

## Presurgical diagnosis of epilepsies – concepts and diagnostic tools

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*Dedicated to my mentor, colleague and friend,  
Prof. Yasuhiro Yonekawa M.D.,  
director of the Department of Neurosurgery,  
University Hospital Zurich, from 1992 to 2007.*

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### SUMMARY

**Introduction.** Numerous reviews of the currently established concepts, strategies and diagnostic tools used in epilepsy surgery have been published. The focus concept which was initially developed by Forster, Penfield and Jasper and popularised and enriched by Lüders, is still fundamental for epilepsy surgery.

**Aim.** To present different conceptual views of the focus concept and to discuss more recent network hypothesis, emphasizing so-called "critical modes of an epileptogenic circuit".

**Method.** A literature search was conducted using keywords: presurgical evaluation, epileptic focus concepts, cortical zones, diagnostic tools.

**Review and remarks.** The theoretical concepts of the epileptic focus are opposed to the network hypothesis. The definitions of the various cortical zones have been conceptualized in the presurgical evaluation of candidates for epilepsy surgery: the seizure onset zone versus the epileptogenic zone, the symptomatogenic zone, the irritative and functional deficit zones are characterized. The epileptogenic lesion, the "eloquent cortex" and secondary epileptogenesis (mirror focus) are dealt with. The current diagnostic techniques used in the definition of these cortical zones, such as video-EEG monitoring, non-invasive and invasive EEG recording techniques, magnetic resonance imaging, ictal single photon emission computed tomography, and positron emission tomography, are discussed and illustrated. Potential modern surrogate markers of epileptogenicity, such as *High frequency oscillations*, *Ictal slow waves/DC shifts*, *Magnetic resonance spectroscopy*, *Functional MRI*, the use of *Magnetized nanoparticles* in MRI, *Transcranial magnetic stimulation*, *Optical intrinsic signal* imaging, and *Seizure prediction* are discussed. Particular emphasis is put on the EEG: Scalp EEG, semi-invasive and invasive EEG (Stereo-electroencephalography) and intraoperative electrocorticography are illustrated. Ictal SPECT and <sup>18</sup>F-FDG PET are very helpful and several other procedures, such as dipole source localization and spike-triggered functional MRI are already widely used. The most important lateralizing and localizing ictal signs and symptoms are summarized. It is anticipated that the other clinically valid surrogate markers of epileptogenesis and epileptogenicity will be further developed in the near future. Until then the concordance of the results of seizure semiology, localization of epileptogenicity by EEG and MRI remains the most important prerequisite for successful epilepsy surgery.

**Conclusions and future perspectives.** Resective epilepsy surgery is a widely accepted and successful therapeutic approach, rendering up to 80% of selected patients seizure free. Although other therapies, such as radiosurgery, and responsive neurostimulation will increasingly play a role in patients with an unresectable lesion, it is unlikely that they will replace selective resective surgery. The hope is that new diagnostic techniques will be developed that permit more direct definition and measurement of the epileptogenic zone.

**Key words:** presurgical evaluation • epileptic focus concept • cortical zones • diagnostic tools

## INTRODUCTION

Several excellent reviews of the currently established concepts, strategies and diagnostic tools used in epilepsy surgery have been published (e.g. Rosenow and Lüders, 2001). The focus concept, as it has been initially developed by Foerster, Penfield and Jasper, Bancaud and Talairach, Wyler, and popularized and enriched by Lüders, is still fundamental for epilepsy surgery (Foerster and Altenburger, 1935; Penfield and Jasper, 1954; Bancaud et al., 1965; Wyler and Ward, 1981; Wieser et al., 1987; Lüders and Awad, 1992; Kahane et al., 2006). However, different conceptual views of the focus concept exist and more recently the network hypothesis with emphasis on the so-called “critical nodes of an epileptogenic circuit” gained attraction (Bragin et al., 2000; Spencer, 2002; Nair et al., 2004; Varotto et al., 2012; Jalo-ta et al., 2016). This “large network” model opposes the regional concept. It contains some important elements of the French school. Talairach and Bancaud (1966) emphasized that the epileptogenic zone involves a distinct set of directly interconnected regions and directed attention to the importance of studying the spatiotemporal dynamics of seizure discharges, and not just their starting point. In the view of the school of Saint Anne (Bancaud et al., 1965; Chauvel, 2001), the epileptogenic zone is considered a complex structure composed of separate *pacemaker and relay and subrelay areas* essential for producing individual ictal symptoms and signs resulting in characteristic *seizure patterns*.

Today, a variety of diagnostic tools, such as analysis of seizure semiology, non-invasive, semi-invasive and invasive electrophysiological recordings, functional testing and neuroimaging techniques are used to study the generation and propagation of focal seizures. Established diagnostic standard methods in determining the location and extent of the epileptogenic zone are video-EEG monitoring and MRI. Fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG PET) is a standard functional imaging technique which is particularly important in non-lesional epilepsy. Magnetoencephalography (MEG) is also used by many centers (Kharkar and Knowlton, 2015). Mostly because of its expenditure, ictal single photon emission computed tomography (SPECT) is performed only in certain cases. Dipole source localization and spike-triggered functional MRI have enriched the presurgical evaluation.

## AIM

To present different conceptual views of the focus and

to discuss more recent network hypothesis with emphasis on the so-called “critical modes of an epileptogenic circuit” – based on own clinico-electrophysiological experience and referring to relevant updated literature.

## METHOD

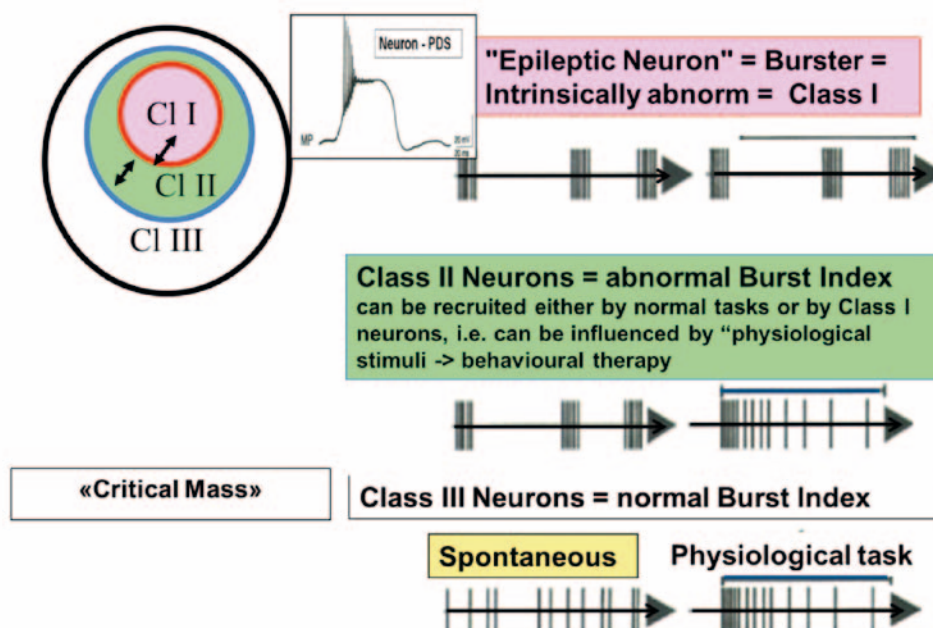
A literature search was conducted using following keywords: presurgical evaluation, epileptic focus concept, cortical zones, diagnostic tools.

## REVIEW AND REMARKS

### Aims of epilepsy surgery

According to the World Health Organization, epilepsy affects about fifty million people worldwide and there are between 16 and 51 cases of new-onset epilepsy per 100 000 people every year (Kwan et al., 2011). The International League against Epilepsy (ILAE) has recently defined drug-resistant epilepsy as a failure of adequate trials of two (or more) tolerated, appropriately chosen, and appropriately used antiepileptic drug regimens (whether administered as monotherapies or in combination) to achieve freedom from seizures (Kwan et al., 2010). This definition is based on the observation that if complete seizure control is not achieved with trials of two appropriate antiepileptic drugs, the likelihood of success with subsequent regimens is much reduced (Kwan and Brodie, 2000). Kwan and Brodie (2000) and Kwan et al. (2011) state that up to, or even more than, 30% of patients do not have remission despite appropriate therapy with antiepileptic drugs. A community-based study in southern France estimated that up to 22.5% of patients with epilepsy have drug-resistant epilepsy (Picot et al., 2008). If we accept that approximately a quarter of patients with seizures have drug-resistant epilepsy and that approximately 60% of these patients have a focal epilepsy with half of them suffering from a surgically remediable form of epilepsy, about 10% of patients with epilepsy are potential candidates for resective epilepsy surgery.

