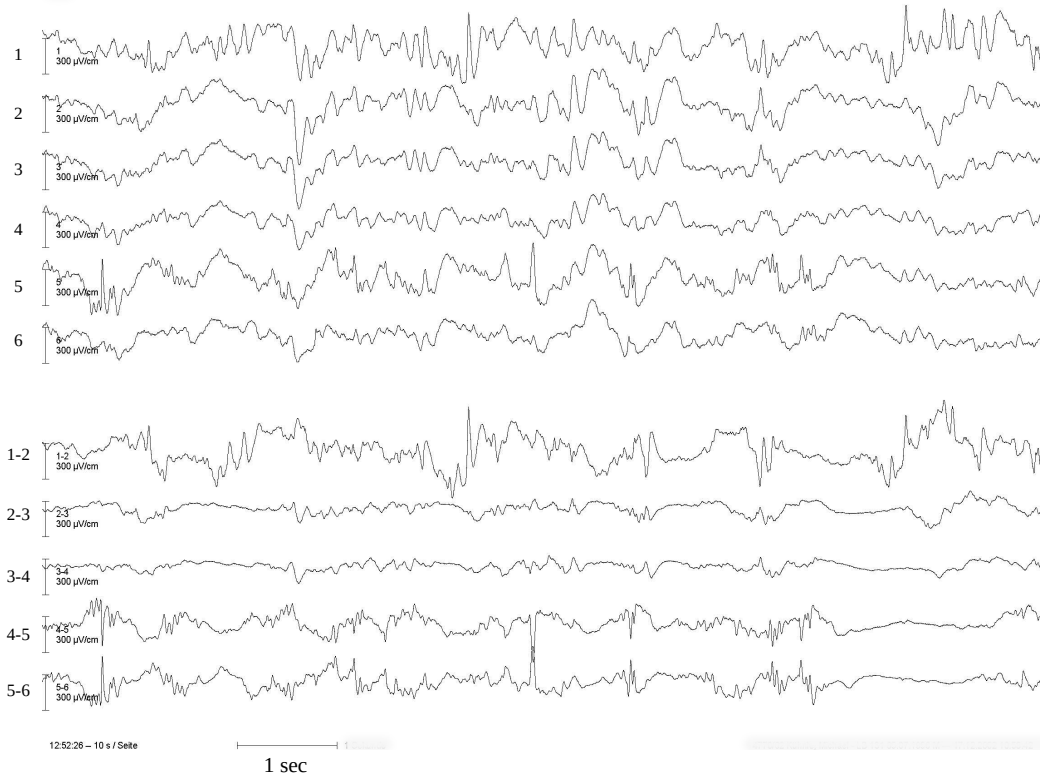

Figure 29 Intraoperative ECoG of patient 11. ***A:*** *No spikes were recorded in MTL on pre-resection ECoG;* ***B:*** *Polyspikes in LTL on pre-resection ECoG;* ***C:*** *Polyspikes in MTL on post-resection ECoG;* ***D:*** *Frequent spikes and polyspikes were recorded in LTL on post-resection ECoG.*

Patient 13:

Female, 39 years old, ambidextrous. Initially at the age of 14, she had three times generalized tonic-clonic seizures following a traffic accident. After that the seizure recurred 1-2 × / year. Since 1995, complex-partial seizures emerged with a frequency of 2-3 × / month. The seizure semiology: unspecific aura → automotor seizure → right versive seizure → generalized tonic-clonic seizure. EEG-monitoring recorded left mesial temporal sharp waves. Ictal onset was observed from left mesial temporal lobe. MRI showed left hippocampal sclerosis. Interictal SPECT showed left temporal hypoperfusion. Wada-test indicated a left language dominance and bilateral memory representation. Intraoperative ECoG recorded only mesial temporal pre-resection spikes. After operation, seizures recurred twice during the follow-up (Engel IIb) (Figure 30 A and 30B, 31A and 31B).

Figure 30A.

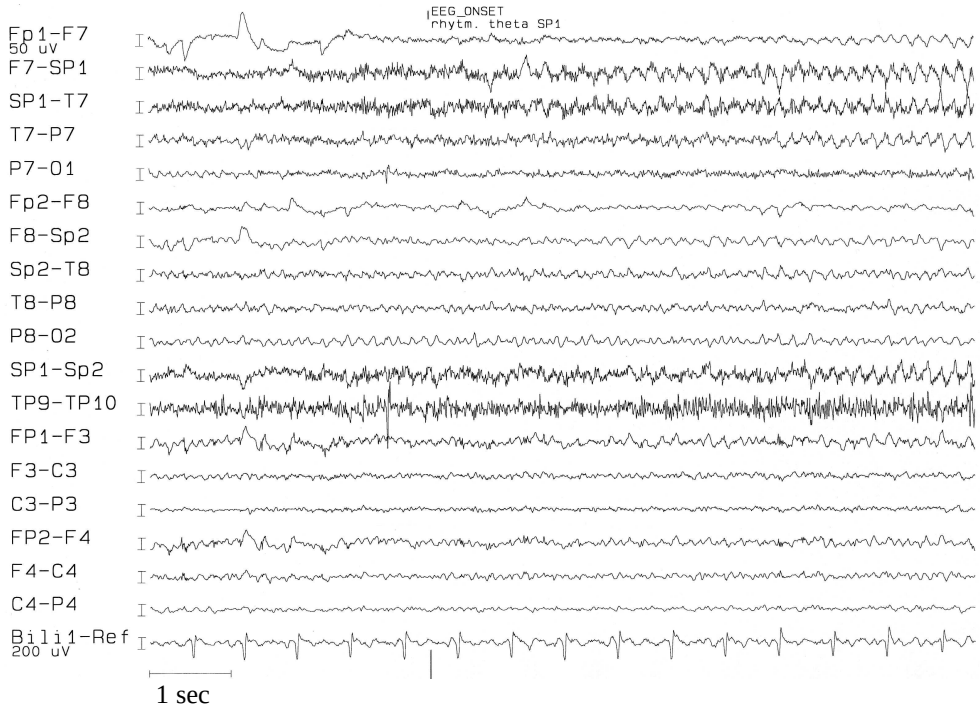

Figure 30 B.

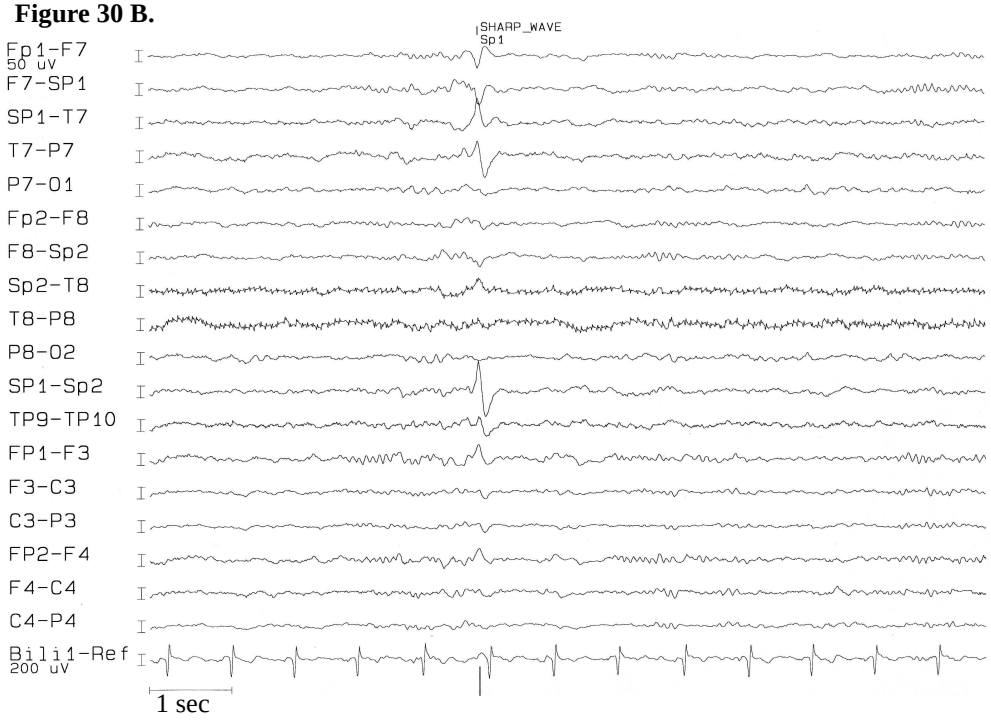

Figure 30 Preoperative Video-EEG monitoring of patient 13. ***A:*** *EEG recorded ictal onset from left mesial temporal region (Sp1);* ***B:*** *Interictal sharp wave recorded in the left mesial temporal lobe (Sp1).*

