Role of epileptogenic lesions in the development of interictal and ictal epileptic disturbance

Ph.D. thesis

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Abbreviations

ADNFLE: Autosomal dominant nocturnal frontal lobe epilepsy

CPS: Complex partial seizures

DNT: Dysembrioplastic neuroepithelial tumor

EL: epileptogenic lesion

ER: Epileptogenic region

FCD: Focal cortical dysplasia

FLE: Frontal lobe epilepsy

HS: Hippocampal sclerosis

IEDs: Interictal epileptiform discharges

ILAE: International League Against Epilepsy

LRFD: local repetitive fast discharges

MRI: Magnetic resonance imaging

MRS: Magnetic resonance spectroscopy

PET: Positron emission tomography

PIV: Pure ictal vocalizations

ref: The number of the reference cited in the Bibliography

SBS: Secondary bilateral synchronization

SGTCS: secondarily generalized tonic-clonic seizures.

SMA: Supplementary motor area

SNH: Subependymal nodular heterotopia

SPECT: Single photon emission computed tomography

SSA: Somatosensory aura

TLE: Temporal lobe epilepsy

Epileptogén léziók szerepe az interiktális és iktális epilepsziás működészavar kialakulásában

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Összefoglalás

A parciális epilepsziák leggyakoribb oka az agy szerkezeti rendellenessége, az epileptogén lézió (EL). MRI segítségével ma már lehetőségünk van az EL in vivo kimutatására. Vizsgálatainkban az EL és a humán epilepszia kapcsolatát elemeztük.

Tanulmányunkban vizsgáltuk az epilepsziás tükörfókuszt meghatározó tényezőket. Hippocampalis sclerosissal járó temporális lebeny epilepsziában (TLE) nem találtunk összefüggést az epilepszia fennállása és a kétoldali spike-ok jelenléte között. Az állatkísérletes eredményektől eltérően, eredményeink nem támasztják alá, hogy az epilepsziás betegek tükörfókuszát progresszív epileptogenesis okozza.

Öt epilepsziás beteg klinikai, EEG és neuroimaging adatait elemeztük, akiknél subependymális noduláris heterotópiát mutattunk ki a peritrigonális régióban. Valamennyi betegünk TLE szindrómában szenvedett az extratemporális EL ellenére.

Amikor vizsgáljuk azokat a prognosztikai tényezőket, melyek az EL sebészi eltávolítását követő rohammentességet determinálják, nem csak az epilepszia sebészi kezelési lehetőségéről, hanem a léziótól független epileptogén agyszövet kiterjedéséről is információt nyerünk. Azért, hogy meghatározzuk ezeket a tényezőket, 61 frontális lebeny epilepszia (FLE) miatt operált betegek adatait elemeztük. Megállapítottuk, hogy a generalizált EEG jelek, a szomatoszensoros aura (SSA), a generalizált rohamok és a negatív MRI sikertelen műtéti kezelést valószínűsít.

Az EL lokalizációjának ismeretében vizsgálni tudjuk az epilepsziás fókusz elhelyezkedése és a klinikai rohamjelenségek összefüggését. Ennek vizsgálata új információt nyújthat a egyes emberi agyi funkciók lokalizációjára és lateralizációjára. Az iktális lateralizációs jelek meghatározása céljából 27 FLE beteg videofelvételét elemeztük. SSA és a fej verziója minden esetben, klónus 92%-ban, míg tónusos megfeszülés 89%-ban a lézióval ellentétes oldalon jelentkezett. Iktális vokalizáció gyakoribb volt bal oldali EL esetében, ami valószínűsíti, hogy emberben nem csak a beszéd, hanem a subverbális szintű vokalizáció is bal féltekehez kötött jelenség.

Role of epileptogenic lesions in the development of interictal and ictal epileptic disturbance

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Summary

Structural brain abnormality (epileptogenic lesion, EL) is the most frequent cause of partial epilepsy. Nowadays, MRI permits us to detect EL in vivo. In our studies, we analyzed different aspects of the relationship between ELs and the human epilepsy.

We analyzed the factors determining the presence of mirror focus. In temporal lobe epilepsy (TLE) with hippocampal sclerosis, we found that the epilepsy duration has no influence on the presence of bitemporal spikes. Unlike the animal studies, our result does not support that the human mirror focus is caused by progressive epileptogenesis.

We evaluated the clinical, electrophysiological, and neuroimaging findings of five epileptic patients with peritrigonal subependymal nodular heterotopia. We concluded that they have TLE syndrome, despite the extratemporal EL.

Investigating the predictive factors for the outcome after the removal of the EL, we could obtain a clinically useful information on epilepsy surgery and on the spatial extension of the epileptogenic tissue independent of the EL. To identify prognostic factors for surgical success, we evaluated the data of patients with frontal lobe epilepsy (FLE) who had resective surgery. We found that generalized EEG signs, somatosensory aura (SSA), generalized seizures, and negative MRI predict the poor outcome.

The increasing knowledge about the localization of EL permits us to observe the relationship between the localization of epileptic focus (e.g. EL) and the clinical features of epilepsy, investigating this relationship provide new information on the localization of epileptogenic region as well as on the physiologic lateralization of human brain. To identify clinical ictal lateralizing signs, we re-evaluated video-recorded seizures of 27 FLE patients with EL. We found that SSA and head version exclusively, whereas clonus in 92%, tonic posturing in 89% appeared contralateral to the EL. Ictal vocalizations occurred more often in patients with left frontal EL, suggesting that not only speech, but vocalization at a subverbal level also shows a left-hemisphere dominance in humans.

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*Only the original author's publications related to the subject of the PhD Thesis are presented here.

1. Introduction

Epilepsy is the second commonest neurological disorder affecting 0.5-1% of the population.[57,80] The term *epilepsy* includes not only recurrent unprovoked seizures, but also ictal and interictal clinical, electric, metabolic, and perfusional disturbances of the human brain. These abnormalities are not only a subject of scientific investigations in order to understand the basic mechanism of epilepsy, but provide a great help in the diagnosis of epilepsy and in the multimodal localization of epileptic focus (*Table 1*).

Table 1. *Major types of ictal and interictal functional disturbances in epilepsy and the most frequently used investigation tools.*

	Ictal disturbance	**Interictal disturbance**
Clinical	1. auto- and heteroanamnesis	1. neurological
	2. ictal video recordings	2. neuropsychological examinations
Electrical	Ictal EEG	interictal EEG
Metabolic		PET
Perfusional	Ictal SPECT	interictal SPECT

The two major causes of epilepsy are genetic abnormality and acquired epileptogenic impairment.[57,98] Morphological brain abnormality (epileptogenic lesion) is the most common type of the acquired epileptogenic impairments[22], however, in some cases it may be itself a consequence of a genetic anomaly.[38,48,79] Cerebral dysgenetic malformations, tumors, and hippocampal sclerosis (HS) are the most frequent epileptogenic lesions.[22]

Although our knowledge about the etiology of epilepsy has been increasing during the past few years[68,69,98] , the current classification of epilepsies is based on the clinical features and EEG findings and not on the specific underlying etiology.[23] This was reasonable for 50-60 years, since till 1980s the EEG had been the only method for

characterizing the spatiotemporal brain abnormalities associated with epilepsy: epileptogenic lesions were detected only postmortem. In the last decade, however, with the increasing usage of new neuroimaging techniques (especially MRI), more and more data have been collected about the structural abnormalities associated with epilepsy.[10,48]

Describing clinical features and investigating the pathophysiology of human epilepsy, nowadays, we should use not only the EEG and clinical data, but also the information revealed by new neuroimaging techniques. Our classic knowledge about the clinical and pathophysiological features of epilepsy should be reevaluated in the highlight of the underlying structural abnormalities. One of the successes of this approach is the delineation of mesial temporal lobe epilepsy as a new entity, which seems to be one of the most consistent epilepsy syndrome with an unusually stereotyped clinical picture.[32,41,116] Moreover, the presence and the type of the MRI-detected epileptogenic lesion seems to be a predictive factor for the failure of pharmacological[66,126,136] and for the success of surgical[13,17,112135] treatment in localization-related epilepsies. Since the localization of the epileptogenic lesion highly correlates with the site of seizure origin[95,122,141] , high-resolution MRI is one of the most accurate non-invasive techniques in detecting the epileptogenic region.