Despite this high demand, Jehi et al. (2015) who profiled the practice of epilepsy surgery between 1991 and 2011 in nine major epilepsy surgery centers in the United States, Germany, and Australia, found a decline rather than increase in anterior temporal lobectomy for hippocampal sclerosis, the most frequent type of epilepsy surgery at the time of the *Second International Palm Desert Conference on the Surgical Treatment of the Epi-*



**Figure 1.** Epileptic focus model (adapted from Wyler and Ward, 1981) with three classes of neurons: Class I neurons are "burststers" with the paroxysmal depolarization shift (PDS), the hallmark of epileptic neurons, Class II neurons have an abnormal burst index, but they can be recruited by a physiological task. This "physiological occupation" of Class II neurons might be the basis for the "behavioral therapy" (Wieser, 1998). Synchronization of Class I neurons with Class II and Class III neurons provide a "critical mass" leading from an interictal to an ictal event.

lepsies (Engel, 1993). However, they found an increase of extratemporal resections, particularly in the context of surgery for nonlesional epilepsy. Also, these authors found that the use of invasive EEG evaluations that do not lead to subsequent brain resections is increasing. Examining the surveys of the U.S. National Association of Epilepsy Centers over the period 2003 to 2012, Kaiboriboon et al. (2015) reached similar conclusions. At the start of the period, 37 member centers reported surgical data, but by the end of the period, the number had increased to 189. Again, a marked increase in epilepsy monitoring unit admissions was documented – including a doubling from 2008 to 2012 – but this was accompanied by a 65% decrease in temporal lobectomy for hippocampal sclerosis over the 4-year period from 2006 to 2010. In contrast, extratemporal surgeries doubled over the last 5 years of the surveys, and beyond 2008 there were more extratemporal than temporal lobe surgeries.

The study of Jehi et al. (2015) about trends in epilepsy surgery has limitations because it focuses on large

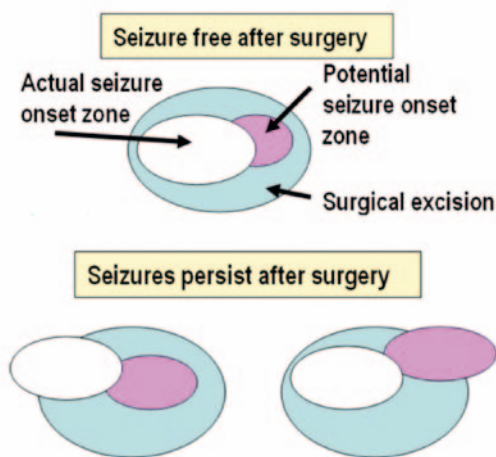
high-volume epilepsy centers, which may fail to capture important changes resulting from the rapid growth of lower volume centers. In addition, both surveys do not take into account the world outside of high-income countries (Spencer, 2016). A recent study from India reported a threefold increase in epilepsy surgeries from the period 1995 to 2000 to the period 2007 to 2012, three-quarters of which were temporal lobe surgeries (Menon and Radhakrishnan, 2015) and reports from China signaled similar trends (Xu and Xu, 2010).

The larger epilepsy centres report average seizure-free rates of about 60–80% (Engel, 1993; Wieser et al., 2003).

The objective of resective epilepsy surgery is seizure-freedom without intolerable deficits. A general accepted opinion is that the complete resection or complete disconnection of the "epileptogenic zone" containing the epileptic neurons (figure 1) is necessary to reach cessation of seizure generation (figure 2). However, opinions differ as to the exact borders of this "epileptogenic zone" in a given patient. Different zones (symptomatic, irritative, ictal onset (= seizure onset zone), ep-

**Table 1.** Descriptions of zones and the epileptogenic lesion (adapted from Lüders and Awad, 1992 and Rosenow and Lüders, 2001)

Seizure onset zone	Region where the clinical seizures originate
Epileptogenic zone	Generates epileptic seizures. Total removal or disconnection of the epileptogenic zone is necessary and sufficient for seizure-freedom
Epileptogenic lesion	Structural lesion that is causally related to the epilepsy syndrome
Ictal symptomatogenic zone	Generates the initial seizure symptoms
Irritative zone	Generates interictal epileptiform discharges in the EEG or MEG
Functional deficit zone	Functionally abnormal in the interictal state, as indicated by neurological examination, neuropsychological testing and functional imaging or non-epileptiform EEG or MEG abnormalities

**Figure 2.** Actual and potential seizure onset zones and their relation to surgical excision (adapted from Lüders et al., 2008).

ileptogenic, functional deficit zone, the epileptogenic lesion, secondary pacemaker zones) have been defined (table 1). Definition and preservation of the “eloquent” cortex is equally important to avoid unacceptable postoperative deficits.

### Definition of cortical zones

#### *Seizure onset zone versus epileptogenic zone*

The epileptogenic zone is a theoretical concept. It can comprise of several different seizure onset zones of different thresholds. The seizure onset zone is the area of the cortex from which clinical seizures actually arise (also named “*actual epileptogenic zone*” – figure 2). Thus, the epileptogenic zone can be more extensive than the seizure onset zone. In such a case, even total resection of the presurgically defined seizure onset zone might not result in seizure-freedom, because after its resection another seizure onset zone of higher threshold may become clinically evident, giving rise to further seizures postoperatively (“*potential seizure onset zones*”

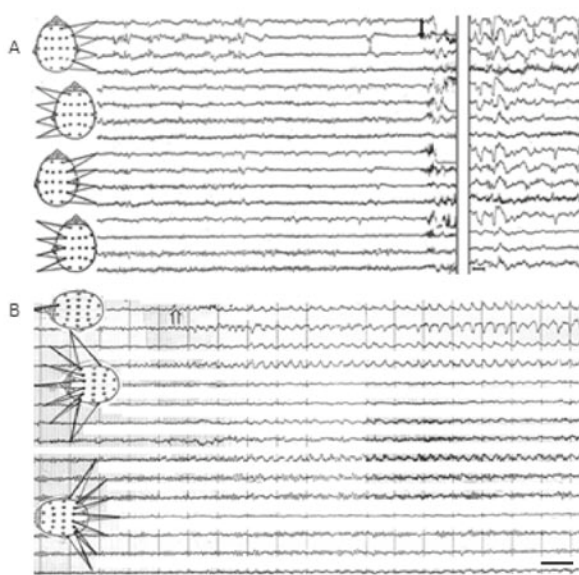
– figure 2). Connected with this distinction are the important questions of the presence of one or more “habitual” seizure types in a given patient, and the “unmasking” of seizures by rapid antiepileptic drug withdrawal.

Postoperative seizure-freedom is the gold standard for definition of the epileptogenic zone, i.e. if the patient is seizure-free after surgery we conclude that the epileptogenic zone must have been included in the resected cortex.

The seizure onset zone is determined by EEG and/or ictal SPECT. EEG is measured by scalp electrodes (figure 3), invasive (stereo-electroencephalography; subdural electrodes) or semi-invasive (foramen ovale electrodes) techniques (Wyler et al., 1984; Wieser et al., 1985; Velasco et al., 2006; Nilsson et al., 2009; Sheth et al., 2014; figures 4 and 5). Sphenoidal electrodes are used infrequently these days because they are often not well tolerated. In addition, it is rare that anterior temporal sharp waves are missed completely by anterior temporal electrodes when no sphenoidal electrodes are used.

The limitations of the different types of EEG-recordings are well known: Scalp (= surface) electrodes are located at a relatively large distance from the cortex and are separated from the brain by a series of barriers (scalp, bone, dura mater) that interfere significantly with the transmission of the electrical signals. Usually scalp electrodes are only capable of detecting a seizure discharge after it has spread considerably. Thus scalp EEG has a relatively low sensitivity. On the other hand, invasive recordings are limited by the extent of their cortical coverage (sampling problem of intracranial electrodes – “tunneled vision”). Invasive EEG techniques should only be used with a clear hypothesis regarding the location of seizure onset and when a specific question must be answered, e.g. from which lesion does the seizure discharge originate in a patient with *dual pathology* or in patients with bilateral mesial temporal sclerosis (Diehl and Lüders, 2000).