Figure 31A. Pre-resection ECoG, MTL

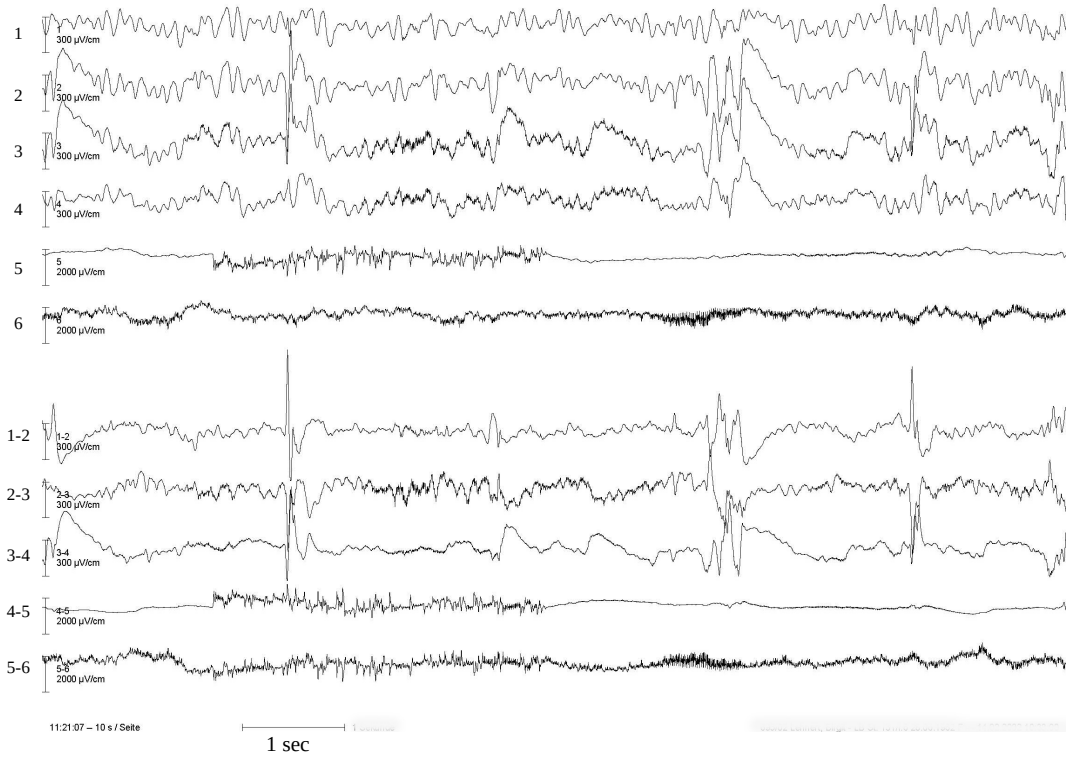

Figure 31B. Post-resection ECoG, MTL

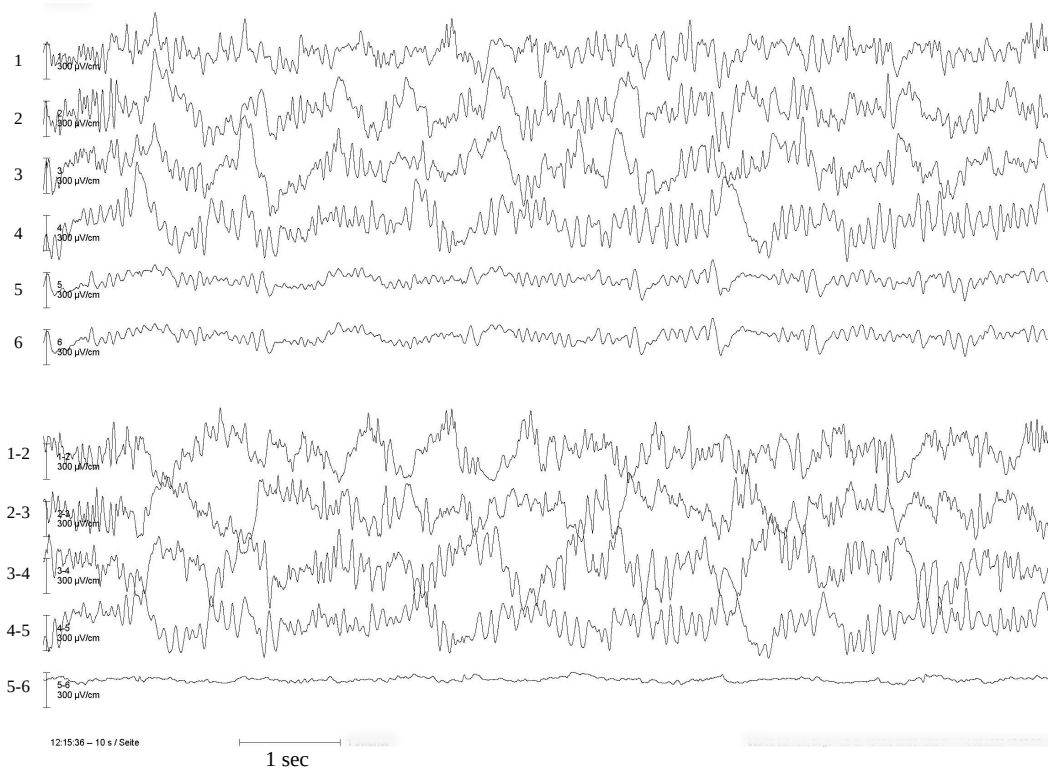

Figure 31 Intraoperative ECoG of patient 13. ***A:*** *Frequent spiking was recorded in MTL on pre-resection ECoG;* ***B:*** *No spikes were recorded after resection.*

Patient 17:

A 56-year-old male, right handed. Seizures began at the age of 29 and continued with the frequency of 1 × / week. The seizure semiology: abdominal aura → right hemispheric automotor seizure → right face clonic seizure → generalized tonic-clonic seizure. EEG-monitoring recorded right mesial temporal sharp waves. Ictal onset was recorded from right mesial temporal. MRI showed right hippocampal sclerosis. Wada-test showed a left language dominance and bilateral memory representation. Intraoperatively, only mesial temporal pre-resection spikes were recorded. After operation, no seizure recurred during the follow-up (Engel Ia) (Figure 32, 33).

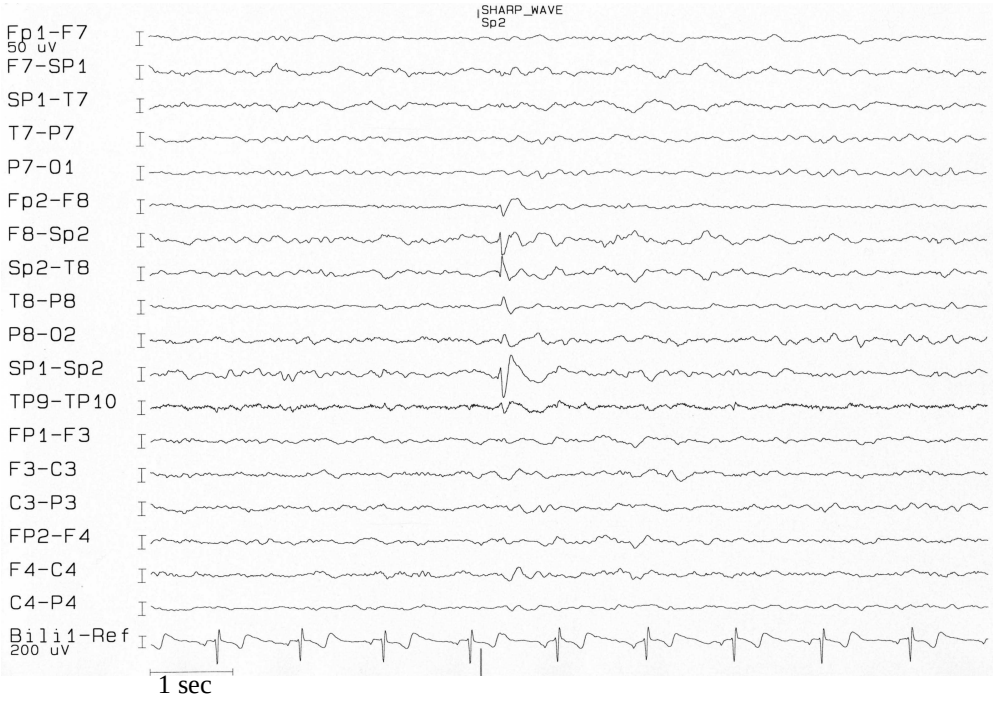

Figure 32 Preoperative Video-EEG monitoring of patient 17. *EEG recorded sharp wave in the right mesial temporal area (Sp2).*