Long-term video-EEG monitoring is a new technique for evaluating the ictal clinical features of epilepsy. The original descriptions of the epileptic seizures and syndromes were created at the beginning of the video-EEG era, consequently they were based on a limited number of video recordings, personal direct observations and on anamnestic data. Nowadays, our knowledge about the ictal clinical features of different epilepsy syndromes should be reevaluated on the basis of careful analyses of ictal video recordings.

This dissertation was written in “PhD Thesis+Publications” format, discussing five studies, which investigated the roles of epileptogenic lesions in human epilepsy. After some background information, we briefly described the purposes, and summarized the five original studies. We tried to highlight the most important results, this work is only a summary, the details are found only in the original papers.

2. Background

2.1. Lesional epilepsies

The current epilepsy classification divides the localization-related epilepsies into three major categories: idiopatic, cryptogenic, and symptomatic.[23] This classification does not consider the etiological factors. Except for three well-defined idiopatic localization-related syndromes, all localization-related epilepsies are classified as symptomatic if there is a definitive etiology; or as cryptogenic, supposing an "undetectable" underlying epileptogenic lesion. This approach, however, is no longer correct. In spite of the more and more accurate high-resolution MRI techniques, no epileptogenic lesion is found in many patients with partial epilepsy. These non-lesional partial epilepsies seem to make up a clinical entity[1], moreover, the response of non-lesional "cryptogenic" partial epilepsy to pharmacological and surgical treatment is different compared with lesional epilepsy.

There are at least three "new" genetically determined partial epilepsy syndromes described after the publication of the current epilepsy classification.[111,123,130] In autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) - one of these three epilepsy syndromes - a mutation was demonstrated in a gene coding the neuronal nicotinic acetylcholin receptor $\alpha 4$ subunit. More recently, a sporadic case with a de novo nicotinic acetylcholin receptor mutation was found.[110] The fact that a receptor gene mutation may lead to a well-defined localization-related epilepsy suggests that in many sporadic non-lesional partial epilepsy not an "undetectable" epileptogenic lesion but a hereditary or acquired receptor abnormality may be the cause of the epileptic disturbance. This hypothesis may explain the different clinical and pharmacological features of lesional and non-lesional epilepsies. In the future, the presence and the type of lesion should be included into the epilepsy classification.

2.2. The epileptic focus in lesional epilepsy

The "epileptic focus" is not a well-defined term, and its localization depends on the methodology used to delineate the epileptogenic tissue in the epileptic brain. The *epileptogenic lesion* (EL) is the structural abnormality, which is the original cause of the epilepsy. The *pacemaker area* or the ictal onset zone is the neuronal population, which

generates the seizures. The term *irritative zone* refers to the brain area, which is responsible for the interictal epileptiform discharges (IEDs) on the EEG. The *functional deficit zone* is the brain area responsible for the interictal neurological and neuropsychological deficits and seems to be hypofunctional on EEG and PET. The *symptomatogenic zone* generates the ictal clinical signs during seizures. The symptomatogenic zone could be the seizure onset area itself but the areas involved during seizure spread, too. The *epileptogenic region* (ER) is the cortical region from which seizures *may* arise and whose removal will result in complete cessation of the seizures. ER is a theoretical concept since there is no methodology available that permits adequate delineation of its boundaries. The boundaries of all the above mentioned zones (irritative, ictal onset, functional deficit, and EL) may coincide, or, more frequently, there may be only partial concordance or even a total divergence.[33,94] *Figure 1* shows the theoretical connections of the EL with irritative, ictal onset, epileptogenic, functional deficit, and symptomatogenic zones.

Although there are four major groups of the symptomatic localization-related epilepsy syndromes categorized according to the brain lobes, the parietal and occipital lobe epilepsies are relatively rare and there are no large series and studies investigating them. Henceforward, we discuss the role of ELs in temporal and frontal epilepsies.

2.3 Structural abnormalities in temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is the most frequent localization-related epilepsy. Neoplasms, HS, vascular malformations are the most common pathological findings in TLE.[4,143] Low-grade astrocytoma, pilocytic astrocytoma, oligodendroglioma, ganglioglioma and dysembrioplastic neuroepithelial tumor (DNT) are the most frequent neoplasms associated with epilepsy.[118,143] The resection of gangliogliomas and DNT may induce a psychosis[3], which may be a lesion-specific clinical feature in epileptology.

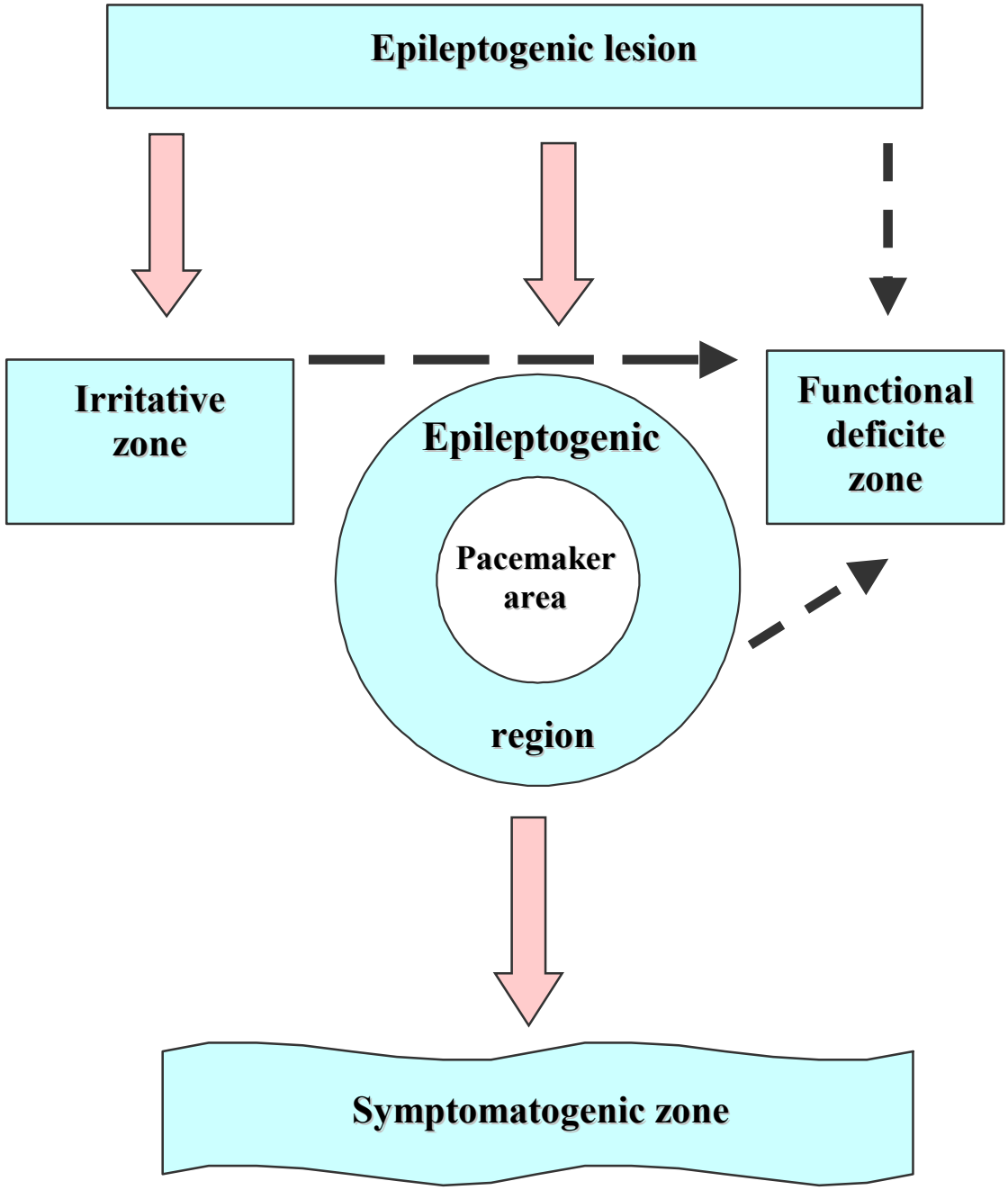

Figure 1 The model of lesional epilepsy, the organization of epileptic focus. Thick arrows represent direct causal relationships, broken line arrows show possible causal relationships. The epileptogenic lesion is thought to be the common cause in the development of epileptogenic region and irritative zone. The epileptogenic region is a brain area capable to generate seizures, consequently it includes the pacemaker area, but the epileptogenic lesion, irritative zone and symptomatogenic areas are not necessary included. Functional deficit in epilepsy may be the consequence of the epileptogenic lesion, but frequent interictal epileptiform discharges (an active irritative zone) may also result in functional disturbances (transient cognitive deficit). Immediately after the seizures, a transient functional deterioration is frequent (postictal Todd's paresis, postictal aphasia). It is suggested that seizures may cause even long term functional changes in the brain areas involved during them. The relationship between the irritative zone and the other areas is not clear yet. Some data suggest that the pacemaker area and seizure spread may also have influence on the irritative zone.[74]