**Figure 3.** Two frequent ictal scalp EEG patterns in temporal lobe epilepsy.

**A.** Scalp EEG with right temporal “preictal” or ictal decrement in a patient with SEEG proven right amygdalar seizure onset, associated with fear and vegetative autonomic signs and symptoms. Arrow: patient reports fear and epigastric aura symptom. He became seizure-free (for 11 yrs.) after a right stereotactic amygdalotomy. Then, similar, but not identical, complex partial seizures recurred. A right selective hippocampectomy and excision of the previously lesioned amygdala was performed. Except for 2 complex partial seizures associated with withdrawal of antiepileptic drugs, the patient remained seizure-free (total follow up 20.5 years). (See Wieser, 2000).

**B.** Scalp EEG with rhythmic ictal activity right anterior temporal. Arrow: The patient reports a “funny feeling”.

Horizontal bar = 1 sec

Scalp EEG depends preferentially on dipoles with a vector *radial to the surface*. For these reasons, epileptiform potentials generated by the mesial cortex or associated with vectors tangential to the surface are difficult to detect by surface EEG. EEG localization is less reliable after a craniotomy.

MEG signals are not subject to distortion by the dura, skull and scalp. Therefore MEG has a theoretical advantage in localization over EEG. Signal attenuation in MEG occurs to a degree equal to the third power of the distance between generator and sensor. It is estimated that as in EEG, 6–8 cm<sup>2</sup> of cortex needs to discharge synchronously to generate a detectable potential. MEG is recording only tangential vector components, i.e. MEG is only capable of sampling the sulci and is un-

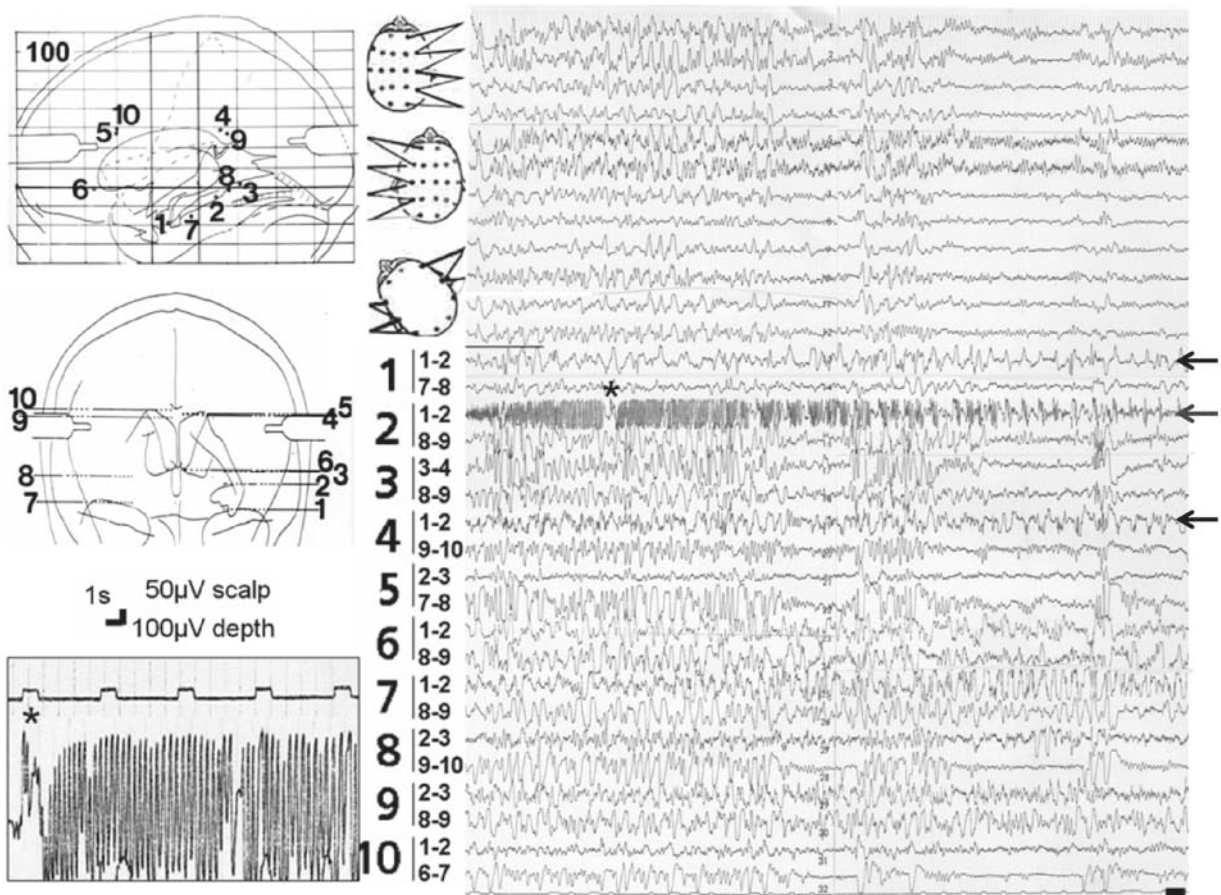
able to detect discharges from the gyral surfaces. With MEG it is impossible to record seizures routinely, which restricts the use of MEG to the definition of the irritative zone. Current use and future directions of MEG in pre-surgical evaluation of epilepsy are summarized by Ahmed and Rutka (2016). Murakami et al. (2016) have provided further evidence that MEG deserves a place in the routine presurgical evaluation. These findings should encourage clinicians to incorporate the technology into their preoperative evaluation and researchers to investigate methods of improving current approaches and discovering new ones.

For EEG electrode placement, the minimal standard is the use of the 10–20 scalp electrode system, plus, in suspected temporal lobe epilepsy, *anterior-temporal electrodes*. In many centres additional electrodes are placed according to the 10–10 system over the areas of interest to provide a greater spatial resolution.

Analogue EEG has now been replaced almost completely by *digital technology* that greatly facilitates the review of the massive amount of EEG data collected during an EEG-video evaluation. Also, this technology has removed significant constraints from EEG data collection. The interpreter can easily reformat the montage, change chart speed, gain and filters, thus facilitating the interpretation of individual electrographic events. Furthermore, digital technology allows automatic spike and seizure detection, computer-based surface mapping of EEG voltages and source localization of EEG generators (Zumsteg et al., 2004; Pellegrino et al., 2016).

*Dipole source modeling* is widely used to localize MEG and EEG potentials (Plummer et al., 2008). On the assumption of single or multiple dipolar generators and a more or less realistic skull model, the contour of the spike voltage field recorded on the surface is used to calculate the location of the dipole that best explains this spike voltage field (Ebersole and Hawes-Ebersole, 2007). Because the assumptions of the model are usually not correct, dipole source modeling has limitations.

When non-invasive studies remain non-concordant or inconclusive regarding the localization and extent of the irritative zone, the seizure onset zone or the eloquent cortex, invasive studies using subdural or depth electrodes may be needed. For a short history of invasive recordings see Reif et al. (2016). The following relative indications for an evaluation with chronic subdural electrodes have been formulated: normal structural imaging, extratemporal location, divergent non-in-



**Figure 4.** Stereoelectroencephalographic (combined depth- and scalp EEG) recording of a seizure discharge originating in the left hippocampus (2/1-2) with spread of the late clonic discharge to the ipsilateral amygdala (1/1-2) and the posterior cingulate gyrus (4/1-2, arrows). The detail (star) shows the early 14/sec discharge. Depth electrodes are numbered with large numerals and their position is shown in the graph. Each depth electrode has 10 contacts, numbered from inside out.