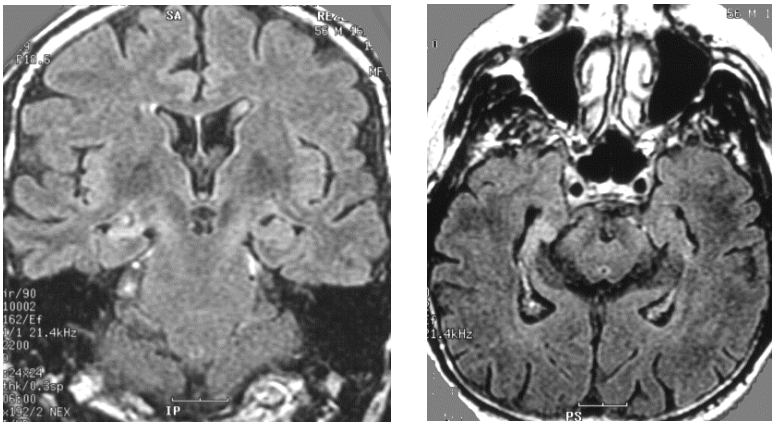

Figure 33 Preoperative MRI of patient 17. *Showing right HS.*

5 DISCUSSION

The main finding of this study is that patients with pre-resection spikes restricted to the mesiobasal temporal lobe tended to have a better outcome (82%) as compared to all other groups (55%). A trend was also present indicating that patients with pre-resection spikes of lower frequency tend to have a better outcome (100% seizure-free) than those with higher frequency spikes (56% seizure-free). The persistence of pre-resection spikes on post- resection ECoG was not related to seizure outcome.

Moreover, patients with unilateral temporal IEDs on preoperative surface EEG became seizure free more frequently than those with bilateral and / or extratemporal IEDs. A combination of the results of preoperative surface EEG and the findings of intraoperative ECoG especially pre-resection ECoG may be more reliable to predict postoperative seizure outcome in patients with hippocampal sclerosis.

5.1 Methodological considerations

It is widely accepted that the postoperative prognosis in temporal lobe epilepsy depends on etiology and that seizure outcome is also influenced by the extension and completeness of the resection of a lesion (Crandall and Mathern 2001; Engel, Jr. et al. 1975; Engel et al. 1993; Wyllie et al. 1987). Therefore, we only included patients undergoing a standard sAHE and only patients with MRI evidence of mesial temporal sclerosis and no other lesions.

5.1.1 Surgery and electrocorticography

Most surgeons believe that maximizing the extent of hippocampal removal improves outcome with respect to seizures. The most common cause of surgical failure in TLE is thought to be inadequate mesial temporal removal (Germano et al. 1994; Polkey et al. 1993). However, no consensus exists as to how much of hippocampus should be resected (Jooma et al. 1995; Kanner et al. 1995; McKhann et al. 2000; Nayel et al. 1991; Stefan et al. 1996). Extended hippocampal resection might lead to greater impairment of verbal and non-verbal memory following dominant and non-dominant

temporal resections, respectively (Helmstaedter and Elger 1998; Katz et al. 1989; Milner 1972; Nunn et al. 1999). One previous larger study by McKhann et al. (McKhann et al. 2000) found that patients with a larger hippocampal resection (>2.5 cm) were not more likely to have seizure-free outcomes than patients with smaller resections, when using an intraoperatively tailored ECoG recording and that the residual mesial epileptiform activity on post-resection ECoG correlated with worse seizure outcomes. Sixty-seven percent of the 140 patients in their study were seizure free or had only a single postoperative seizure, with follow-up time of at least 18 months. The authors concluded that intraoperative hippocampal ECoG can predict how much hippocampus should be resected to achieve maximal seizure-free outcome, thus allowing to spare the functionally important hippocampus. However, the anterior and lateral temporal cortex was also resected in their study, before the hippocampus was exposed. Accordingly, the results of this study can not be applied to sAHE. Moreover, the completely seizure-free patients were not distinguished from the patients with a single postoperative seizure. In our study, only the mesial structures were resected and the relation of intraoperative ECoG and seizure outcome was analyzed independently of the extension of resection. We found that pre-resection MTL spikes, which were recorded from the area to be resected, were clinically associated with a better seizure outcome. Sixty-eight percent of our series were completely seizure free (Engel 1a). We conclude that intraoperative ECoG may be a useful tool to predict seizure outcome. A larger study with more that 102 patients is needed to prove this hypothesis. The question whether the resection margins of sAHE can be defined by ECoG remains to be investigated in a separate study.

5.1.2 Anesthesia and electrocorticography

Anesthesia during ECoG is problematic because presence, frequency and distribution of spikes can be influenced to variable degrees by different agents. On the other hand, the control of anesthetic levels can be used to optimize the display of epileptiform discharges (Kuruvilla and Flink 2003). The general anesthetic medication used for the operative procedure can have significant effects on the ECoG. The local anesthesia, favorable to intraoperative functional mapping, avoids such problems; but creates more technical difficulties. In addition, local anesthesia may not be feasible in young

children and apprehensive adults (MacDonald and Pillay 2000). In our study, general anesthesia was maintained with relative low concentrations of sevoflurane and sufentanil during the ECoG recording. Sevoflurane belongs to halogenated inhalational anesthetics, which have been reported to produce dose-related reduction in amplitude and frequency of EEG activity after initial activation (Sloan 1998). Sufentanil has been reported to produce epileptiform changes on ECoG. To minimize the variability of these effects, we used a standardized regimen with low sevoflurane concentration during the 10 minutes before and until the end of ECoG. According to our experience, barbiturates, propofol and benzodiazepines would disturb the recording of epileptiform activity, therefore these anesthetic agents should be avoided, if EEG or ECoG recording are to be performed.

5.1.3 Preoperative magnetic resonance imaging

The diagnosis of unilateral hippocampal sclerosis by preoperative MRI was based on hippocampal and amygdalar atrophy and an increased signal on T_2-weighted and FLAIR sequences. MRI findings have been shown to be highly accurate for in vivo diagnosis of hippocampal sclerosis with a sensitivity of 90% and a specificity of 85% (Bronen et al. 1997; Jackson et al. 1993; Watson et al. 1992; Watson et al. 1997), while some coexisting abnormalities (dual pathology) such as neuronal heterotopias and microdysgenesis, which are predictive of a poorer outcome (Sisodiya et al. 1997), can often only be detected microscopically or by special imaging analysis techniques. Since temporal neocortex was not resected in this series we cannot comment on the correlation of LTL spikes and dual pathology.

A major limitation of MRI as an indirect marker of the epileptogenic zone is that, it can only find the macroscopic epileptogenic lesions but cannot find the cellular and subcellular abnormalities (such as microdysgenesis) that result in recurrent spontaneous abnormal and synchronous neuronal discharges and contribute to spontaneous partial-onset seizures (Jack, Jr. 2001). For example, neurons in dysplastic cortex lacking their normal synaptic targets seek out targets that lie in “normal” cortex adjacent to the area of cortical dysgenesis. This abnormal circuitry involves both the area of macro- or microscopic cortical dysplasia (dysgenesis) as well as adjacent “normal” cortex (Jack, Jr. 2001). hippocampal sclerosis has been widely believed to

be initiated by an early-life insult that results in selective cellular damage in the hippocampal hilus (Falconer 1971; Falconer et al. 1964; Sloviter 1994). As a result of the cell loss, mossy fiber sprouting leads to the formation of the abnormal self-excitatory circuitry which is actually responsible for recurrent seizures. The cell damage and resultant astrogliosis would result in the two major MRI features of hippocampal sclerosis: atrophy and increased T2 signal (Bronen et al. 1991). Therefore, the specific histopathological changes that are responsible for the MRI findings and those that are responsible for producing seizures are different (Jack, Jr. 2001). This explains why MRI sometimes fails to detect coexisting epileptogenic abnormalities in patients with hippocampal sclerosis. However, as a widely used preoperative means to localize the epileptogenic lesion, MRI has revolutionized the management of patients with hippocampal sclerosis, since the detection of HS in these patients is now feasible in a noninvasive way (Diehl 2004). Further efforts should be directed at identifying other imaging criteria of MRI, SPECT and PET, which can provide useful localizing information in case that conventional MRI is inadequate. Recently, three Tesla MRI using phased array head coil has been shown to be available in that respect. Knake et al. (Knake et al. 2005) found that in the subgroup of patients with prior 1.5T MRI interpreted as normal, 3T PA-MRI resulted in the detection of a new lesion in 65%; in the subgroup of patients with known lesions, 3T PA-MRI better defined the lesion in 33%. Therefore, compared to routine clinical 1.5T MRI, 3T PA-MRI can improve the presurgical evaluation of patients with focal epilepsy. It can be expected that 3T PA-MRI will contribute to the improvement of the localization of the epileptogenic lesion in TLE and may provide more use information for the epilepsy surgery.