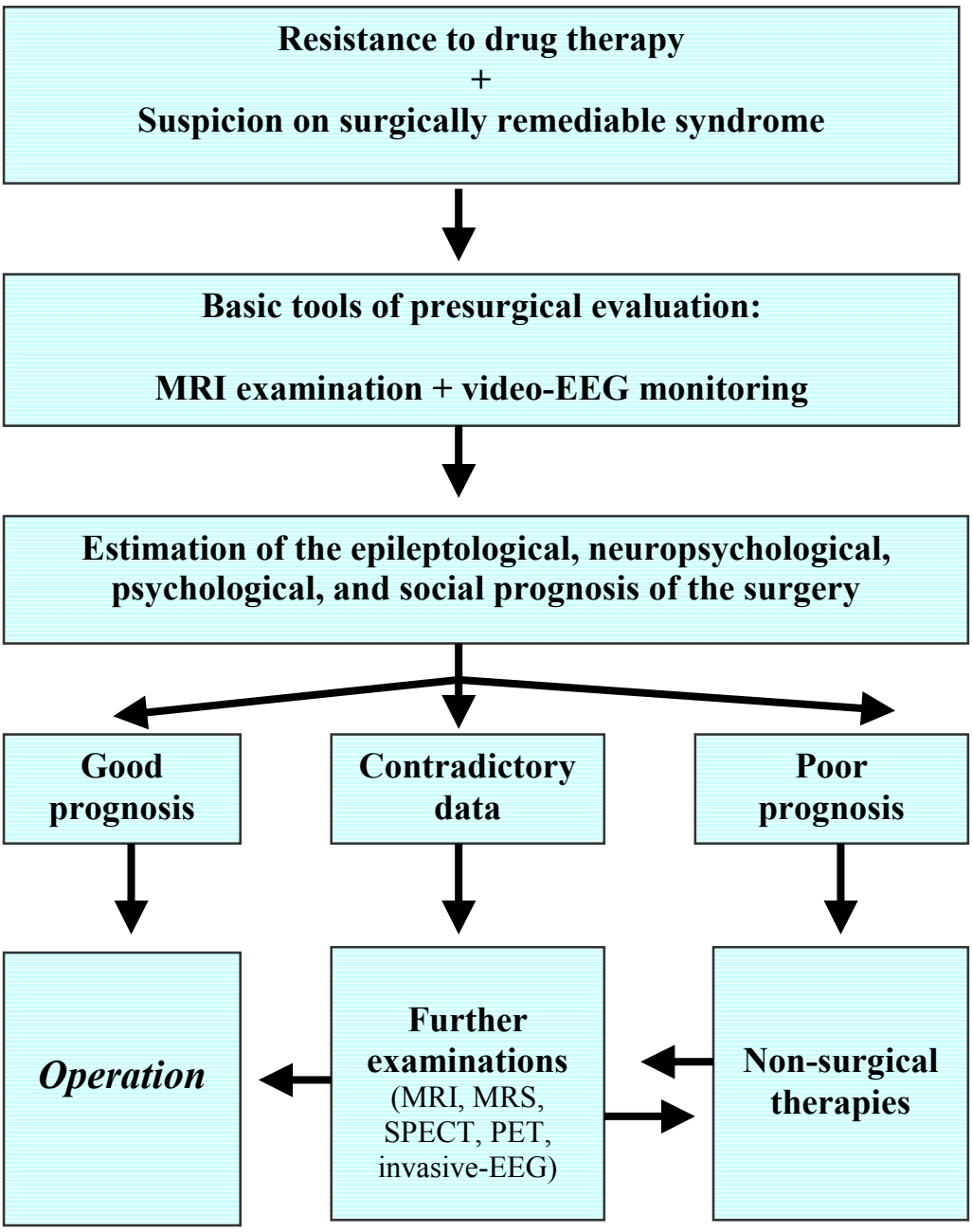

Figure 3 Presurgical evaluation of epileptic patients

2.3.1. Hippocampal sclerosis

In TLE, HS is the most common morphological abnormality (*Figure* 2).[60] More than 70% of patients with HS had a history of febrile seizures during childhood.[36,41] It is not clear whether HS is a cause or consequence of seizures or what the connection is between TLE, HS, and febrile seizures. The irritative zone in patients with HS is much more circumscribed and restricted to the mesiotemporal region than in patients with mesiotemporal tumors, suggesting that in HS, the epileptogenic region is located in the hippocampal formation.[60,72] Recent investigations suggest that HS is not a homogenous disorder. The endfolium sclerosis selectively affects the CA4 sector of the hippocampus. This HS form may be a consequence of seizures, and not an EL. Conversely, the "classic" HS predominantly with CA1 and CA3 abnormalities is possibly a "true" EL.[6] It may be a consequence of unspecific brain damages (most often febrile seizures) occurring in early childhood[18,70,99], but it is able to generate seizures itself.

Recent data suggest that a genetic predisposition to abnormal proinflammatory citokine reaction may be responsible for febrile seizures leading to HS, while in individuals without such an abnormal immune response, no HS develops during febrile seizures.[79] Another recent theory about the evolution of HS is that some preexisting hippocampal abnormality (probably hippocampal malrotation[10]) predisposes patients to develop febrile seizures. Febrile seizures result in HS, and finally the HS is responsible for the TLE.[37]

2.3.2. Subependymal nodular heterotopia

Heterotopia means that normal neurons are localized abnormally in brain sites usually not containing them. It is one of the most frequent epileptogenic dysgeneses.[11] Different forms of heterotopia are categorized according to localization: subcortical or subependymal; diffuse, laminar or nodular.[11] Subependymal nodular heterotopia (SNH) is almost always associated with epilepsy appearing most frequently in the posterior, peritrigonal region.[25,117] On one hand, SNH occurs relatively rarely in TLE patients, on the other hand, SNH in peritrigonal region is very frequently associated with TLE.