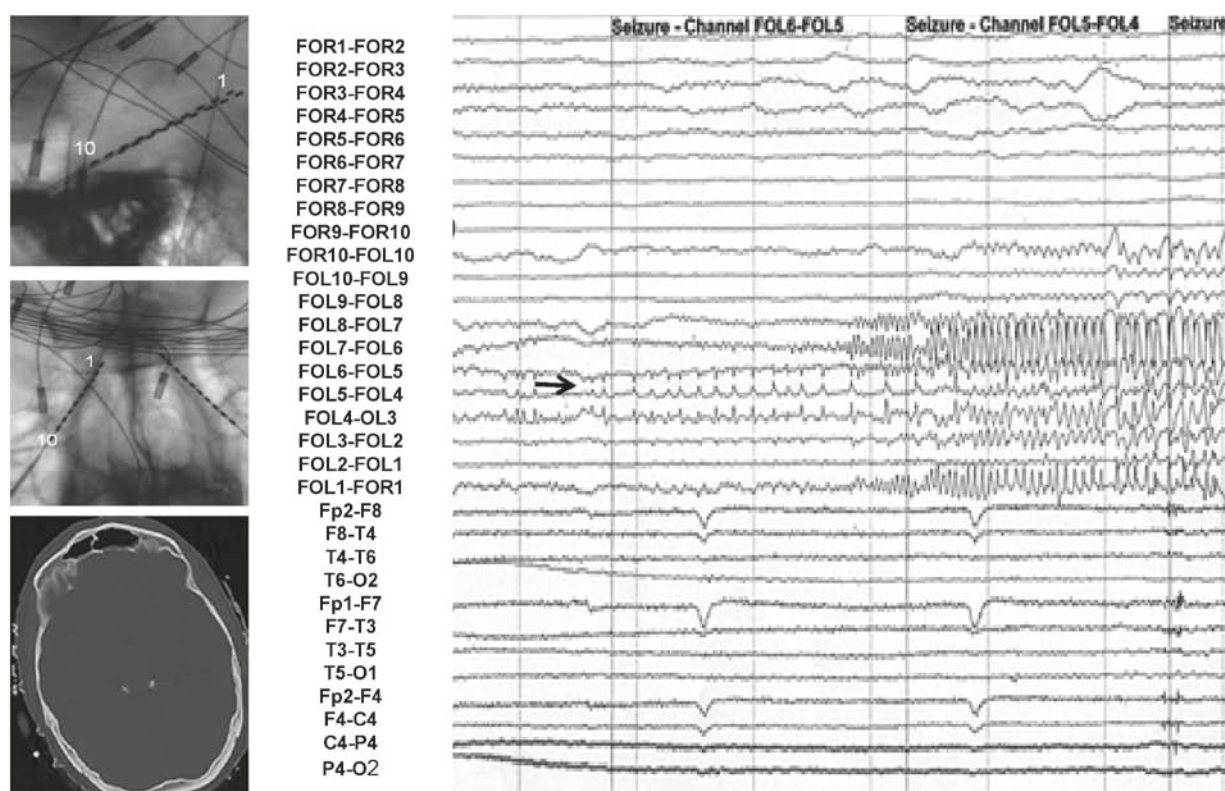
vasive data, encroachment on eloquent cortex, tuberos sclerosis and cortical dysplasia. The use of invasive electrodes depends on certain preconditions. The patient should have a (uni-) focal epilepsy and should be likely to profit from a resection. There should be a clear hypothesis regarding the location of the epileptogenic zone, derived from non-invasive studies. Clear questions that can be answered by the chosen invasive procedure should be formulated (Jayakar et al., 2016).

Despite the fact that recent data concerning the complication rate of placement of depth electrodes is lower than the complication rates reported for other methods of extraoperative invasive monitoring (Mullin et al., 2016), there are concerns regarding the safety of the “stereotactic” method. It is hoped that the proportion of patients evaluated by invasive long-term monitoring will decrease over the next decades, mainly be-

cause of our increasing ability to localize the epileptogenic lesion and the seizure onset zone non-invasively. However, there remains a fraction of patients who profit from the use of invasive long-term recordings.

The increased interest in the study of EEG activity outside the conventional frequency has shown that EEG activity in the 70–600 Hz range, termed high frequency oscillations (HFOs), can provide a new measure for localizing epileptogenicity (see section *Potential modern surrogate markers of epileptogenesis and epileptogenicity*). Along with HFOs, analysis of ictal baseline shifts (IBSs or direct current shifts) and infraslow activity (<0.1 Hz) attracted attention (John et al., 2005; Imamura et al., 2011; Modur 2014). It has been shown that the initial ictal slow shift may be seen as the first sign of an ictal event, occurring at the time of conventional EEG seizure onset or before the later typical





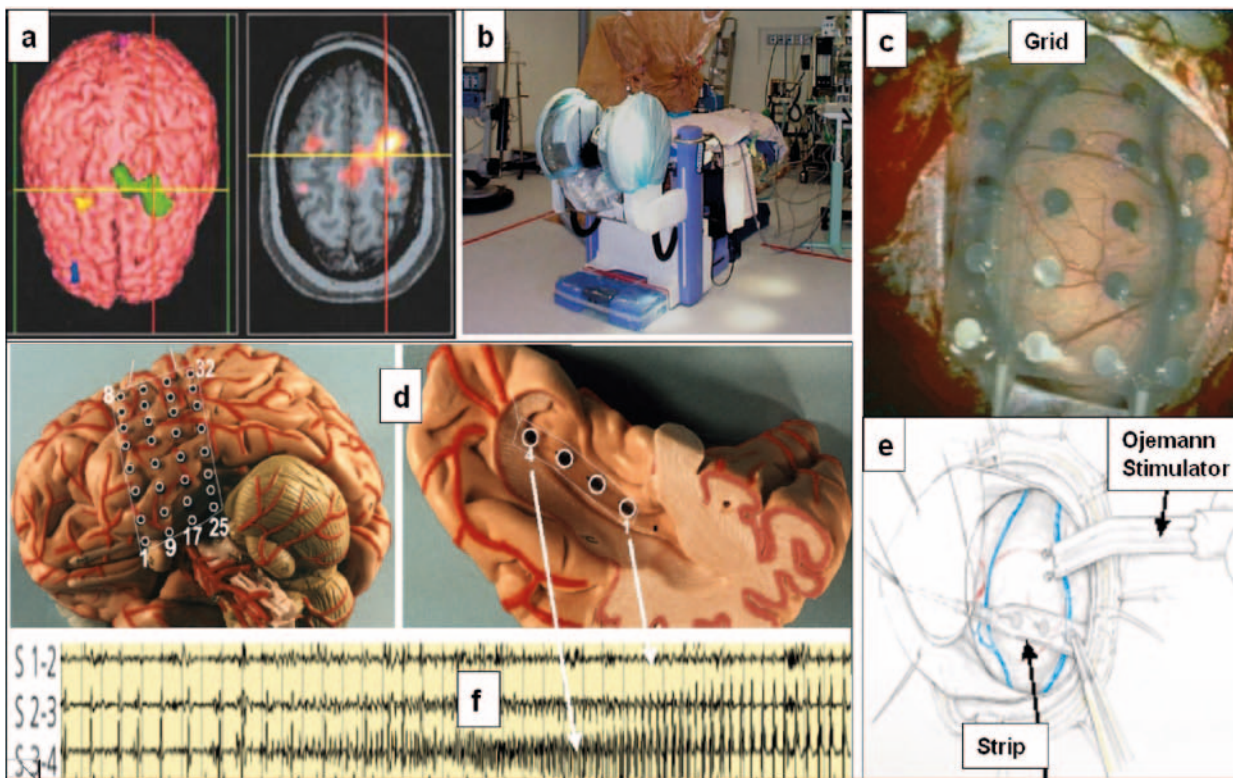
**Figure 5.** Seizure onset in the left foramen ovale electrode contact 5 (FOL5, arrow). The positions of the 10-contact FO electrodes are shown left (x-ray and CT). Bipolar FO electrode recording is in a closed chain starting with the deepest right posterior contact (FOR1).

rhythms of a seizure. IBSs can be recorded using the routine AC amplifiers with long time constants and in a restricted spatial distribution compared with conventional frequencies.

Bragin et al. (2007) analysed initial slow waves (ISWs) at seizure onset in 24 patients implanted with depth and grid electrodes because of refractory temporal lobe epilepsy. ISWs are characterized by a slow wave at the seizure onset followed by low voltage fast activity. The duration of ISWs varied between 0.3 to 6.0 s and maximum amplitude varied from 0.2 to 1.4 mV. Imamura et al. (2011) found that in wideband ECoG, negative slow shifts coexisted with HFO (100–300 Hz) in the ictal onset zone in all investigated seizures. Slow shifts always preceded HFO and conventional initial EEG changes by a mean value of 1.6 and 20.4 s, respectively. The slow shifts and HFOs were observed only in the restricted ictal onset zone. In the study of Ikeda et al. (1999) ictal direct current shifts were observed in 85% of 89 recorded seizures among the six patients, and they corresponded with the electrodes at which the conventional initial ictal EEG change was also observed. Whereas Ikeda et

al. (1999) found *focal* ictal direct current shifts, Perucca et al. (2013) noted that preictal increases occurred in each frequency band activity and were widespread, being observed in the seizure-onset zone and lesional tissue, as well as in remote regions.