5.2 Outcome classification

Engel´s classification is now used extensively (Table 3), however, its disadvantages have also been reported (Wieser et al. 2001). In Engel´s category I, seizure-free patients are included with others who still have seizures. Most centers do not report outcomes using Engel´s subcategories, which makes the actual number of seizure-free patients frequently obscure. In present study, patients in Engel class Ia were compared to the remainder because complete seizure freedom has the most relevant impact on

the patients quality of life (Vickrey et al. 1995) and the persistence of any seizures indicates that the epileptogenic zone has not been resected completely (Rosenow and Luders 2001).

5.3 Preoperative surface electroencephalography

In our series, seventy-one percent of patients with interictal epileptiform discharges on preoperative surface EEG ipsilateral to the hippocampal sclerosis had IEDs restricted to the ATL The restricted anterior temporal discharges in HS patients have also been reported by previous studies (Ebner and Hoppe 1995; Hamer et al. 1999) and may suggest a smaller irritative zone, in comparison with that in patients with mesial temporal lesions (Hamer et al. 1999; Quesney et al. 1988). The possible sources of interictal discharges in HS patients may be: 1) the mesiobasal aspect of the temporal lobe (hippocampus and parahippocampal gyrus), which was followed within 40 ms by activation of the ATL neocortex; 2) spreading of epileptic discharges to the temporal neocortex or to the orbitofrontal cortex via the limbic system, which contributes to the rare occurrence of lateral temporal and frontal IEDs in HS (Baumgartner et al. 1995; Ebersole and Wade 1991). Frequent posterior or extratemporal IEDs may decrease the certainty of the diagnosis of hippocampal sclerosis (Hamer et al. 1999). In our series, two patients had ipsilateral extratemporal IEDs (No. 1 and No. 9). Patient 1 had only one frontal spike during the EEG monitoring and patient 9 had generalized spikes. In patient 4, no IEDs were recorded. However, temporal intermittent rhythmic delta activity (TIRDA) was recorded in both patient 9 and 4. In addition to IED, TIRDA was also strongly correlated with the temporal seizure origin and could be recorded in a high proportion of patients with medically refractory TLE (Blume et al. 1993; Gambardella et al. 1996). Therefore, the lateralization of TIRDA could indicate the side of temporal seizure origin in both patients.

On surface EEG, the interictal discharges may have a more reliable lateralizing value than ictal changes in TLE and can almost always predict seizure origin and good postoperative outcome if they are exclusive or clearly preponderant in a single region or on the side of surgery (Hamer and Katsarou 2004; Holmes et al. 1996). In a study of 59 cases undergoing temporal lobectomy, 92% of patients with >90% lateralization

had a good surgical outcome, whereas only 50% with <90% lateralization had a favorable outcome (Chung et al. 1991). Similarly, in our cases undergoing sAHE, we found that the patients with unilateral temporal IEDs ipsilateral to the hippocampal sclerosis on preoperative surface EEG became more frequently seizure free (92%) than those with bilateral and / or extratemporal IEDs (25%). Moreover, the presence of unilateral interictal IED foci in the ATL has also been reported to predicted accurately temporal lobe onset (Kanner et al. 1993). In our study, the patients with restricted IEDs in the ATL ipsilateral to the HS became more frequently seizure free (90%) than those with IEDs in the ipsilateral LTL, extratemporal lobe, and with bilateral IEDs (45%), although this was not statistically significant. It remains unclear why bilateral discharges occur in hippocampal sclerosis. This may represent additional less severe contralateral hippocampal sclerosis (Margerison and Corsellis 1966) and independent bitemporal excitability (Sirven et al. 1997), or secondary epileptogenesis reflecting a “mirror focus” (Sammaritano et al. 1987). Therefore, bilateral IEDs may decrease the chances of a favorable postoperative outcome in patients with hippocampal sclerosis (Schulz et al. 2000).

5.4 Intraoperative electrocorticography vs. seizure outcome

5.4.1 Pre-resection electrocorticography vs. seizure outcome

There have been several studies on ECoG and seizure outcomes after surgical treatment of mesial temporal lobe epilepsy. Some investigators reported that persistent spikes after temporal lobectomy were associated with a poorer outcome (Bengzon et al. 1968; Fiol et al. 1991; Jasper et al. 1961; McBride et al. 1991; Rasmussen 1983; So et al. 1989; Wyllie et al. 1987). Others found no significant relation between the presence of post-resection spikes and seizure outcome (Cascino et al. 1995; Devinsky et al. 1992; Falconer and Serafetinides 1963; Kanazawa et al. 1996). Furthermore, Engel et al. in a study of 59 patients subjected to a standard unilateral anterior temporal lobectomy found a trend toward worse outcome in patients with predominantly lateral as opposed to mesial temporal spikes foci (Engel, Jr. et al. 1975). However, in most of these studies the extent of the resection was guided by the ECoG findings and, therefore, the correlation of ECoG findings with surgical outcome was not analyzed independently. More recently two studies were performed in patients

who underwent antero-mesial temporal lobectomy regardless of ECoG findings (Schwartz et al. 1997; Tran et al. 1995). These showed that intraoperative ECoG findings were not significantly related to seizure outcome. However, in the larger study of 47 patients pre-resection spikes localized to the posterior temporal neocortex (not included in the resection) were more frequent in patients with seizure recurrence (64%) than in seizure free patients (39%). This difference of 25% was not statistically significant but could be regarded as clinically relevant (Tran et al. 1995) and resembles the differences found in the present study. None of these studies on ECoG in TLE had sufficient power to prove or exclude a clinically relevant predictive effect. There are three previous studies on the prognostic relevance of ECoG in patients undergoing sAHE including only up to 16 patients (Cendes et al. 1993; McBride et al. 1991; Niemeyer 1958). These studies, however, provide no data regarding the predictive value of the localization of spikes recorded in the pre-resection ECoG. The relevance of pre-resection ECoG for outcome was not investigated by Cendes et al. (Cendes et al. 1993) and Niemeyer did not correlate ECoG-findings with outcome (Niemeyer 1958). McBride et al. reported on 15 patients undergoing a transsylvian sAHE who were part of a larger mixed group of 76 patients (McBride et al. 1991). They found that in the subgroup of 58 TLE patients subtemporal spiking was associated with a lower likelihood to record spikes outside the temporal lobe and that a post-resection reduction in spiking of less than 50% was associated with a poorer seizure outcome in this group (McBride et al. 1991). However, outcome was not correlated with the presence of spikes outside the area of resection. Unfortunately, data for the sAHE group were not analyzed separately. Our study suggests that the presence of spikes restricted to the MTL may indicate a higher likelihood to obtain a seizure-free outcome. Therefore, a larger prospective study is warranted to evaluate this issue further.

5.4.2 Post-resection electrocorticography vs. seizure outcome

New epileptiform discharges can appear after the resection. When recorded along the margin of the resection, they may represent a cortical disturbance caused by the manipulation of the brain at the time of surgery and may not have prognostic significance. Some authors hypothesized that discharges at some distance from the

resection margin may be more predictive of a poor surgical outcome (Keene et al. 2000). However, this still remains controversial, especially in patients in whom sAHE was done. In this situation, new epileptiform discharges were often recorded from the temporal cortex after completion of the procedure. These discharges were found to have no predictive value (Blume et al. 1997; Cendes et al. 1993). Cendes et al. reported on 16 patients with MTLE including two lesional cases undergoing sAHE by a transtemporal transsulcal approach. Similar to earlier observations by Niemeyer (Niemeyer 1958), they reported an increase in spiking from the most anterior temporal area following the resection in all patients and suggested that acute disconnection between lateral cortex and mesial structures may explain this observation. Similarly, our results indicate, that post-resection ECoG has no predictive value regarding outcome. The persistence of spikes in our study was actually more frequent in completely seizure free patients as compared to those not becoming seizure free.