2.3.3. Mirror focus in temporal lobe epilepsy

Approximately 35-61% of patients with TLE had IEDs above both temporal regions.[28,35,101,139] Compared to unitemporal spike focus, bitemporal IEDs (e.g. bitemporal irritative zones) may represent an extended ER since they are more often associated with bitemporal independent seizure onset and seizure propagation as well as with poor surgical outcome after temporal lobectomy.[112,129] On the other hand, in patients with bilateral IEDs - although less likely than in individuals with unitemporal IEDs - seizures are *usually* generated in only one area, moreover, after the removal of the primary epileptogenic focus, contralateral spikes *usually* disappear, suggesting that bitemporal irritative zone does not automatically mean a bilateral ER.[62,128]

Morrel hypothesized that the presence of bitemporal IEDs is a sign of the progressive nature of epileptogenesis.[101] He made an artificial epileptogenic focus in rats and cats.[100] A contralateral spike focus appeared several days to weeks later. He hypothesized the same mechanism for bilateral spike foci in human epilepsy: spreading through neuronal pathways the epileptic activity of primary focus is capable of generating a secondary (mirror) focus in the contralateral homotopic brain region. He also found some evidences supporting this theory by investigating human tumorous epilepsies.[101] Morrel's hypothesis; however, has never been unequivocally confirmed in human epilepsy.[47]

2.4 Lesions associated with frontal lobe epilepsy

FLE is the second largest group of localization related epilepsies occurring in 6-30% of all surgically treated epilepsy patients.[87,140] Compared to TLE, FLE shows a large clinical diversity.[44] It is hard to delineate FLE from other epilepsy syndromes. Even sleep disorders (most frequently parasomnias) should be considered during the differentialdiagnosis.[76,113,124] The most often seen seizure types in FLE are tonic-clonic seizures, clonic seizures, tonic seizures. FLE seizures occur predominantly at night, they are often characterized by bimanual-bipedal automatisms, and vocalization.[87,101,140] Infants and preschool children with FLE have different seizure semiology: tonic-clonic seizures and automatism do not occur, while epileptic spasm and subtle behavior changes are the characteristic phenomena.[39,40] Vocalization is one of the most

characteristic sign of FLE occurring in 43-63%.[87] Although ictal speech is a well-accepted lateralizing sign in TLE[44], it is rare in FLE. Whether non-speech vocalizations are related to the side of the EL (or seizure origin) in FLE is not known.

Although some authors found that MRI-detectable lesion is a good prognostic factor for frontal lobe epilepsy surgery[17,135] , there are only a limited number of studies investigating the role and types of lesions associated with FLE. The most frequent pathological abnormality in FLE is the focal cortical dysplasia (FCD)[127], but low-grade tumors, perinatal lesions and vascular malformations also occur.[87]

Low grade astrocytomas or vascular scars generate seizures due to chemical or mechanical effects of the lesion, the pacemaker area occurs obviously outside the lesion, in the adjacent brain tissue. Conversely, unlike other ELs, FCD has an intrinsic epileptogenicity. In FCD, the seizure onset zone is localized intralesional: the lesion generates seizures itself.[108,127] Due to the intrinsic epileptogenicity of FCD, ictal-like bursting patterns appear on intracranial EEG.[108] The scalp EEG in cortical dysplasias may show ictal- like electrical patterns. Local repetitive fast discharges (LRFD) characterized by high-frequency (> 10 Hz) spike bursts with more than 1 second duration. LRFD is often accompanied by dysplasia.[71] It may be a lesion-specific electrographic phenomenon.[67] Not only FCD, but diencephalic hamartomas[85] and some tumors with dysplastic features (DNT, gangliogioma) may also have intrinsic epileptogenicity.

2.5. Surgical treatment of epilepsies

20-25% of epileptic patients do not become seizure free on adequate medication due to inefficacy, or severe side effects may prohibit the adequate therapy.[24,31,73] If the ER is circumscribed and well localizable, the resection of this region may lead to cessation of seizures in patients resistant to drug therapies. The surgical intervention in TLE results in seizure freedom in 60-90% of the patients.[112,125] Even in patients in whom the epilepsy surgery does not lead to the cessation of seizures, the reduction of seizure number may significantly improve the quality of life.[131]

The possible ER is determined by multimodal investigation methods (*Table 1*). The basic (routine) tools during the presurgical evaluation are: clinical history, seizure

semiology, high resolution MRI and long-term video-EEG recordings.[56] The latter includes interictal and ictal EEG as well as video recordings of the seizures. In some cases, ictal SPECT, interictal PET, MRS, or intracranial EEG recordings are also necessary.[53,56,89,132] *Figure* 3 shows the flowsheet of the presurgical evaluation in epilepsy.

2.5.1. Morphological and functional epilepsy surgery

There are two main *theoretical* strategies of epilepsy surgery: functional and morphological approaches.

The functional approach is classically based on electrophysiology: we try to determine the epileptogenic brain tissue capable of generating seizures by using intracranial and scalp EEG and/or other functional investigating tools presented on *Table 1*. This strategy disregards the morphological abnormalities. The functional approach seems to be reasonable since the seizure is not a permanent phenomenon, results from a transitory imbalance of the pro- and anticonvulsive neuronal processes. However, there is no methodology available that permits adequate delineation of the boundaries of ER (see Chapter 2.2.). Although there are some success of pure functional approach (some patients without MRI-detectable EL have also been successfully operated), outcome studies revealed that the morphological abnormality can not be disregarded in epilepsy surgery.

The principal type of surgery based on the morphological approach is the lesionectomy. Lesionectomy is a surgical procedure that is directed at the structural lesion (e.g. EL) believed to be the etiology of the seizure disorder, without attempting to resect the ER.[42] The advent of MRI has been associated with an increase in the use of lesionectomy. Postoperative seizure free rates is 50-90% in reported lesionectomy series.[42] However, the outcome of lesionectomy depends on the underlying histopathology.

In tumors and vascular malformations the sensitivity of MRI is 100%, the boundaries of the lesion are well defined and the surgery is indicated not only due to chronic epilepsy but also due to risks of bleeding or of neoplastic progression. In these cases, lesionectomy is a widely acceptable surgical procedure.

In cases of the two most frequent lesions underlying chronic epilepsy - HS and dysgenetic lesions - the morphological approach is questionable. Concerning HS, firstly, it is not clear, whether HS is a true EL (see Chapter 2.3.1). Secondly, HS is often associated with a widespread mesiotemporal abnormality (mesiotemporal sclerosis) affecting regions outside the hippocampal formation[143] or with another dysplastic lesion ("dual pathology"). In HS-associated TLE, anterior temporal lobectomy is the most accepted operation.

Although dysplastic lesions probably have intrinsic epileptogenicity (see Chapter 2.4), the lesionectomy in these cases is also problematic due to the rather poor sensitivity of MRI in detecting subtle dysgenetic abnormalities.[9] Even if MRI shows a circumscribed dysgenetic EL, a microscopic dysplastic tissue could occur in remote brain regions. Hence, in FCD, functional investigations can add further information since EEG may indicate microdysgenesis (see Chapter 2.4.).

The pure morphological approach could fail not only in cases of "micro" ELs undetectable by MRI, but also due to self-sustained epileptogenic brain tissue. ELs could hypothetically cause epilepsy in three different ways: they can generate seizures themselves (see Chapter 2.4.), they can cause seizures by their chronic mechanical or chemical effect, or they alter the normal brain tissue to be epileptogenic. In the latter case, the lesionectomy can not lead to success. Unfortunately, at present, we are not able to unequivocally determine, which of the three possibilities is true in a particular patient, whether EL is itself the ER, EL controls the ER, or EL is only a precipitating factor for the development of a lesion-independent ER. On the other hand, not only the self-sustained epileptogenic brain tissue, but the secondary epileptogenesis could also be an argument against the pure morphological approach (see Chapter 2.3.3.). This means that not only morphologically but also functionally disturbed brain areas should be resected since the epilepsy itself may generate remote ERs capable of generating seizures even after the removal of the primary (morphologically destructed) focus. Recently, Juhász et al. found that flumazenil (FMZ) binding abnormalities demonstrated by FMZ-PET show an excellent correlation with the ER. They demonstrated that there are areas around the lesion with abnormal FMZ bindings, which may also be ERs independent of the MRI-detectable lesion. These perilesional areas show a large inter-individual variability (0-56

cm^2), but most often (in 82% of cases) they were <10 cm^2. The authors also found areas relatively far from the the EL, showing disturbed FMZ binding. They hypothesized that these areas may be caused by the secondary epileptogenesis.[78]

In conclusion, it is clear that functional and morphological approaches in epilepsies surgery are two theoretical *extremities*. The outcome studies revealed that both functional and morphological data predict the result of epilepsy surgery[112], hence both of these approaches weighted differently should be taken into account in a particular patient. The extended lesionectomy (e.g. lesionectomy plus the resection of surrounding cortex considered to be epileptogenic by functional investigation tools) represents this "mixed" approach.[42]

2.5.2. The timing of surgical treatment

The timing of surgical intervention is a matter of debate.[34,54] In the past few years more and more new antiepileptic drugs appeared on the market. The number of possible mono-, bi-, and tritherapy is so high that trying all combinations of antiepileptic drugs could be lifelong lasted. When can we say that the patient is resistant to drug therapy and a candidate for epilepsy surgery? In TLE patients ,this question seems to be answered by the determination of prognostic factors. A TLE patient with HS and unitemporal EEG spike focus has a 90% chance to become seizure free after adequate surgical treatment, but has only 11% probability to become seizure free on adequate drug therapy.[112,126] This aspect led to introduction of the term "surgically remediable syndromes".[30] In these syndromes (mesial TLE with HS, lesional neocortical - in most cases frontal - epilepsy, hemispheric epilepsy), surgery is not an "ultima ratio" therapy, and should be considered if the initial two antiepileptic drug therapies failed.[14] To prevent the psychosocial deterioration of the patients with intractable epilepsy[8,57,75], in surgically remediable syndromes, the operation should be performed as early as possible, within 1-3 years after the epilepsy onset.