Several EEG patterns of seizure onset have been described: Dericioglu and Saygi (2008) found that the most common onset pattern in mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) was the cessation of interictal discharges (35.2%). The most common ictal pattern following the initial changes was ipsilateral temporal rhythmic theta-delta activity (85.2%) that occurred on the average 13.4 seconds after onset. Malter et al. (2016) reported that in MTLE-HS rhythmic activity at seizure-onset had a frequency of  $4.7 \pm 1.5/s$  (range 1–8/s), and was mostly localized in the anterior temporal region. Rhythmic activity in the delta-band was more often observed with shorter epilepsy duration. In this study postsurgical seizure outcome was not associated with any clinical or electrophysiological feature. Jiménez-Jiménez et al. (2016), in a depth-EEG study, looked at the second ictal pattern



**Figure 6abcdef.** Elements of modern epilepsy surgery: (a) mapping of seizure onset (Ictal SPECT – SISCOM); (b) intraoperative MRI; (c,d) intraoperative electrocorticography (ECoG) using a 4-contact strip and a 32-contact grid electrode; (e) intraoperative electrostimulation ("functional mapping"); (f) anterior hippocampal discharge (S3-S4).

(SIP, that follows the first ictal pattern) and found that the electrodecremental event was the most common SIP seen in 41%, followed by fast activity (19%), spike-wave activity (18%), alpha activity (8%), sharp-wave activity (8%), delta activity (3%), runs of spikes (2%) and theta activity (2%). The electrodecremental event (see figure 3) was associated with favourable outcome when compared with fast activity.

Advanced centres combine various EEG technologies with addition of synchronized video-recording and polygraphic recordings (EMG, heart rate, respiration, galvanic skin response, etc; the latter for detection of autonomic signs and symptoms). This combined video-EEG-monitoring over prolonged time periods usually is able to localize the seizure onset. Stereoelectroencephalography provided major insights into the nature of human epilepsy (Bancaud et al., 1965).

Nowadays *Ictal SPECT* is a standard procedure in many centres. The use of SPECT to demonstrate ictal hyperperfusion, first described in 1983, has since been refined in multiple studies. Early injection of the tracer, usually technetium-99m ECD (ethyl cysteinyl dimer)

or technetium-99m HMPAO (hexamethylpropylene amine oxime), is of paramount importance. The sensitivity of ictal SPECT can be improved by comparison with interictal SPECT images and the coregistration of SPECT scans with the MRI of the patient (*SISCOM*, Subtraction Ictal SPECT CO-registered to MRI, see figure 6a). False localization has been reported in ictal SPECT. Thus, the results of ictal SPECT need to be seen in the context of the ictal EEG and other localizing information (Duncan, 2004).

#### *The epileptogenic lesion*

This is a morphological lesion responsible for or causally related to the epileptic seizures. It is defined by high-resolution MRI. However, not all lesions seen in a patient with epileptic seizures are epileptogenic. Some lesions may be unrelated to the clinical seizures. Structural imaging does not indicate epileptogenicity and does not, *per se*, provide information that could be considered surrogate markers of epileptogenicity or epileptogenesis. Therefore, it is mandatory to prove the epileptogenicity of a lesion. That means, that even when we



**Table 2.** Brain lesions associated with drug-resistant focal epilepsies (adapted from Blümcke et al., 2015). Principle histopathological categories of brain lesions associated with drug-resistant focal epilepsies submitted for epilepsy surgery in Germany, Austria and Switzerland. Data from all 5603 cases of the German Neuropathology Reference Centre. In this list 7% had “no lesion”, maybe due to sampling problems. It does not imply that microstructural functional changes are not present

Hippocampal sclerosis	37%
Tumours with early epilepsy onset: gangliogliomas, dysembryoplastic neuroepithelial tumors	21%
Malformations of cortical development (MCD): focal cortical dysplasia, nodular heterotopia, hemimegalencephaly, polymicrogyria, cortical tubers	19%
Glial Scars: bleeding, ischemic or traumatic brain injuries	6%
Malformative vascular lesions: cavernomas, arterio-venous malformations, Sturge-Weber syndrome	5%
Dual pathology	4%
Encephalitis: Rasmussen, Limbic	2%

see a lesion on the MRI we still have to use other methods to verify (usually by video-EEG monitoring and/or seizure semiology) that the lesion is indeed responsible for the patient's seizures.

It has been thought that complete resection of the epileptogenic lesion is necessary to obtain seizure-freedom. This is not always true, as evidenced by patients who became seizure-free although only a partial resection of the lesional cortex was possible because of its location in eloquent cortex. In such a case we have to assume that the remainder of the lesion was either never epileptogenic or was dependent on the resected tissue to elicit seizures in the sense that post resection the “critical volume” of epileptogenic tissue was no longer present. However, more often seizures persist despite complete resection of the MRI lesion. This is frequently seen in patients with cortical dysplasia (CD) because the sensitivity of MRI in detecting the totality of the CD is low. Brain tissue adjacent to a morphological lesion may consist of epileptogenic tissue alterations that are invisible on MRI. In patients with CD often only the “tip of the iceberg” is visible on MRI. Some lesions are known to have intrinsic epileptogenicity (e.g. hypothalamic hamartoma, Munari et al., 1995) or a perilesional epileptogenic rim (e.g. cavernous haemangioma). Therefore, in such cases lesionectomy and/or lesionectomy with resection of the adjacent perilesional tissue is usually successful. Comprehensive textbooks deal with the brain lesions associated with focal epilepsies (Shorvon et al., 2011; Blümcke et al., 2015; table 2).

MRI techniques have become the method of choice in detecting and defining epileptogenic lesions. Sequences, slice orientation and thickness have to be adapted to the questions posed. Usually,  $T_1$ -weighted,  $T_2$ -weighted and fluid attenuation inversion recovery (FLAIR) sequences are used for the basic investi-

gation. These sequences are highly (>99%) sensitive for tumorous epileptogenic lesions. As MTLE-HS is one of the most frequent epilepsy syndromes and remediable by surgery, thin, coronal  $T_2$ -weighted and FLAIR images, which are the most sensitive MRI sequences for this condition, need to be included. If mesial temporal sclerosis is suspected but not clearly visible, 1–2 mm  $T_1$ -weighted coronal volume acquisition images can be obtained to allow *volumetry* of the hippocampus and the amygdala, which is time-consuming but, in the hands of experienced investigators, may be somewhat more sensitive than visual inspection alone. A combination of volumetry and quantitative measurements of  $T_2$  relaxation time can slightly increase the sensitivity of MRI for unilateral or bilateral hippocampal atrophy. Volumetry is an important research tool, but its direct impact on patient management is limited.

*Curvilinear reformatting* was reported to be helpful in detecting subtle dysplastic lesions in otherwise MRI-negative cases. Automated segmentation and quantification of cerebral grey matter can identify subtle structural changes not otherwise detected. Special gradient echo sequences are the most sensitive sequences in the detection of cavernous angiomas.

Cortical dysgenesis as a frequent cause of medically intractable epilepsy is not always detected by the sequences used for the basic investigation. FLAIR and  $T_2$ -weighted inversion recovery sequences are currently considered most sensitive in this respect, the latter being especially useful to detect blurring of the grey-white matter junction.

In accordance with other studies Bien et al. (2009) found that the outcome in “non-lesional” (i.e. MRI-negative) cases is less favorable compared to “lesional” cases. However, patients with MRI-negative drug-resistant epilepsy can be successfully treated with surgery. Sur-

gical failures in patients without histopathological lesions mostly result from extensive epileptogenic areas. The most common epileptic pathological correlate not visualized by MRI is focal cortical dysplasia. Among the focal cortical dysplasia subtypes, non-balloon-cell focal cortical dysplasia type I (by either classification, ILAE type I or Palmini type I) is the most common (Wang et al., 2013). Improved sensitivity of MRI improves the outcomes of presurgically studied patients (Wang et al., 2016). Wang et al. (2015) demonstrated that a voxel-based MRI postprocessing technique, implemented in a morphometric analysis program (MAP on  $T_1$ -weighted MRI), facilitated detection of subtle abnormalities in a consecutive cohort of 150 MRI-negative surgical candidates. In this study MAP showed a 43% positive rate, sensitivity of 0.9, and specificity of 0.67. Patients with the MAP-positive region completely resected had the best seizure outcomes, followed by the MAP-negative patients. Patients who had no/partial resection of the MAP-positive region had the worst outcome.

Tumors and vascular malformations present the main indications for the application of contrast media in the MRI diagnosis of epilepsy.