5.4.3 Frequency of electrocorticography spikes vs. seizure outcome

ECoG rarely records ictal events, but rather interictal epileptiform activity. The relationship between the epileptic zone (area of origin of the epileptic seizure) and the irritative zone (area of cortex that generates interictal epileptiform discharges) is not completely understood. In particular, the degree to which the two zones overlap, especially on the ECoG recording is unclear. It has been hypothesized that the more frequent these discharges are within an area, the more likely it is that this area lies within the epileptic zone (Alarcon et al. 1997). If the area of maximal discharge was completely removed, the surgical outcome was more likely to be favorable. Alarcon et al. (Alarcon et al. 1997) by using a computerized spike detection program found that the removal of the area with most frequent epileptiform discharges was associated with a good postoperative seizure outcome, even if areas with less frequent discharges were left untouched. The study by Tran et al. (Tran et al. 1995) did not find association between surgical outcome and frequency of epileptiform discharges on pre-resection and post-resection ECoG, using a conventional visual analysis of the ECoG recorded by the electroencephalographer. Different analyzing methods used by both studies might contribute to their different conclusions. In our study, a visual analysis of ECoG was also used and a trend could be found that patients with frequent

spiking on pre-resection ECoG were less frequently seizure free as compared to those with infrequent spiking, although this difference was not statistically significant. Frequent spiking, especially when continuous, has been found to be associated with cortical dysplasia (Palmini et al. 1995; Rosenow et al. 1998). In this series of patients with HS the recording of continuous frequent spiking or of polyspikes did not exclude seizure-free outcome. New methods of analysis of intraoperative ECoG activity are needed to address these issues further.

McBride et al. (McBride et al. 1991) reported a correlation between low frequency spiking of less than 1 spike in 4 minutes and a poorer outcome in five out of 6 patients who showed this finding. This group may be similar to our patients with no recorded spikes, who had a worse outcome as compared to those with MTL spikes only. Given the small number of patients with this finding undergoing sAHE (1 in the study by McBride et al. and 7 in our study) no firm conclusions can be drawn. The lack of mesial temporal spikes represents a lack of supportive evidence for an epileptogenic zone located in the MTL and may indicate a different pathophysiology as compared to patients with MTL spiking.

5.5 Pre-resection electrocorticography and presurgical electroencephalography

We found that the patients with both preoperative IEDs restricted to the TL or ATL and pre-resection ECoG spikes restricted to the MTL remained more often seizure free than other patients. Although these differences were not statistically significant, they were clinically relevant. Surface EEG has been widely used in the preoperative diagnosis in patients with intractable epilepsy and can usually predict the seizure origin and postoperative seizure outcome. However, because cerebral activity is attenuated by the impedance of the cerebrospinal fluid, meninges, skull and scalp, and interictal activity arising from deep or midline structures is usually not reflected on surface EEG, the distribution of IEDs can sometimes fail to localize the region or hemisphere of seizure origin, (Hamer et al. 1999). It has been reported that IEDs in hippocampal sclerosis have a very localized field which is frequently missed by scalp electrodes (So 2001). The value of intraoperative ECoG in predicting location of the seizure focus still remains controversial. Whereas, ECoG has the advantage to record signals from relatively small areas of cortex and to record interictal activity arising

from the mesial temporal regions. Consequently, it may be more reliable, if the results of preoperative surface EEG and the findings of intraoperative ECoG especially pre-resection ECoG are combined to localize the epileptogenic zone and to predict postoperative seizure outcome in patients with hippocampal sclerosis.

6 CONCLUSION

1. Pre-resection ECoG may be helpful in the prediction of seizure outcome in patients undergoing selective amygdalohippocampectomy for mesial temporal lobe epilepsy. Patients with ECoG spikes restricted to the mesial temporal lobe remained seizure free more often than others. Pre-resection spikes of lower frequency tended to be associated with a better postoperative seizure outcome than those of higher frequency.
2. Post-resection ECoG had no predictive value regarding seizure outcome.
3. The lateralization of interictal epileptiform discharges on preoperative surface EEG was associated with seizure outcome. Patients with unilateral temporal IEDs on preoperative surface EEG became seizure free more frequently than those with bilateral and / or extratemporal IEDs.
4. A combination of the results of preoperative surface EEG and the findings of intraoperative ECoG especially pre-resection ECoG may be more reliable to localize the epileptogenic zone and to predict postoperative seizure outcome in patients with hippocampal sclerosis.
5. In order to prove further or exclude the predictive value of the findings regarding intraoperative ECoG, a large prospective study with more than 102 patients is necessary.

7 ZUSAMMENFASSUNG

Die Elektrokortikographie (ECoG) wird seit langer Zeit als ein Routineverfahren in der Epilepsiechirurgie angewendet. Dennoch sind die klinische Rolle und der Nutzen noch strittig. Die Ergebnisse der meisten früheren Untersuchungen waren davon beeinflusst, dass der Umfang der Resektion durch den Befund der intraoperativen ECoG beeinflusst wurde oder dass läsionelle und nicht-läsionelle Fälle eingeschlossen wurden, so dass die prognostische Bedeutung des intraoperativen Befundes bezüglich der Anfallsprognose nicht unabhängig analysiert werden konnte. Die selektive Amygdalohippokampektomie (sAHE) wird schon seit den 50er Jahren eingesetzt und ist heutzutage zur chirurgischen Behandlung der Temporallappenepilepsie weitverbreitet. Bisher wurden nur wenige Studien über die Rolle der ECoG bei sAHE publiziert.

Ziel der vorliegenden Studie war es, den prädiktiven Wert der ECoG und der oberflächen Elektroenzephalographie (EEG) bei Patienten mit einer pharmakoresistenten mesialen Temporallappenepilepsie (MTLE) aufgrund einer einseitigen Hippocampus-Sklerose (HS) zu untersuchen.

Bei 22 Patienten mit pharmakoresistenter MTLE und HS wurde prä- und postresektionell routinemäßig eine ECoG durchgeführt. Die sAHE erfolgte standardisiert und ohne Berücksichtigung der intraoperativen ECoG-Befunde. Die vom mesiobasalen Temporallappen (MTL) und lateralen Temporallappen (LTL) prä- und postresektionell registrierten ECoG-Befunde sowie die präoperativ aufgezeichneten EEG-Befunde wurden mit dem postoperativen Anfallsverlauf korreliert. Es wurden vier ECoG-Gruppen gebildet: 1) ausschließlich MTL Spikes, 2) keine Spikes, 3) ausschließlich LTL Spikes, 4) MTL und LTL Spikes.

Außerdem wurden laut der Verteilung der präoperativen interiktalen epilepsietypischen Potentiale (IEDs) vier Gruppen gebildet: 1) ipsilaterale anterior temporale IEDs, 2) ipsilaterale temporo-laterale IEDs, 3) ipsilaterale extratemporale IEDs, 4) kontralaterale IEDs.

Der Nachuntersuchungszeitraum nach sAHE lag bei 12 Monaten. Nach Anfallsverlauf wurde in 2 Gruppen eingeteilt: 1) vollständig anfallsfrei (Engel-Klassifikation Ia), 2) nicht vollständig anfallsfrei.

Die statistische Auswertung erfolgte mittels Fisher´s exaktem Test.