Although more than 100 patients suffering from chronic epilepsy were operated on in Hungary resulting in 67-79% of postoperative seizure freedom[5,55,57,58,115], concerning the epidemiological data, there must be more than 5000 patients with poorly controlled epilepsy in Hungary who may benefit from surgical intervention.[34]

2.5.3. Surgical treatment of lesional FLE

Compared to TLE, surgical outcome for FLE is less favorable, 20-50% of patients become seizure-free.[50,87,120] The reason for the relative large number of surgical failures in FLE is obscure and may be multicausal. In contrast to TLE, there is a large diversity in FLE. The frontal lobe consists of different parts with different physiological functions (see Figure of ref **II**): frontocentral, dorsolateral, frontopolar, frontoorbital and frontomedial regions[140], consequently, various seizure types emerge in these different regions, moreover, there is only a weak correlation between the phenomenology and the seizure origin.[52] The frontobasal and -medial areas are hidden for interictal or even for ictal scalp EEG detection. In the frontal lobe, seizures spread more rapidly than in the temporal lobe, consequently, ictal scalp EEG remains frequently non-localizable, moreover, artifacts from frontal muscles disturb the interpretation.[121]Also SPECT and PET provide less information than in TLE.[26,61] Eloquent areas may prohibit a complete resection even when they have been found to be epileptogenic. Nevertheless, due to the introduction of long-term video-EEG, subdural electrodes and modern neuroimaging techniques, the surgical results have become more promising.[53,87,106]

Unlike in TLE, no study determined the prognostic factors for the success of the FLE surgery. Because of the less favorable outcome results, however, the determination of prognostic factors is important not only in the prediction of seizure outcome, but also and in decisions regarding the use of intracranial electrodes or the extension of surgery in FLE patients. In addition, the identification of prognostic factors may improve our general understanding of the pathophysiology of postoperative failure, of the spatial extension of ER, and the relationship between the EL and ER.

2.5.4. Ictal lateralizing signs

The term *ictal lateralizing sign* means that a clinical phenomenon during or immediately after the seizure has a predictive value in lateralizing the ER. The significance of ictal clinical lateralizing signs has increased during past years, adding further information to the localization of the ER, which is especially useful in presurgical investigation of intractable epilepsy. Ictal lateralizing signs also provide information on the physiological lateralization in human brain.

Although there are many studies correlating ictal signs with lateralization of the ER in focal epilepsy, these studies investigated mainly[15,20,77,142] or exclusively[12,27,83,88,96] TLE patients (see *Table 2*), whereas FLE patients constitute only a small portion of these patients. Some clinical phenomena identified as lateralizing signs in TLE patients rarely occur in FLE. Unilateral automatism, automatism with preserved consciousness, ictal speech, postictal aphasia, or dystonic posturing are infrequent or absent in FLE[15,20], nevertheless, other clinical phenomena, such as cloni, tonic posturing, or somatosensory aura are characteristics of FLE rather than TLE.[114] The clinical significance of the lateralization value of unilateral motor and somatosensory manifestations in frontal lobe seizures should be evaluated.

Table 2. Clinical ictal lateralizing signs in TLE

Version	+++	**C**
Non-forced head deviation	-	
Dystonia	+++	**C**
Clonus in face or in the distal part of the extremity	+++	**C**
Clonus in the proximal part of the extremity	-	
Unilateral mouth deviation	++	**C**
Unilateral hand automatism	+	**I**
Unilateral blinking	+	**I**
Postictal hemisyndrome	++	**C**
Postictal nose wiping	++	**I**
Ictal vegetative signs: vomiting, spitting, urinary urge	+	**ND**
Ictal speech	++	**ND**
Automatism with preserved consciousness	+++	**ND**
Postictal aphasia	++	**D**

Abbrevations: **-** : no lateralizing value

+: questionable lateralizing sign (not enough data or relatively week predictive)

++: reliable lateralizing sign +++: very reliable lateralizing sign

D: dominant, **ND**: non-dominant, **I**: ipsilateral **C**: contralateral epileptogenic region is suspected

3. Purposes

The aim of the following five studies is to observe the clinical and electro-physiological features of different localization-related epilepsies with morphological abnormalities, to evaluate the relationships of epileptogenic lesions with the epileptogenic region and pacemaker area (ref **I**,**II**), irritative zone (ref **I**,**II,V)**, symptomatogenic zone (ref **I**,**III,IV)** by observing epileptic patients by using MRI and long-term video-EEG. Our increasing knowledge about the exact localization of the epileptogenic lesion permits us to observe the relationship between the localization of epileptic focus (e.g. epileptogenic lesion) and the clinical features of epilepsy. Moreover, the localization of the epileptogenic lesion and the clinical features of epilepsy together provide new information on the physiologic lateralization in human brain. Our studies was aimed at analyzing the following questions:

1. What is the role of HS in the development of bitemporal irritative zone (of mirror epileptic foci)? Does epilepsy duration or other clinical features of epilepsy have influence on the development of bitemporal IEDs in humans (ref **V**)?

2. What are the clinical and electrophysiological features of epilepsy associated with subependymal nodular heterotopia? What is the connection between the morphological abnormality and the electroclinical syndrome (ref **I**)?

3. What are the predictive factors for the seizure- free outcome in lesional frontal lobe epilepsy surgery? What is the pathophysiology of the surgical failure? What is the relationship between the epileptogenic lesion and the spatial extension of epileptogenic region (ref **II**)?

4. What is the association between the localization (lateralization) of the lesion and ictal symptoms, e.g. ictal vocalization, ictal unilateral somatosensory and motor phenomena in lesional FLE (ref **III,IV**)?

4. Methods

4.1. Mirror focus in HS-associated temporal lobe epilepsy

We evaluated the findings of 42 TLE patients in whom HS was revealed by a high-resolution MRI.[10] Only patients with sufficient EEG data were included who had temporal IEDs. Patients were divided into two categories: if all IEDs appeared over one temporal lobe, we categorized the patients into the *unitemporal group*, patients having bitemporal independent IEDs were categorized into the *bitemporal group*. We categorized the patients into *early-onset epilepsy group* if the epilepsy started < age 5. For this study, we defined *drug-resistancy*, if the patients had ≥1 disabling seizure/month with adequate antiepileptic therapy for at least 1 year under our care (ref **V**).

4.2.Temporal lobe epilepsy and peritrigonal nodular heterotopia

We analyzed the clinical, electrophysiological, and neuroimaging data of five epileptic women, who had SNH in the peritrigonal area (Figure 1 of ref **I**).

4.3. Surgical outcome in lesional frontal lobe epilepsy

We performed a multivariate study to identify predictive factors for the success of surgery in lesional FLE. We included patients who had consecutively undergone presurgical evaluation with MRI and long-term video-EEG examinations, had a resective surgery involving the frontal lobe (lesionectomy, extended lesionectomy, topectomy, subtotal or total lobectomy), and returned for the postoperative clinical, EEG and MRI examinations. Sixty-one patients met inclusion criteria.

We investigated the following groups of variables: clinical history, seizure semiology, EEG and neuroimaging data, localization of resected area, underlying pathology and postoperative data. We divided the patients into two categories: seizure- free or non-seizure-free.