In certain cases, PET is helpful to identify seizure-generating brain tissue. In patients with tuberous sclerosis complex (TSC) who have multiple brain tubers and epileptic seizures, only one or a few tubers might be epileptogenic and resection of it/them can render a patient seizure-free. Despite its low sensitivity, Chugani et al. (1998) concluded that alpha-[11C]methyl-L-tryptophan ([11C]AMT-PET is a powerful tool in differentiating between epileptogenic and nonepileptogenic tubers. AMT uptake appears to detect the presence of increased activity in the kynurenine pathway, which may be important for the epileptogenicity of this condition (Du et al., 1993).

#### *The symptomatogenic zone*

The initial ictal symptoms are produced by the so-called symptomatogenic zone. However, the activation of a cortical area by an epileptiform discharge or by direct cortical electrical stimulation is often not accompanied by any symptoms (then the term symptomatically “silent” cortex has been used). Therefore the definition of the symptomatogenic zone depends on the specific type of ictal symptoms and on the type (“strength”) of the activation. Frequently there is no close relation between the symptomatogenic zone and the epileptogenic zone. Often the ictal signs and symptoms are due

to spread of the discharge from an epileptogenic zone located in a symptomatically “silent” area to a distant area of eloquent cortex that is outside the epileptogenic zone. At least in automotor (formerly named “psychomotor” or “complex partial”; Lüders et al., 1998; Kotagal, 2000) seizures spread of the epileptic discharge is not random but follows preferential pathways, most often the known hodology of the brain (Wieser, 1983).

Careful analysis of the ictal symptomatology with a thorough seizure history and/or the analysis of ictal video recordings are necessary to define the symptomatogenic zone. The question of recording and studying “habitual” seizures of the patient is extremely important in presurgical evaluation, particularly also with reference to rapid reduction/withdrawal of antiepileptic drugs during EEG video monitoring. Closed-circuit video-EEG monitoring has provided a tool that allows repeated careful analysis of the ictal and post-ictal symptoms (Stoyke et al., 2011; Kobulashvili et al., 2016). Sophisticated anatomo-electro-clinical correlations have shed some light into the organization of propagating seizure discharges and permitted the distinction of “primictal symptoms” (“signal-symptom” – Bancaud et al., 1965) *versus* secondary ictal and post-ictal symptoms.

Semiology is dependent upon electrical activity produced by epileptic seizures that is organized within existing neural pathways. Epileptic discharge spreads in both time and space. Signs and symptoms occur with variable time lag after seizure onset and then emerge more or less rapidly depending on seizure type. The level of complexity of semiological features varies according to the degree of involvement of the primary or associative cortex, with the former having a direct relation to peripheral sensory and motor systems with production of hallucinations (visual and auditory) or elementary sensorimotor signs. Depending on propagation patterns, these signs can occur in a “march” fashion as described by Jackson (1931). On the other hand, seizures involving the associative cortex, having a less direct relation with the peripheral nervous system, and necessarily involving more widely distributed networks manifest with altered cognitive and/or behavioral signs whose neural substrate involves a network of cortical structures. Chauvel and McGonigal (2014) stress the fact that studies of functional coupling within networks underlying complex ictal behavior indicate that the clinical semiology of a given seizure depends upon neither the anatomical origin of ictal discharge nor the

**Table 3.** The most important lateralizing ictal and postictal symptoms in patients with temporal lobe or extratemporal epilepsy (adapted from Rosenow and Lüders, 2001)

Symptom/Sign	Location of the epileptogenic zone	Specificity	Frequency	References
Forced head-version (<10 s) before secondary generalization	cl	90%	TLE 35% ETE 40%	Wyllie et al., 1986; Kernan et al., 1993; Bleasel et al., 1997; Chee et al., 1993
Unilateral ictal dystonia	cl	90–100%	TLE 35% ETE 20%	Kotagal et al., 1989; Steinhoff et al., 1998; Bleasel et al., 1997
Figure of four	cl	90%	65% of pts. with sGTCSs	Kotagal et al., 2000
Ictal speech	n-d	> 80%	10–20%	Chee et al., 1993
Preserved consciousness during ictal automatisms	n-d	100%	Rare, 5%	Ebner et al., 1995
Postictal dysphasia	d	> 80%	20% (depends on the testing)	Steinhoff et al., 1998; Chee et al., 1993
Postictal nosewiping	il	80–90%	TLE 40–50% FLE 10%	Geyer et al., 1999; Hirsch et al., 1998; Leutmezer et al., 1998; Al-Hail et al., 2011
Unilateral eyeblinking	il	80%	Rare 1.5%	Benbadis et al., 1996
Ictal vomiting	n-d	> 90%	Rare	Kramer et al., 1988

Abbreviations: TLE – temporal lobe epilepsy; ETE – extratemporal epilepsy; FLE – frontal lobe epilepsy; sGTCSs – secondary generalized tonic-clonic seizures; il – ipsilateral; cl – contralateral; d – dominant; n-d – non-dominant

target areas of its propagation alone but on the dynamic interaction between these. Therefore, careful mapping of the ictal network in its full spread offers essential information as to the localization of seizure onset.

The localizing/lateralizing value of several signs and symptoms has been studied and there exist several reviews on the value and limitations of the seizure semiology in localizing the epileptogenic zone (Wieser and Williamson, 1993; Fried, 1997; Rosenow and Lüders, 2001; Rona, 2008; Nagaraddi and Lüders, 2008; Tufenkjian and Lüders, 2012; Dupont et al., 2015). Table 3 lists a few of the most important lateralizing ictal and postictal symptoms and table 4 that of autonomic seizures. It is clear that such tables often are not very helpful, because they do not take into account the “march of symptoms” and the context and the overall “gestalt”.

Taking into account the spatio-temporal sequence of signs and symptoms, fairly characteristic *seizure patterns* have been described. Some signs and symptoms are relatively characteristic for a specific epileptic syndrome. For example, hypomotor seizures of mesial temporal limbic origin often start with a motionless stare or behavioral arrest (Delgado-Escueta et al., 1977; Delgado-Escueta and Walsh, 1985). Maldonado et al. (1988) found that 39% of seizures of amygdalar and hippocampal origin started with motionless staring, 25% with nonfocal discrete movements, and 21% with oroalimentary automatism.

Hypermotor seizures of *frontal lobe origin* have been characterized by a cluster of signs and symptoms and the overall “gestalt”. Features that distinguish these seizures from focal seizures originating elsewhere include brief, frequent attacks often occurring during sleep, complex motor automatisms with bicycle pedaling motions and pelvic thrusting, kicking and thrashing, sexual automatisms, vocalization often with screaming profanities or laugh, and frequent development of status epilepticus. The constellation of clinical characteristics is often “bizarre”, leading to the erroneous diagnosis of a psychiatric disorder (“hysteria”; Williamson et al., 1985; Williamson, 1995).

Other examples are the following *motor patterns*: the versive seizure, the tonic or clonic seizure of the face, the M2e sign (Ajmone-Marsan and Ralston created the term “M2e” in 1957) and the “sign of four”. They have a good lateralizing value, but except the M2e sign which is associated with the SSMA, do not localize the seizure origin with confidence.

The tonic face seizure and the versive seizure lateralize the seizure to the contralateral side. The fencing position (M2e) lateralizes to the hemisphere contralateral to the raised arm, and the asymmetric tonic limb posturing “sign of four” lateralizes to the hemisphere contralateral to the extended arm. Versive head rotation, unilateral dystonic limb posturing, asymmetric tonic limb posturing, and the combination of unilater-



**Table 4.** Localizing and lateralizing value of autonomic seizures (adapted from Nagaraddi and Lüders, 2008)

Ictal Cardiac manifestations	Tachycardia Bradycardia Asystole Arrhythmia	R mesial T bilateral T L.T., L.F., L cingulate gyrus, implicated in SUDEP n-lo & n-lat
Ictal Respiratory manifestations	Hyperventilation Apnea Dyspnea and stridor Postictal nose wiping/postictal coughing:	mesial > lateral T > F T, No not well defined entity (R mesial T?). T (the hand used in postictal nose wiping points to ipsilat. T); Ictal: insula
Gastrointestinal manifestations	Epigastric Abdominal: (abdominal pain) Vomiting (Ictus emeticus) Spitting (Ictus exoratus) Hypersalivation Defecation	mesial T, insula T T, insular, spread from O to T T, insula, more often n-d MTLE, n-d Rare (R?)
Cutaneous manifestations	Sweating, cyanosis, purpura Piloerection (goose bumps) Pallor Flushing	no-lo, no-lat mostly T, no-lo, no-lat L? T? no-lo, no-lat
Pupillary manifestations	Unilateral ictal mydriasis and ictal myosis	Rare & inconsistent findings
Urogenital manifestations	Urine incontinence urinary urge Sexual/orgasmic Genital aura Sexual automatisms Genital automatisms	most often; no-lo, no-lat n-d T, but also L T more often R T parasagittal postcentral; SSII (?). associated with F; no-lo, no-lat

Abbreviations: R – right, L – left, T – temporal, F – frontal, SUDEP – sudden unexpected death in epilepsy, ipsilat – ipsilateral, no-lo – not localizing, no-lat – not lateralizing, n-d – non-dominant

al hand automatisms and dystonic posturing were determined as the semiologic signs with the highest lateralizing values (90–100%) (table 3).