Fünfzehn Patienten (68%) blieben vollständig anfallsfrei (Engel Ia) und 19 Patienten (86%) blieben postoperativ in Engel-Klasse I.
Präoperativ wurden IEDs bei 21 Patienten mit HS gefunden. Die Patienten mit ipsilateralen temporalen IEDs blieben häufiger anfallsfrei (92%) als Patienten mit bilateralen und / oder ipsilateralen extratemporalen IEDs (25%)(p = 0,003). Patienten mit auf den anterioren Temporallappen (ATL) beschränkten IEDs hatten leicht bessere Anfallsprognose (90%) als die Patienten mit ipsilateralen LTL-IEDs, extratemporalen IEDs und bilateralen IEDs (45%)(p = 0,06).
Präresektionelle ECoG-Spikes waren bei 11 Patienten auf den MTL beschränkt und wiesen bei weiteren 11 Patienten andere Verteilungen auf. Diejenigen Patienten, die präresektionell auf den MTL beschränkte Spikes hatten, blieben im Vergleich zur anderen Hälfte der Patienten häufiger anfallsfrei (82% vs. 55%, p=0.36). Zwei der vier Patienten mit LTL-Spike Wave und vier der sieben Patienten ohne präresektionelle Spike Wave blieben anfallsfrei. Es bestand auch ein Trend für ein besseres Outcome, wenn die Spike-Frequenz niedriger war. Dagegen zeigte die Persistenz von Spikes nach der Resektion keinen wesentlichen Einfluß auf die Anfallsprognose.
Bei 9 Patienten waren sowohl die präoperative IEDs auf den Temporallappen beschränkt als auch die präresektionelle ECoG-Spikes auf den MTL beschränkt. Acht aus dieser Gruppe (89%) blieben anfallsfrei, dagegen sind 7 von den anderen 13 Patienten (54%) anfallsfrei geworden (p = 0,16). Unter 7 Patienten, die präoperativ auf den ATL beschränkte IEDs und präresektionell auf den MTL beschränkte ECoG-Spikes hatten, blieben sechs Patienten (86%) anfallsfrei, hingegen nur 9 von den anderen 15 Patienten (60%) nach sAHE (p = 0,35).

Zusammenfassend läßt sich schlussfolgern, dass die präresektionelle ECoG möglicherweise bei der Bewertung der postoperativen Anfallsprognose von Patienten mit pharmakoresistenter MTLE nach sAHE hilfreich ist. Patienten mit auf den mesiobasalen TL beschränkten Spikes bleiben nach sAHE 27% häufiger anfallsfrei. Um diesen Unterschied statistisch abzusichern, wäre eine größere (multizentrische) Studie mit mindestens 102 Fällen erforderlich. Es besteht ein Trend für ein besseres Outcome, wenn die Spike-Frequenz niedriger ist.

Der Nachweis des präoperativen IEDs hat einen Einfluss auf die Anfallsprognose. Patienten mit unilateralen temporalen EEG-IEDs bleiben häufiger anfallsfrei als Patienten mit bilateralen und / oder extratemporalen EEG-IEDs. Eine Verknüpfung der Befunde des präoperativen EEGs und der intraoperativen ECoG könnte bei der Bewertung der Anfallsprognose nach sAHE hilfreich sein.

Darüber hinaus regt die vorliegende Arbeit weitere Studien an, um neue Methoden zur Analyse der intraoperativen ECoG-Aktivität zu finden und die Beziehung zwischen der Natur der epileptogenen Läsion, ECoG- und EEG-Befunden, sowie Anfallsprognose genauer zu verstehen.

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9 APPENDIX

9.1 Abbreviations

3T PA-MRI	3 Tesla phased array MRI
ABCN	American Board of Clinical Neurophysiology
AEDs	antiepileptic drugs
AHP	afterhyperpolarization potential
ATL	anterior temporal lobe
DGKN	German Society of Clinical Neurophysiology
ECoG	electrocorticography
EEG	electroencephalography
EPSPs	excitatory postsynaptic potentials
FLAIR	fluid-attenuated inversion recovery
fMRI	functional MRI
FO	foramen ovale
fTCD	functional transcranial doppler-sonography
HS	hippocampal sclerosis
IEDs	interictal epileptiform discharges
ILAE	the international League Against Epilepsy
IPSPs	inhibitory postsynaptic potentials
LTL	lateral temporal lobe
MCA	middle cerebral artery
MEG	magnetoencephalography
MRI	magnetic resonance imaging
MTL	mesial temporal lobe
MTLE	mesial temporal lobe epilepsy
PET	positron-emission tomography
PSPs	postsynaptic potentials
sAHE	selective amygdalohippocampectomy
SPECT	single-photon emission computed tomography
TL	temporal lobe
TLE	temporal lobe epilepsy

9.2 List of Figures

9.3 List of Tables

9.4 Publikationen

Originalartikel

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9.5 Akademische Lehrer

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ORIGINAL ARTICLE

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Predictive value of electrocorticography in epilepsy patients with unilateral hippocampal sclerosis undergoing selective amygdalohippocampectomy

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Abstract The purpose of this study was to evaluate the predictive value of intraoperative electro-corticography (ECoG) in patients with unilateral hippocampal sclerosis (HS) undergoing transsylvian selective amygdalohippocampectomy (sAHE). ECoG was recorded before and after resection in 22 patients with medication-resistant mesial temporal lobe epilepsy. The sAHE was performed, regardless of ECoG findings. ECoG findings recorded from the mesiobasal temporal lobe (MTL) and lateral temporal lobe (LTL) before and after the sAHE were correlated with seizure outcome 12 months later. Ten patients had right-sided and 12 left-sided HS. Average age was 37.1 years. Pre-resection spikes were restricted to the MTL in 11 patients and to the LTL in one. In three patients spikes were recorded from MTL and LTL and in seven no spikes were recorded before the resection. Fifteen patients (68%) remained completely seizure-free and 19 (86%) were in Engel's class I post-operatively. Patients with pre-resection spikes restricted to the MTL (n=11) remained seizure-free more frequently (9/11, 82%) compared with other patients (6/11, 55%; P=0.36). Pre-resection ECoG may be helpful in the prediction of seizure outcome in patients undergoing sAHE for mesial temporal lobe epilepsy. A larger study including more than 100 patients is needed to determine the predictive value of ECoG in patients with mesial temporal lobe epilepsy.

Keywords Electrocorticography · Selective amygdalohippocampectomy · Temporal lobe epilepsy · Mesial temporal sclerosis · Seizure outcome

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Introduction

Even though electro-corticography (ECoG) has been used by many centers for a long time as a standard procedure, its role and clinical utility remains controversial. Some authors have emphasized the importance of pre- and postoperative ECoG in guiding the extent of both mesial and lateral temporal lobe resections [1, 9, 10, 14, 18, 23, 27], others have advanced a standard operation regardless of ECoG findings [2, 5, 8, 11, 17, 26]. In most reports, the extent of the resection was influenced by the ECoG findings and patients with both, lesional and nonlesional, epilepsy were included [1, 2, 5, 8–11, 15, 23, 26, 27]. Even though selective amygdalohippocampectomy (sAHE) was initially described in 1958 [15] and introduced into clinical practice in the late 1970s [12], few studies have addressed the role of ECoG in sAHE [3, 14, 15]. We retrospectively studied the prognostic value of intraoperative ECoG findings in patients with unilateral hippocampal sclerosis (HS), who underwent a standard sAHE, regardless of the ECoG findings. We hypothesized that pre-resection spikes restricted to the mesiobasal temporal lobe (MTL) may indicate a restricted mesial temporal epileptogenic zone and, therefore, a good outcome, whereas pre-resection lateral temporal lobe (LTL) spikes might indicate a more extensive epileptogenic zone, e.g., dual pathology (HS and MR-negative cortical dysgenesis), an entity known to be associated with poorer seizure outcome [22] and possibly not adequately treated by sAHE. Furthermore, we inves-

tigated the question of whether the disappearance of pre-resection spikes following the resection predicts a better seizure outcome.

Material and methods

Patient selection

All patients with medication-resistant unilateral mesial temporal lobe epilepsy and MRI evidence of mesial temporal sclerosis without other lesions, who underwent sAHE by a transsylvian approach at the Interdisciplinary Epilepsy Center, Marburg between 2000 and 2003 were included. Patients with evidence of bilateral seizure onset were excluded. Twenty-two patients met these criteria and underwent intraoperative ECoG and sAHE. All patients received noninvasive presurgical evaluation that included video-EEG monitoring with sphenoidal electrodes, neuropsychological testing and an MRI of the head including coronal T2 and FLAIR images perpendicular to the axis of the hippocampus. An intracarotid amobarbital test (n=17) and functional transcranial Doppler sonography (fTCD, n=11) were used when necessary.

Intraoperative ECoG recording

Pre-resection recordings were made unilaterally as a standard procedure, using a strip electrode (1×8 contact with 1-cm spacing, AD-TECH medical instrument corporation, Racine, Wis., USA) sequentially positioned over the lateral temporal surface and, following the preparation of the sylvian fissure, over the mesial-basal temporal region (Fig. 1). Post-resection recording was made from the same positions only if pre-resection spikes had been recorded. Pre- and post-resection ECoG activity was recorded for a minimum of 2 min per position. Recordings were referential using a scalp reference. The sensitivity was set to 300 or 500 μV/cm, the high and low frequency filters were 70 Hz and 0.5 Hz, a 50 Hz notch filter was used when necessary. The ECoG was usually recorded digitally with 200 samples/s using the Brainlab® software (Schwarzer, Munich, Germany). Occasionally paper recordings were used (ED24, Schwarzer, Munich, Germany).