For statistical analyses, Mann-Whitney, Chi-square, Fisher's exact and binomial tests were carried out. To identify which variables could predict the outcome *independently*, we performed a stepwise logistic regression for variables

demonstrating a significant effect in univariate analyses. To evaluate the individual predictability of outcome we computed a discriminant analysis (ref **II**).

4.4. Lateralization in lesional frontal lobe epilepsy

Twenty-seven patients were included in this study who had consecutively undergone a presurgical evaluation, had had resective epilepsy surgery involving the frontal lobe, and who had remained seizure-free >1 year postoperatively. All patients had MRI, long-term EEG monitoring, and ictal audio-video recordings. Fifteen patients had right-sided, 12 patients had left-sided ERs. All of them had an MRI-detected lesion in the frontal lobe. Histopathology revealed the following abnormalities: FCD, 17 cases; tumor, 6 cases; arteriovenous malformation, one case; ischemic lesion, three cases. Postoperative MRI confirmed a complete removal of the lesions in all cases.

Information regarding somatosensory aura was obtained from medical records, while vocalization and the unilateral motor manifestations on video recordings were re-evaluated by two investigators, one of them was blinded to patients' clinical data. Except for the measurement of inter-observer agreement, only the observations of the *blinded* investigator were used. Audible ictal non-speech sounds of audio-video-recordings were divided into the two categories:

1. Sounds of motor or vegetative seizures activities, e.g. apnea, clonic, or secondarily generalized tonic-clonic seizures (SGTCS)

2. Pure ictal vocalization (PIV) if the *ictal* vocalization had no speech quality, did not accompany by the above-mentioned motor or vegetative phenomena (ref **III,IV**).

5. Results

5.1. Mirror focus in HS-associated temporal lobe epilepsy

Of the 42 TLE patients with HS, 19 patients (45.2%) had bitemporal IEDs. In cases of unitemporal HS and IEDs, the EEG and MRI results were always concordant. We found no difference between the two groups according to febrile seizures, epilepsy duration, and therapy resistance. Early-onset epilepsy occurred significantly more

frequently in the unitemporal group than in the bitemporal group, all eight patients in whom the epilepsy started before age 5 had a unitemporal irritative zone (ref **V**).

5.2.Temporal lobe epilepsy and peritrigonal nodular heterotopia

The patients' first seizures appeared between the age of 9 and 24. Only one patient had risk factors for epilepsy: neonatal asphyxia and febrile convulsions. Three patients had auras. These were cephalic, visceral, and non-identifiable auras. All the patients had complex partial seizures (CPS) with temporolimbic symptoms. In two cases, there was SNH on the right side, in three cases, bilateral peritrigonal heterotopia was detected (Figures 1 and 2 of ref **I**). EEG showed IEDs exclusively in the temporal region: anterior temporal in two cases, middle temporal in two cases, and posterior temporal in one patient. In one patient, LRFD was present.

Due to pharmacoresistancy, heterotopic noduli and the anterior two thirds of the hippocampus were surgically removed in one patient. Intracranial, intraoperative EEG during general anesthesia showed no epileptic activity in the heterotopia, or in temporal convexity and hippocampus. Postoperatively, the patient had one non-habitual seizure (ref **I**). Two years after the original publication (ref **I**), the patient is seizure free. After the original publication, a second patient (none of the five patients presented here) with typical TLE and *bilateral* peritrigonal SNH was operated on. A temporal lobectomy was performed without resection of the SNH. The two-year postsurgical outcome was poor.

5.3. Surgical outcome in lesional frontal lobe epilepsy

Thirty of 61 patients (49%) became seizure-free after the FLE surgery.

Univariate analysis. Generalized IEDs, generalized slowing, no generalized signs on the EEG, and use of invasive electrodes showed a significant association with the outcome: the absence of generalized signs was associated with a seizure-free outcome, other variables with a non-seizure-free outcome. Two postoperative variables were associated with poor surgical results: the incomplete resection according to postoperative MRI ($p=0.002$) and postoperative IEDs ($P=0.001$). In eight patients, the postoperative MRI revealed an incomplete resection. None of them became seizure free. In two cases, the incomplete resection was due to the large extension of pathology. In

the other six patients the extension of the pathology was not recognizable intraoperatively, and the incomplete resection was only recognized by the postoperative MRI. All of the latter six patients had FCD.

Independence of variables and multivariate analysis. Investigating the three preoperative biological factors found to be significant by univariate analysis, only the absence of generalized EEG signs correlated independently with surgical outcome. According to discriminant analysis, four variables can significantly predict the seizure outcome: no generalized signs on the EEG, somatosensory aura, SGTCS and MRI-detected pathology. Somatosensory aura and SGTCS were independently associated with non-seizure free outcome, the other two with seizure-free one. Although somatosensory aura, SGTCS, and lesional MRI showed no correlation with outcome by univariate analysis, their addition to the model significantly improved the outcome prediction. Discriminant analysis resulted in an equation:

predicted outcome (PO) = 0.99 x NGS +0.43 x MRPAT -0.55 x SGTCS -0.48xSSA

(Abbreviations: NGS=1 if no generalized EEG signs are present, and NGS=0 if generalized IEDs or slowing is present. MRPAT=1, if MRI shows pathology. SGTCS=1, if the patient has SGTCS. SSA=1, if somatosensory aura is present. When PO is above 0, then a seizure-free outcome is predicted. Negative values predict a non-seizure-free outcome).

By using this equation it was possible to correctly classify 79% of the 61 patients. If a patient within our investigated population had a PO>0, then he had a 73% chance of seizure-freedom. When PO<0, then this probability was only 13.5% (ref **II**).

5.4. Lateralization in lesional frontal lobe epilepsy

We analyzed 153 seizures of 27 patients. Tonic seizures were present in 67%, CPS in 48%, clonic seizures in 18%, and myoclonic seizures in 11% of the cases (ref **III,IV**).

5.4.1. Ictal vocalizations

Ictal, non-speech sounds were present in 21 patients. They occurred significantly more often in patients with left-sided ER (12 of 12 patients, 100%) than with right-sided

ER (9 of 15 patients, 60%, p=0.02). All the patients who had no clear audible sounds during video-recordings had right-sided foci. Moreover, observing only the PIV, this difference was highly significant. PIV occurred in 11 patients. It was present in 75% of patients with left-sided lesion (nine patients) and in 13% with right sided lesion (two patients), p=0.002. There was a trend towards the dorso-lateral localization of the EL in patients with PIV (see Figure of ref **III**).

5.4.2 Ictal unilateral motor and somatosensory manifestations

The most common unilateral phenomenon was the unilateral tonic posturing occurring in 48% of all patients and in 25% of all seizures. Somatosensory aura and head version appeared exclusively contralateral, whereas clonus occurred in 92% of seizures contralateral, unilateral tonic posturing appeared in 89% of seizures contralateral to the ER. Non-forced head turning and postictal nose wiping showed no lateralizing significance. We did not find dystonic posturing in any of our patients.

We observed ipsilateral cloni or ipsilateral tonic posturing in three patients. Two of them had also contralateral lateralizing signs. In one patient, both ipsilateral cloni and tonic posturing occurred; however, contralateral cloni, tonic posturing, and contralateral version appeared, too. A second patient had ipsilateral cloni with contralateral somatosensory auras and contralateral tonic posturing. A third patient had ipsilateral tonic posturing without other lateralizing signs. Both patients with ipsilateral tonic posturing had orbito-polar ERs, patients with ipsilateral cloni had orbitio-polar and frontomedial ERs.

Unilateral cloni and somatosensory aura occurred most often in patients with frontocentral and frontomedial ELs. Head version appeared most frequently in patients with dorsolateral EL. Postictal nose wiping was the most characteristic sign of an orbito-polar ER (ref **IV**).