Of particular interest is the localizing and lateralizing value of *epileptic auras*. Auras as the “primictal” symptom are usually categorized according to their complexity (simple, complex) and their sensory modalities: somatosensory, visual, auditory, olfactory, gustatory, viscerosensory phenomena, cephalic sensations, vertigo and dizziness, and diffuse warm and cold sensations. They can be positive or negative phenomena. They can also be classified into illusions, hallucinations and emotions. Penfield and Jasper (1954) regarded illusions and emotions as “interpretative,” in the sense that they involve interpretation of the present. The localizing and lateralizing value of epileptic auras have been summarized by Wieser and Williamson, 1993; Jobst and Williamson, 2005; Rona 2008; Tufenkjian and Lüders, 2012.

*Somatosensory* phenomena include tingling, numbness, or pain and thermal sensations in a particular region or side of the body. A highly localized somatosensory aura, such as paresthesias of one or two fingers

(i.e. unilateral and distal) at the beginning of a seizure, clearly localizes to the corresponding primary sensory area. Bilateral, more widespread, and more proximal somatosensory auras are associated with the supplementary sensorimotor area (SSMA) and second somatosensory area (SSII; located in the superior bank of the Sylvian fissure and/or posterior insula). On the other hand, a poorly defined body sensation has little localizing or lateralizing value.

*Visual auras* include simple positive phenomena, such as phosphenes, static, flashing, or moving lights/shapes, colours; and negative symptoms such as scotoma, hemianopia, amaurosis, i.e. loss or “whitening” of vision. Simple visual auras are caused mostly by abnormal activity in the primary visual cortex (Brodmann area 17 and 18). They can be lateralized to one contralateral hemifield or to a quadrant.

Illusions may involve macroscopia or microscopia, as well as seeing objects nearer or farther. Complex phenomena (hallucinations) include images such as a scene, a face, people and objects. Complex visual auras are associated with parieto-temporal cortex and result from stimulation of the temporo-occipital junc-

tion, more frequently in the non-dominant hemisphere.

*Auditory* auras include simple auditory sensations, mainly ringing in the ears or humming. Illusions may involve changes in the quality of sound, e.g., loud or soft, clear or faint. More complex sensations include voices or music. Simple auditory auras localize to the Heschl's gyrus, complex auditory point to the temporal and frontal lobes.

*Olfactory* or *gustatory* phenomena include "foul odour," "burning smell," "odd, sour and bad taste." Olfactory auras localize the epileptogenic zone to the amygdala and insula and are often found to be associated with tumorous lesions involving the amygdala.

*Viscerosensory* auras include epigastric sensations (usually a feeling of "rising"), nausea or a "sickening feeling," and chest sensations. Some authors classify *epigastric* (*abdominal epigastric*) sensations as a separate subgroup because of their frequent occurrence and their plethora of symptoms (tenseness, knot, squeezing, rolling or whirling movements in the abdomen, tickling, tingling, fluttering or butterfly sensations, sudden descent in an elevator). It has been said that they may be linked to an increased peristalsis (borborygmi) and localize to the insula, mesial temporal and mesial frontal lobe and basal ganglia.

*Autonomic* symptoms include throat constriction, breathing difficulties, palpitations, thermodyregulation and urinary urge. Their localizing and lateralizing value are summarized in table 4.

*Cephalic* auras include sensations such as a "funny feeling in the head," "pressure in the head," and "something crawling in my head." They have been described more often with frontal and temporal localization, but all lobes are possible. They have no lateralizing value.

*Dizziness*, vertigo, or light-headedness prior to seizures can be classified as a separate group. Rare are ictal vomiting and ictal spitting (Schindler and Wieser, 2006; Kellinghaus et al., 2003).

The most intriguing auras have been those that patients reported as similar to real-life experience; hence the term *experiential* auras. Jackson (1931) regarded these auras as "the most elaborate psychical states" and used the term intellectual aura, dreamy states, "doubling of consciousness" or "mental diplopia". The experiential phenomena elicited by electrical stimulation are often specific to the individual patient. Experiential auras include experiences such as déjà vu (an intense feeling of visual familiarity), jamais vu (a feeling of visual strangeness), the auditory counterparts déjà

entendu and jamais entendu, sentiment de l'inconnu (such as a "feeling of things being different"), "memory flashbacks", forced thoughts, complex visual or auditory illusions or hallucinations, and emotional experiences, mostly fear.

Some auras include illusions involving self-image, such as depersonalization, remoteness, and "out-of-body" experiences.

Jackson thought that these responses reflect release from inhibition, whereas Penfield viewed them as the expression of active physiological processes. Gloor et al. (1982) reported that most experiential phenomena were evoked by stimulation of medial rather than lateral temporal lobe sites. Of the sites involved in experiential responses, the amygdala predominated, followed by the hippocampus and the parahippocampal gyrus. This was true not only for emotional responses, but also for complex visual and auditory hallucinations, activation of memory recall, and illusions of familiarity. In those cases where lateral temporal lobe stimulation evoked experiential phenomena, there was always spread of excitation to medial temporal lobe sites.

Gloor (1990) proposed a neurobiological substrate for experiential phenomena based on models of parallel distributed processing and concluded that the aura, like memory, may be represented in a distributed network. This explains that, following circumscribed surgical removal of the presumed epileptogenic zone, as many as 35% of patients retain their auras in spite of being seizure-free.

Gupta et al. (1983) found that right hemispheric EEG abnormalities were more likely in patients with psychic or autonomic auras. Heydrich et al. (2015) suggest a lateralising value for experiential hallucinations to the left temporal lobe.

Sometimes sophisticated testing is crucial to detect transient cognitive symptoms associated with epileptiform discharges (ED) (Wieser et al., 1985; Binnie, 2003). With very sensitive testing brief episodes of cognitive function have been documented associated with EDs (Binnie, 2003), supporting the notion that antiepileptic medication can improve psychosocial function.

Short ED of 10 seconds or less (so-called subclinical discharges) can disturb cognition and influence daily performance at school and at home. Several studies have been performed to show the negative effect of these epileptiform EEG discharges on choice reaction time tests, short term memory tests (verbal and non-verbal), and on school performance tasks such as read-

ing, writing, and arithmetic. About one-half of children with subclinical discharges will show transient cognitive impairment during these discharges: those with predominantly left-sided discharges are poorer on reading and those with right-sided discharges are poorer on visual spatial tasks (Kasteleijn-Nolst Trenité, 1995). In individual cases, suppression of the epileptiform EEG discharges with antiepileptic drug improved cognitive performance and therefore can be beneficial.

Aldenkamp and Arends (2004) reviewed the existing evidence on the cognitive impact of interictal epileptiform EEG discharges. "Transient cognitive impairment" occurs exclusively in direct relation to episodes of epileptiform EEG discharges and must be distinguished from (post) ictal seizure effects and from the non-periodic long-term "stable" interictal effects caused by the clinical syndrome or the underlying etiology. Epidemiological data show that the prevalence of cognitive impairment during epileptiform EEG discharges is low. However, early detection of cognitive effects of epileptiform EEG discharges and subsequent treatment may prevent a definite impact on cognitive and educational development. The disruptive effects of epileptiform EEG discharges on long-term potentiation, as established in animal experiments, may be one of the neurophysiological mechanisms underlying this accumulation. Therefore the authors concluded that the concept of "transient cognitive impairment" is still valid, but refinement of methodology has shown that a large proportion of presumed transient cognitive impairment can be attributed to subtle seizures.

Holmes and Lenck-Santini (2006) suggest that interictal spikes, particularly if frequent and widespread, can impair cognitive abilities, through interference with waking learning and memory, and memory consolidation during sleep. They argue with the syndrome of continuous spikes and slow waves during sleep (CSWS – electrical status epilepticus during slow sleep, ESES).