Surgery

All patients were treated by a standardized unilateral sAHE using a transsylvian transsventricular approach [28], including the microsurgical excision of the head and the anterior body of the hippocampus, the amygdala, parts of the uncus, with preservation of the fusiform gyrus and parts of the parahippocampal gyrus. The extent of the resection was not influenced by the ECoG results. The antiepileptic medication was continued unchanged and sevoflurane 0.4–0.7% (Sevorane) and sufentanil (Sufenta) were used to maintain anesthesia during and before the ECoG.

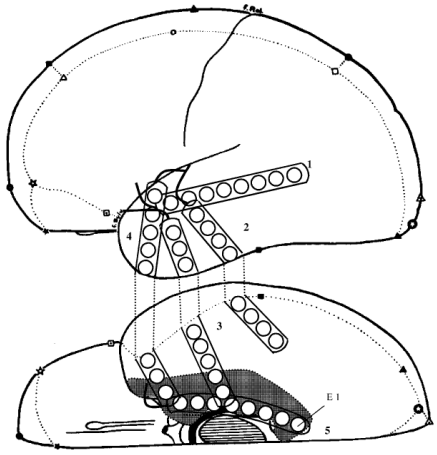

Fig. 1 Placement of electrocorticography strip electrodes. Definition of the regions mesiobasal versus lateral temporal lobe

ECoG analysis

All ECoG data were sampled by experienced, board certified (ABCN) clinical neurophysiologists (F.R., H.M. H.) and were reviewed retrospectively by one electroencephalographer who was blinded to the outcomes of the patients. The position of the strip electrode was marked in a drawing during the operation. A spike was defined as a paroxysmal fast transient waveform with a pointed peak and negative polarity with an amplitude of at least twice as high as the background activity and lasting less than 80 ms [20]. ECoG results were classified by the presence and localization of spikes recorded (see Fig. 1). According to pre-resection ECoG findings, patients were divided into the following subgroups: (1) pre-resection spikes restricted to the MTL; (2) pre-resection spikes both in MTL and LTL; (3) pre-resection spikes restricted to the LTL; (4) no pre-resection spikes recorded. For each of the recording sites, the electrode contact with the greatest number of spikes was identified and the spike-pattern was classified as described previously [20]: (1) infrequent spiking (<5 spikes/10 s), (1a) continuous infrequent spiking (pattern 1 lasting for ≥30 s), (2) frequent spiking (5–20 spikes/10 s), (2a) continuous frequent spiking (pattern 2 lasting for ≥30 s), (3) very frequent spiking (>20 spikes/10 s), (3a) continuous very frequent spiking (pattern 3 lasting for ≥30 s).

Outcome and follow-up

The follow-up time was 12 months. Based on seizure occurrence after sAHE, patients were divided into two

groups: group 1 included only patients completely free of seizures and auras (Engel Classification Ia) [7]; group 2 included patients with post-operative occurrence of any types of seizure or aura.

Statistical analysis

The main hypothesis tested was whether or not patients with pre-resection spikes restricted to the MTL have a higher seizure-free rate than patients with other ECoG findings, such as LTL only, MLT+LTL or no spikes.

Furthermore, the influence of the spike frequency and the persistence of spikes after the sAHE on seizure outcome was analysed. Fisher's exact test was used. The results were considered to be statistically significant when $P<0.05$. The software SAS 8.1 was used for statistical analysis. Based on the results of this study, the number of patients needed to provide statistical evidence of a predictive value of certain spike distributions was calculated.

Results

Twelve (55%) of 22 patients were women. The age at the time of operation ranged from 10 to 57 years (mean 37.1 years). Twelve patients (55%) underwent a left-sided and ten a right-sided sAHE. Fifteen of 22 patients (68%) were completely free of seizures and auras (group 1), seven patients (32%) were in group 2 (three were Ib, one was Ic, one was IIb, two were IIIa). Thus, a total 19 patients (86%) were Engel class I (Table 1).

Pre-resection ECoG results

In 11 patients (50%), spikes were restricted to the MTL. In one of the remaining 11 patients spikes were recorded only from the LTL, three had spikes in both MTL and LTL and in seven patients no spikes were recorded (Table 1, Fig. 2a). Patients with pre-resection spikes restricted to the MTL remained seizure-free more frequently (82%) compared with the remainder of the patients (55% group 1). This difference was not statistically significant ($P=0.36$). Two of four patients with LTL-spikes and four of seven patients without pre-resection spikes remained seizure-free (Table 2, Fig. 3). Based on these data, it was calculated that a minimum of 102 patients is needed to evaluate such a 27% difference in outcome with a power of 80% and a significance level of 0.05 using a two-sided test. In order to prove a clinically still significant difference of 20% in outcome and assuming a less equal distribution regarding the ECoG groups, a study with 220 patients would be necessary.

The patterns of interictal ECoG-spikes observed included frequent spiking (nine patients, five in group 1) and infrequent spiking (six patients, all in group 1), very

Table 1 Patient characteristics, ECoG results and seizure outcome

Age (years)	Sex[a]	Side of HS (MRI)[b]	Localization of epileptiform potentials during surface video-EEG monitoring[c]	ECoG (pre-OP)[d]		ECoG (post-OP)[d]		Outcome group (Engel class)[e]
				MTL	LTL	MTL	LTL	
47	m	R	RATL	+		++		1 (Ia)
23	f	L	LATL	++		+		1 (Ia)
19	f	L	LTL	+				1 (Ia)
45	f	L	LATL	++		+		1 (Ia)
32	f	L	LTL	++				1 (Ia)
40	f	L	LATL	++				2 (IIIa)
38	m	L	LATL	+		+		1 (Ia)
37	f	R	RATL	+		+		1 (Ia)
57	m	R	RTL	+				1 (Ia)
33	f	R	RTL	++		++		1 (Ia)
22	f	R	RTL	++		+		2 (IIb)
39	f	L	LATL +LFL	++, CS	+	++	+	2 (Ib)
10	f	L	LPTL	++	+			2 (Ic)
19	m	R	RTL	++, CS	++	+	+	1 (Ia)
46	m	R	RTL		+, PS	+, PS	++, PS	1 (Ia)
33	f	R	RTL					2 (Ib)
38	m	R	RTL					1 (Ia)
51	m	L	LATL			+	++, PS	2 (IIIa)
44	f	L	LTL					1 (Ia)
41	m	L	LTL					1 (Ia)
57	m	L	LATL			ND	ND	1 (Ia)
45	f	R	RATL					2 (Ib)

[a] *f* female, *m* male
[b] *R* right, *L* left
[c] *RATL* right anterior temporal lobe, *LATL* left anterior temporal lobe, *RTL* right temporal lobe, *LTL* left temporal lobe, *LFL* left frontal lobe, *LPTL* left posterior temporal lobe
[d] *OP* operation, *MTL* mesiobasal temporal lobe, *LTL* lateral temporal lobe, *PS* polyspikes, *CS* continuous spikes, + <5 spikes/10 s (infrequent spiking), ++ 5 20 spikes/10 s (frequent spiking), *ND* ECoG was not done
[e] *Outcome group 1* completely seizure-free (Engel class Ia), *group 2* not completely seizure-free

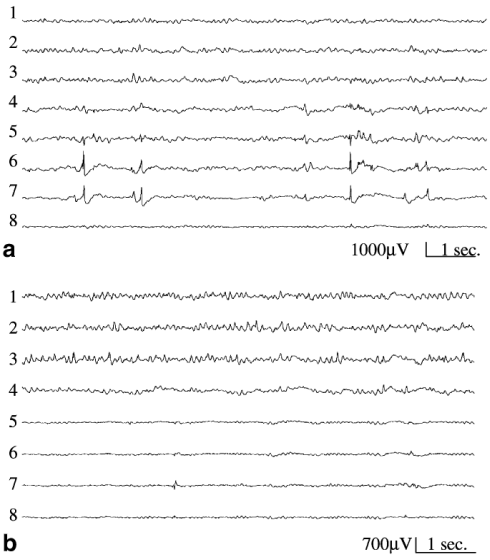

Fig. 2a, b ECoG of patient no.4. **a** Pre-resection ECoG showing frequent spiking (5 20 spikes/10 s) recorded from anterior mesial temporal lobe only [position 5 (Fig. 1), electrodes 5 7]. **b** Post-resection ECoG from the same position showing infrequent spiking (<5 spikes/10 s, electrode 7) and a low amplitude background activity (electrodes 5 8)

frequent spiking was not recorded. Continuous frequent spiking was recorded from MTL in two patients. One remained completely seizure-free and the other had seizures during the follow-up. Polyspikes were recorded from LTL in one patient who remained completely seizure-free. In the nine patients with frequent spiking (>5 spikes/10 s) a seizure-free outcome was non-significantly less frequent (56%) than in those six with infrequent spikes who all became seizure-free (P=0.1; Table 3). In summary, the frequency of pre-resection spikes was not consistently related to seizure outcome.