6. Discussion

6.1. Mirror focus in HS-associated temporal lobe epilepsy

Unlike the results of animal studies, the significance of secondary epileptogenesis

in humans is not clear. Some authors found that patients with bilateral IEDs had a longer duration of epilepsy[49,101], while others did not find such a correlation.[46,92,104] Two studies observed the evolution of IEDs by observing serial EEGs. Hughes (1985) found that 1% of unilateral spike foci become bilateral pro year[65]; however, others found that EEG findings in epileptic patients remain unchanged over time.[63] Moreover, the epilepsy duration has no effect on the outcome of epilepsy surgery[112] (**ref II**), suggesting that the ER does not extend over time.

An explanation for these controversial results could be that - in contrast to animal models -, in human series the localization and the type of ELs showed a large variability, which may also have an influence on the evolution of bitemporal IEDs, drug resistancy and epilepsy duration. Epileptogenicity of different brain regions and of different ELs (Chapter 2.4.) may also have an influence on the formation of mirror foci. The fact that various ELs cause TLE at different ages[70] with various degree of drug-resistancy[126] may also influence the onset, duration, and drug-resistancy of epilepsy.

To avoid the influence of pathological and localization differences, we investigated TLE patients who had HS. To our knowledge, no other study observed the clinical features associated with bitemporal IEDs in HS. This is an important question because HS is not only the most common pathological abnormality in TLE[4,139] but also the clinical features of bitemporal IEDs can clearly be modeled in this homogenous population with the same pathology in the same localization. In bitemporal vs. unitemporal patients we found no difference in epilepsy duration. Thus we could not support the hypothesis that the duration of epilepsy may have an influence on the development of bitemporal IEDs. The contradiction between our results and those of Morrel may be explained by the fact that Morrel's conception was based on studying neuronal plasticity in animal models and human tumorous epilepsies and not on the classic chronic human epilepsies e.g. HS-associated TLE.[101]

In subprimate species, the mirror focus usually develops after some days to months. In primates, however, it takes years.[101,47] An explanation of our results may be that the formation of bitemporal IEDs is fast, therefore other factors than the epilepsy duration may play a role in the promotion or inhibition of the development of bitemporal IEDs. We have already mentioned the possibility of histopathological and

localization influences. Another factor could be the age at the first seizure. In some aspects, the immature brain has a higher threshold of the excitatory stimuli and seizure-induced changes than the adult brain. There is an inverse correlation between the age and the thresholds of afterdischarges as well as sensorimotor responses of cortical stimulation: the younger the children the higher the thresholds.[2] There are experimental evidences that kindling and secondary hippocampal damage is less expressed in developing rats than in adult animals.[103,105] We found that all of eight patients whose epilepsy began before age 5 had unitemporal spike focus. Our results confirm the experimental data suggesting that seizures in the early lifetime do not cause secondary epileptogenic foci in humans (ref **V**).

6.2.Temporal lobe epilepsy and peritrigonal nodular heterotopia

All of our patients with peritrigonal SNH had a typical TLE syndrome. Reviewing the literature, we suggest that in most cases, peritrigonal SNH is associated with temporal lobe epilepsy and temporal IEDs.[25,90,117] What could be the relationship between the peritrigonal SNH and TLE? Can we speak about temporal lobe epilepsy, if the EL is extratemporal? First of all, there is no "official" definition for TLE. The ILAE classification of epilepsy syndromes describes the characteristic features of TLE, but provides no definition.[23] In our everyday practice, we define the TLE if the patient suffers from complex or simplex partial seizures suggesting a *temporal* origin *and* the EEG shows episodic abnormalities above the *temporal* region. Our patients fulfilled both of these criteria. On the other hand, neither our study, nor other investigations proved that SNH is an EL.

According to the relationship of the EL, pacemaker area, and the symptomatogenic zone, TLE can be divided into three categories:

1. TLE associated with HS or other mesiotemporal EL (mesiotemporal epilepsy syndrome).

2. TLE associated with neocortical temporal lobe pathology (neocortical TLE).[107,29]

3. There is an extratemporal EL, but the seizure activity quickly involves the temporolimbic structures, resulting in a temporolimbic seizure semiology ("pseudotemporal epilepsy").[6,32]

There may be three hypothetical relationships between the peritrigonal SNH and the TLE syndromes of our patients:

1. *The ER is located in the temporal lobe and not in the SNH*. This assumption could be supported by the fact that SNH is the most frequent dual pathology (The latter means that HS is associated with other probable EL).[117,90] Our patients had seizures characteristic of temporal lobe origin and IEDs above the temporal region. A possible mechanism may be that the SNH cause the HS by secondary epileptogenesis and not the primary lesion, but the HS is responsible for TLE.[117] Another possibility that SNH is a part of an extended neuronal dysgenesis, and a cortical (temporal) microdysgenesis is the real EL. The first argument against this theory is that SNH is nearly always associated with epilepsy, suggesting that SNH is not an epileptologically silent area.[25] The second argument is that anterior temporal lobectomy or amygdalo-hippocampectomy in TLE accompanied by SNH does not usually lead to long term seizure freedom neither one of our two operated cases nor in published surgical series.[90] Although we used an MRI protocol sensitive to mesiotemporal pathology, none of our patients had HS. None of them reported epigastric aura characteristic of mesiotemporal seizure origin.[29] Moreover, anterior temporal spike focus characteristic of mesial TLE[139] was present in only two patients. These data suggest that the ER in our patients is not restricted to the mesiotemporal area.

2. *The epileptic seizure is generated from the heterotopic gray matter but spreads to the temporal lobe, which is responsible for seizure semiology*. An argument against this assumption that either in our operated patient or in another published case[90], no intracranial epileptiform activity could be registered in the heterotopic noduli.

3. Seizures are independently generated both from the temporomedial structures and from the SNH: there are at least two independent pacemaker areas. The best surgical results in patients with TLE accompanied by SNH can be achieved if both the mesiotemporal structures and the heterotopic noduli are resected.[90] Moreover, the

intracranial EEG in a published case revealed independent seizure origin in SNH and in the temporal lobe, supporting the existence of two pacemaker areas.[25] In one of our patients, EEG showed LRFD, suggesting a cortical dysgenesis.[67] This rises the possibility that SNH is associated with a microdysgenesis not detectable by MRI, suggesting that SNH is a part of an extended dysgenesis with extended ER and multiple pacemaker areas (ref **I**). An argument against this theory is, however, that most of our patients had one seizure type only, suggesting a unifocal seizure origin.

6.3. Surgical outcome in lesional frontal lobe epilepsy

We found three preoperative biological variables associated with surgical outcome: generalized IEDs, generalized slowing, and no generalized signs on the EEG (IEDs or slowing), but only the latter could be held as an independent predictive factor. Both postoperative IEDs and incomplete resection detected by MRI correlated with poor outcome.

For individual prediction of surgical outcome, a discriminant analysis resulted in an equation consisting of four variables. This equation contains four variables: absence of generalized EEG signs, presence of MRI pathology, somatosensory aura, and SGTCS. The first two factors correlated with seizure-free outcome, the second two with poor outcome.

Since all but two patients had MRI-detectable lesions (96.7%) confirmed by neuropathological investigations, there was no correlation between MRI findings and the outcome according to univariate analysis. This ratio is higher than the proportion of lesional MRI reported in other studies.[87,93,120] This reflects the fact that by using high-resolution MRI, morphological abnormalities could be detected more often. Especially FCD diagnosed in 57% of our patients can only be detected by high-resolution MRI.[9] Since almost all of our patients had a lesional MRI, we identified variables, which could predict the surgical outcome independent of lesional MRIs, but not of negative MRIs.

Ipsi- and contralateral frontal, extrafrontal, multifocal, and generalized epileptiform activity can appear in FLE.[87,114,121] Our results showed that generalized IEDs correlated with poor surgical outcome but not independently of generalized

slowing. These two variables were closely related. Generalized IEDs in focal epilepsy occurring most frequently in FLE[114] is termed secondary bilateral synchrony (SBS).[133] The pathomechanism of SBS is not clear, but it is likely that discharges from the primary focus spread through the thalamus or through the corpus callosum to the corresponding contralateral area, producing a nearly synchronized discharge.[81,133] An alternative explanation is that SBS arises from an interaction of multiple active foci.[16] In focal epilepsy, de novo appearance of SBS with drug-resistant tonic axial seizures suggests a progressive nature of epileptogenesis.[51,59] Our findings of a correlation between generalized epileptiform activity and poor outcome support the assumption that SBS represents a widespread ER probably caused by progressive epileptogenesis (ref **II**).

After the publication of our results (ref **II**), another study was published [102] determining predictive factors for FLE surgery. Although they investigated other variables than our work, they also found the MRI-detected EL to be a good prognostic factor.[102] A second study - after the publication of our study (ref **II**) – also revealed that the EEG predicts the outcome of extratemporal epilepsy surgery.[64]

6.4. Lateralization in lesional frontal lobe epilepsy

6.4.1. Ictal vocalizations

We found that ictal non-speech vocalizations occurred significantly more frequently in patients with left-sided FLE (75 %) than those with right-sided FLE (13%).

Only one study mentioned lateralization differences of ictal vocalization in FLE. Bancaud and Talairach stated that the vocalization was characteristic to the seizures of *dominant* inferior frontal gyrus[7], however, it was mentioned only in a table, without defining the relative frequency or lateralization value of ictal vocalization. Moreover, these data were based on personal observations without blinded investigators. In that study, vocalization was also a prominent feature of seizures originating from the supplementary motor area (SMA) and anterior cingulate gyrus; however, concerning these areas, lateralization differences were not reported. Another study dealing with 16 FLE patients[87], found no association between the lateralization and vocalization; however, no distinction was mentioned between PIV and sounds due to motor or

vegetative ictal activity. Gabr et al. found that TLE patients with dominant ER had ictal vocalizations more often than those with non-dominant ER (62% vs. 37%), but this trend was not significant.[44]

There are some physiological arguments for the lateralization of vocalization. Vocalization could be elicited by direct electrical stimulation of two frontal lobe areas: from the Broca and also from the contralateral Broca-homologue area.[109] When stimulating the SMA areas, vocalization appeared more often in the dominant than in the non-dominant SMA.[19,43] The presence of aphasic symptoms or the lack of the speech initiation following the infarction or removal of the left SMA also supports a lateralized participation of the region in sound generation.[97,84,119] During automatic speech, the dominant SMA shows a more marked hyperperfusion than the non-dominant SMA.[86] Moreover, the lateralization of sound production is not a human-specific phenomenon, subhuman vertebrates appear to have left-hemisphere dominance of vocal productions.[137]

We suspect two areas, the Broca and the SMA areas, in the generation of PIV. These areas show lateralized and non-lateralized features in the generation of sound production. The trend towards the dorso-lateral localization of the EL in our patients with PIV and the observations of Bancaud and Talairach may raise the possibility that the lateralization of PIV in FLE may be primary caused by the activation of the Broca region (ref **III**).

6.4.2 Ictal unilateral motor and somatosensory manifestations

We found that somatosensory aura, head version, unilateral cloni and tonic posturing could be considered as lateralizing signs to the contralateral ER in FLE.

The lateralizing value of tonic posturing is obscure: some authors found it to provide a good lateralizing value[82,96,138], while others[15,83] did not. Previous studies found that in FLE patients, unilateral tonic posturing may occur in dorsolateral frontal[95] or in frontomedial foci.[120] We found no localizing value of this phenomenon.

In our study, ictal cloni occurred in 92% of seizures contralateral. Two patients exhibited ipsilateral cloni. The localizations of ER in ipsilateral phenomena in our and

in other published cases suggest that the epileptogenic activity causing these phenomena is not localized in the primer motor area.[21]

Ictal head version occurred most often in patients who had an ER in the dorsolateral frontal region, supporting that the ictal version results from the activation of frontal contraversive fields anterior to the precentral area.[142]

All somatosensory auras were reported contralateral to the ER, suggesting that it is a useful lateralization sign. Somatosensory aura is a negative prognostic factor for FLE surgery (ref **II**), which might indicate that this phenomenon arises in some patients in extrafrontal regions. However, even in patients who become seizure-free after frontal lobe surgery, this is the most frequent type of aura.[114] In our patients, somatosensory aura was most often associated with frontocentral and frontomedial ERs. Thus, surgical failures could also be explained by the closeness of the eloquent motor cortex, too, resulting in only an incomplete resection of the ER. Conversely, somatosensory aura may be caused not only by the activation of primary sensory area but also of SMA.[91,120]

Two studies[45,88] demonstrated that postictal nose wiping occurs in 86.5%-89% ipsilateral to the focus in *temporal* seizures, but has no lateralizing significance in extratemporal epilepsy. They also found that it is frequent in temporal seizures and rare in extratemporal epilepsy. We found no lateralizing value of postictal nose wiping in FLE either, however, postictal nose wiping occurred in 37% of our patients, suggesting that this sign is not specific to the postictal state of temporal seizures. Postictal nose wiping might be a result of the ictal upper airway secretion generated by the seizure activation of uncus.[45] Our findings also support this theory since it was associated with orbito-polar ER suggesting the activation of the rhinencephalic structures (ref **IV**).

6.5. Conclusions

In our studies, we analyzed different aspects of the relationships of epileptogenic lesions with the epileptogenic region and pacemaker area (ref **I**,**II**), irritative zone (ref **I**,**II,V)**, symptomatogenic zone (ref **I**,**III,IV)** in human epilepsy by using MRI and long-term video-EEG.

1. We were the first who investigated the mirror focus in temporal lobe epilepsy associated with HS. We found that the duration of epilepsy has no influence on the presence of bitemporal spikes. We assume that other factors, such as the age at the first seizure may play a role in this process, because we found a high correlation between the early-onset epilepsy and unitemporal spike foci. Unlike the experimental data, our results may suggest that mirror foci in humans are not a result of progressive epileptogenesis (ref **V)**.

2. We found that all patients with subependymal nodular heterotopia suffered from temporal lobe epilepsy syndrome, despite the presence of an extratemporal morphological lesion. It is not clear, whether the pacemaker area is located in the heterotopic noduli, or another hidden "microdysgenesis" is the epileptogenic lesion, or the nodular heterotopia is a part of an extended dysgenesis with extended epileptogenic regions and multiple pacemaker areas. The question may be answered by long term follow-up results of the epilepsy surgery performed in such patients (ref **I)**.

3. We first identified the prognostic factors for the outcome of FLE surgery based on MRI and video-EEG monitoring. We found that the absence of generalized EEG signs (generalized slowing or spikes) is the most predictive variable for a seizure-free outcome in lesional FLE surgery. Furthermore, non-lesional MRI, somatosensory aura, and secondarily generalized seizures are risk factors for poor surgical results. The use of these variables offers a rational basis for counseling of patients considered FLE surgery. Our findings of a correlation between generalized epileptiform activity with poor outcome support the assumption that generalized spikes in FLE represent not only an extend irritative area but also a widespread epileptogenic region. Due to the absence of a circumscribed epileptogenic region, in such cases the pure lesion-oriented epilepsy surgery should be avoided (ref **II)**.

4. We first demonstrated that ictal vocalization could be a lateralizing sign in frontal lobe seizures. The lateralization difference in the ictal non-speech sounds suggests that not only speech but the vocalization at a subverbal level also shows a left-hemisphere dominance in humans (ref **III)**.

5. We are the first who investigated the ictal lateralizing sings of frontal seizures in a systematic way. We found that not only the ictal vocalizations, but ictal cloni, tonic posturing, head version, and somatosensory aura are also useful lateralizing signs in FLE. The fact that seizure semiology can predict the lateralization of epileptic focus in FLE may have a great clinical importance in many aspects since the focus localization in FLE is more problematic than in TLE. On one hand, the interictal and ictal scalp-EEG often remains silent or non-localizable. On the other hand, the most common morphological finding in FLE is focal cortical dysplasia, which can often only be detected by repeated high-resolution MRI, hence, clinical lateralizing signs may help us in searching for the MRI lesion by delineating the region of interest and better determining the epileptogenic region during presurgical video-EEG monitoring, and finally help us in the surgical treatment of intractable FLE. Identifying the ictal lateralizing signs also provide information on the physiological lateralization in human brain (ref **IV)**.

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9.Original publications