Table 2 Seizure outcome with regard to the distribution of pre-resection spikes (in MTL only vs others)

Distribution of pre-resection spikes	Seizure-free (group 1)	Persistent seizures (group 2)
MTL spikes only (n=11)	9 (82%)	2 (18%)
Other groups (n=11)	6 (55%)	5 (45%)
-MTL and LTL spikes	1	2
-LTL spikes only	1	0
-No spikes recorded	4	3
Total	15 (68%)	7 (32%)
P=0.36		

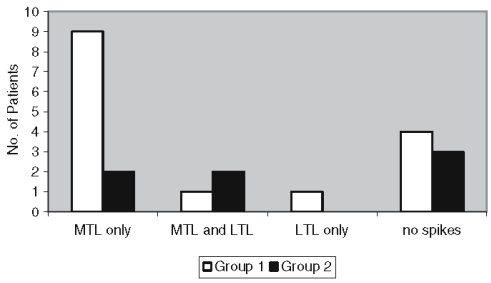

Fig. 3 The number of patients with different spike-distributions in the outcome group 1 (completely seizure-free) and group 2 (not completely seizure-free)

Post-resection ECoG results

In five of the 15 patients with pre-resection spikes these were no longer recorded after the resection and three (66%) of these remained seizure-free. Of the ten patients with persistent spikes, eight (80%) remained seizure-free. There was no correlation between seizure outcome and the presence of persistent spikes recorded on post-operative ECoG (Table 4, Fig. 2b).

Discussion

The main finding of this study is that patients with pre-resection spikes restricted to the mesiobasal temporal lobe tended to have a better outcome (82%) compared with all other groups (55%). The frequency of pre-resection spikes and the persistence of pre-resection spikes on post-resection ECoG were not related to seizure outcome.

Pre- and post-resection ECoG vs seizure outcome

There have been several studies on ECoG and seizure outcomes after surgical treatment of mesial temporal lobe epilepsy. Some investigators reported that persistent spikes after temporal lobectomy were associated with a poorer outcome [1, 9, 10, 14, 18, 23, 27]. Others found no significant relation between the presence of post-resection spikes and seizure outcome [2, 5, 8, 11, 26]. Furthermore, Engel et al. [6] in a study of 59 patients subjected to a

Table 3 Seizure outcome with regard to the spike frequency on pre-resection ECoG (*Group 1* completely seizure-free, *Group 2* not completely seizure-free)

Frequency of spiking	Group 1	Group 2
Frequent spiking (5 20 spikes/10 s)	5 (56%)	4 (44%)
Infrequent spiking (<5 spikes/10 s)	6 (100%)	0 (0%)
Total	11 (73%)	4 (27%)
P=0.10		

Table 4 Seizure outcome with regard to the persistence of pre-resection spikes on post-resection ECoG (*Group 1* completely seizure-free, *Group 2* not completely seizure-free)

Pre-resection spikes on post-resection ECoG	Group 1	Group 2
Persisting	8 (80%)	2 (20%)
Disappearing	3 (60%)	2 (40%)
Total	11 (73%)	4 (27%)
P=0.56		

standard unilateral anterior temporal lobectomy found a trend toward worse outcome in patients with predominantly lateral as opposed to mesial temporal spike foci. However, in most of these studies the extent of the resection was guided by the ECoG findings and, therefore, the effect of ECoG spikes on the surgical outcome was not analysed independently. More recently, two studies were performed on patients who underwent antero-mesial temporal lobectomy regardless of ECoG findings [21, 24]. These showed that intraoperative ECoG findings were not significantly related to seizure outcome. However, in the larger study of 47 patients, pre-resection spikes localized to the posterior temporal neocortex (not included in the resection) were more frequent in patients with seizure recurrence (64%) than in seizure-free patients (39%). This difference of 25% was not statistically significant but could be regarded as clinically relevant [24] and resembles the differences found in the present study. None of these studies on ECoG in TLE had sufficient power to prove or exclude a clinically relevant predictive effect.

There are three previous studies on the prognostic relevance of ECoG in patients undergoing sAHE, including up to 16 patients [3, 14, 15]. These studies, however, provide no data regarding the predictive value of the localization of spikes recorded in the pre-resection ECoG. The relevance of pre-resection ECoG for outcome was not investigated by Cendes et al. [3] and Niemeyer [15] did not correlate ECoG-findings with outcome. McBride et al. [14] reported on 15 patients undergoing a transsylvian sAHE who were part of a larger mixed group of 76 patients. They found that in the subgroup of 58 TLE patients subtemporal spiking was associated with a lower likelihood to record spikes outside the temporal lobe and that a post-resection reduction in spiking of less than 50% was associated with a poorer seizure outcome in this group [14]. However, outcome was not correlated with the presence of spikes outside the area of resection. Unfortunately, data for the sAHE group were not analysed separately. Our study suggests that the presence of spikes restricted to the MTL may indicate a higher likelihood of obtaining a seizure-free outcome. Therefore, a larger prospective study is warranted to further evaluate this issue.

Cendes et al. [3] reported on 16 patients with MTLE including two lesional cases undergoing sAHE by a transtemporal transsulcal approach. Similar to earlier observations by Niemeyer [15], they reported an increase in spiking following the resection in all patients, and suggested that acute disconnection between lateral cortex and mesial structures may explain this observation. Similarly, our results indicate that post-resection ECoG has no predictive value regarding outcome. The persistence of spikes in our study was actually more frequent in completely seizure-free patients compared with those not becoming seizure-free.

McBride et al. [14] found a correlation between low frequency spiking of less than one spike in four min and a poorer outcome in five out of six patients who showed this finding. This group may be similar to our patients with no recorded spikes, who had a worse outcome compared with those with MTL spikes only. Given the small number of patients with this finding undergoing sAHE (one in the study by McBride et al. and seven in our study) no firm conclusions can be drawn. The lack of mesial temporal spikes represents a lack of supportive evidence for an epileptogenic zone located in the MTL and may indicate a different pathopysiology compared with patients with MTL spiking.

Frequent spiking, especially when continuous, has been found to be associated with cortical dysplasia [16, 20]. In this series of patients with HS the recording of continuous frequent spiking or of polyspikes did not exclude seizure-free outcome. Patients with frequent spiking were less frequently seizure-free compared with those with infrequent spiking; however, this difference was not significant.

Methodological considerations

It is widely accepted that the postoperative prognosis in temporal lobe epilepsy depends on etiology and that seizure outcome is also influenced by the extension and completeness of the resection of a lesion [4, 6, 7, 27]. Therefore, we only included patients undergoing a standard sAHE and only patients with MRI evidence of mesial temporal sclerosis and no other lesions. MRI findings have been shown to be highly accurate for in vivo diagnosis of HS [13], while some coexisting abnormalities, such as neuronal heterotopias and microdysgenesis, can often only be detected microscopically or by special imaging analysis techniques and are predictive of a poorer outcome [22]. Since temporal neocortex was not resected in this series, we cannot comment on the correlation of LTL spikes and dual pathology. Patients in Engel class 1a were compared with the remainder because complete seizure freedom has the most relevant impact on the patients quality of life [25] and the persistence of any seizures indicates that the epileptogenic zone has not been completely resected [19].

Conclusion

Pre-resection ECoG may be helpful in the prediction of seizure outcome in patients undergoing selective amygdalohippocampectomy for mesial temporal lobe epilepsy. Patients with ECoG spikes restricted to the mesio-basal temporal lobe more frequently remained seizure-free than

others. In order to prove or exclude the predictive value of this finding a large prospective study is necessary.

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