#### *The irritative zone*

The irritative zone is that area that generates interictal epileptiform discharges (ED, i.e. spikes and sharp waves). The irritative zone is measured by EEG, MEG, or functional MRI (fMRI) triggered by interictal spikes. Spikes that are generated within an eloquent cortical area can be accompanied by clinical symptoms, as is often the case with myoclonic jerks associated with spikes in the primary motor cortex. Myoclonus may be positive or negative motor phenomenon. In general,

however, isolated, independent spikes will not generate any clinical symptoms. To produce symptoms, usually runs of EDs (afterdischarges, "semi-ictal discharges") are necessary. "Semi-ictal" was introduced by us to describe a transitional state from interictal to ictal.

Many spikes in intracranial EEG are not seen in scalp EEG. It has been estimated that activation of 6 cm<sup>3</sup> or about 10 cm<sup>2</sup> of gyral cortex is necessary to produce a scalp EEG ED (Tao et al., 2005).

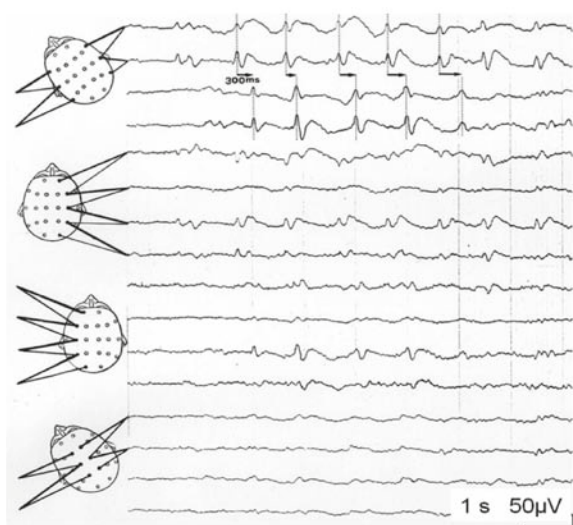
EDs in scalp EEG are nearly always of negative polarity. Focal EDs can be localized in a referential montage by maximum voltage amplitude and in a bipolar montage with phase reversal.

Factors affecting the irritative zone are the type of epilepsy syndrome, vigilance, temperature, age, anesthetic and antiepileptic drugs. Interictal EDs can be found in a small percentage of persons, who never develop epilepsy. Differentiation of epileptiform spikes from nonepileptiform transients is another problem: a number of sharply contoured graphoelements have been shown to be normal variants or so-called "patterns of doubtful significance" (Zumsteg et al., 2004). Therefore spikes might not have the same meaning. It has been shown that in cortical dysplasia spikes signify a high intrinsic epileptogenic property, whereas in MTLE contralateral spikes might disappear following unilateral resection. Theodore Rasmussen at the Montreal Neurological Institute noted that there are "red" spikes and "green spikes". The problem is that attempts to distinguish red from green spikes based on aspects of spike morphology, such as rise time, sharpness, or the following slow waves, by patterns of recurrence, such as frequency, or by response to suppression by drugs, such as methohexital, were generally unsuccessful.

#### *Mirror focus*

The development of a so-called mirror-focus exhibiting "dependent" (figure 7) or "independent" spikes is well known (Morrell and deToledo-Morrell, 1999). Morrell coined the term secondary epileptogenesis and subsequently referred to it as the mirror focus. He demonstrated that following the creation of an epileptic primary focus, an independent epileptic focus can develop in the homotopic area of the contralateral hemisphere, i.e., in that region to which the primary focus sends a direct synaptic projection. In its early stages of development, this secondary epileptic zone is dependent on the integrity of the corpus callosum and subcortical connections. When in the mirror focus "matures",





**Figure 7.** Scalp EEG with about 1/sec repetitive sharp-slow-waves in both anterior temporal regions, the right-sided precede the left with about 300 ms. The patient had been aura- and seizure-free for 20 years following a right selective amygdalohippampectomy. Histology revealed a small schwannoma in the excised tissue. The EEG normalized within 6 months postoperatively including the dependent left-sided "mirror focus".

abolition of the primary focus, or section of the corpus callosum and/or interruption of subcortical connections, does not abolish the secondary epileptic zone.

Spike mapping during intraoperative electrocorticography (ECoG, see figure 6c,d) was and still is a common technique for determining the size of brain resections in focal epilepsy, but the high degree of false localization based on this method is well-recognized. With regard to tailoring the resections there is evidence that more extensive spiking beyond the margins of the planned resection or the persistence of interictal or ictal epileptiform activity, especially when remote from the margins of the resection, is indicative of a poorer surgical outcome (Greiner et al., 2016). The advantages of intraoperative ECoG over chronically implanted subdural electrodes are that ECoG is less invasive and less expensive, carries a lower risk of complications, is no burden to the patient and allows postresection recordings. The disadvantages are the shorter recording time, which does not usually allow the recording of seizures and limits cortical stimulation. The poorly defined influence of anesthetics might be another problem. Therefore, intraoperative ECoG is restricted to the definition of the irritative zone and cannot be used to delineate the seizure onset zone or the eloquent cortex sufficiently.

#### *The functional deficit zone*

The functional deficit zone is functionally abnormal in the interictal period. Methods that can measure it are neurological examination, neuropsychological testing, EEG, [ $^{18}\text{F}$ ]fluorodeoxyglucose-PET (FDG-PET) scanning, and interictal SPECT. Frequently the functional deficit zone is more extended compared with the zones that are related more directly to epileptogenesis. An example is FDG-PET in MTLE-HS. Although in MTLE-HS the epileptogenic zone is usually limited to the mesial temporal region and seizure-freedom is often achieved with selective amygdalohippampectomy (seLAHE; Wieser, 1986), FDG-PET studies often reveal extensive hypometabolic regions outside the resected tissue. We have documented that these hypometabolic lateral temporal regions can normalize following successful seLAHE (Hajek et al., 1991).

PET is a technique to define cortical areas of functional deficit. Areas of interictal cortical hypometabolism imaged by FDG-PET in patients with temporal lobe epilepsy correlate extremely well with the presumed lateralization of the epileptogenic zone, as defined by depth EEG (Engel et al., 1982). The value of FDG-PET in the lateralization and even localization of extratemporal epilepsies was also demonstrated by a number of investigators. PET studies, using a variety of other ligands, such as flumazenil, are currently being evaluated in an attempt to find a method that may identify more precisely the area of functional deficit or even give a more specific measurement of epileptogenicity (Komoto et al., 2015).

#### *"Eloquent" cortex*

Not infrequently resective epilepsy surgery is limited by the need to spare the eloquent cortex in order to avoid new, unacceptable deficits for the patient. Methods commonly used to detect the "eloquent cortex" include electrical stimulation of the cortex, evoked potentials, MEG, fMRI and, to a lesser extent, PET. A possible loss of function as a consequence of the epilepsy surgery should at least be predictable and discussed with the patient prior to the procedure. Presurgical and/or intraoperative "functional mapping" (figure 6e) with the use of subdural electrodes is used to define the location and extent of the "eloquent" cortex. In a small proportion of the patients we performed the intraoperative "mapping" in the awake patient which can be of considerable value in the interpretation of obtained responses (Fandino et al., 1999).



**Figure 8.** Illustration of the stimulus material (cards with verbal and figural items) used in selective temporal lobe Amytal test. In the storage phase the patient is presented with cards containing a word (e.g. OVER) and a figure (e.g. bicycle). In the recognition phase the stimulus cards consist of either a word or a figure; 50% of the items are targets, i.e. have been presented to the patient in the storage phase and ask for a button press to be counted as a correct answer.

The *intracarotid amobarbital (Amytal) procedure* or *Wada test*, first described in 1949, was used initially to lateralize only language function (Wada, 1949). In 1959, the use of this test was expanded to the lateralization of memory function in an attempt to identify areas of functional deficit and to predict postsurgical outcome. In modern neuropsychology, the Wada test is used mainly to localize the eloquent cortex with regard to language and memory (Rausch et al., 1993). To predict memory function after selective amygdalohippocampectomy we have developed the so-called selective temporal lobe Amytal memory test (Wieser et al., 1997). Figures 8 and 9 illustrate this test.

In the last decade fMRI has also been used to localize the eloquent cortex and there is accumulating evidence that fMRI may replace the Wada test. Today the value of the Wada test is controversial. Elshorst et al. (2009) stated that the Wada test is of no added value to preoperative neuropsychological assessment and MRI in postoperative memory prediction in left temporal lobe epilepsy.

#### *Potential modern surrogate markers of epileptogenesis and epileptogenicity*

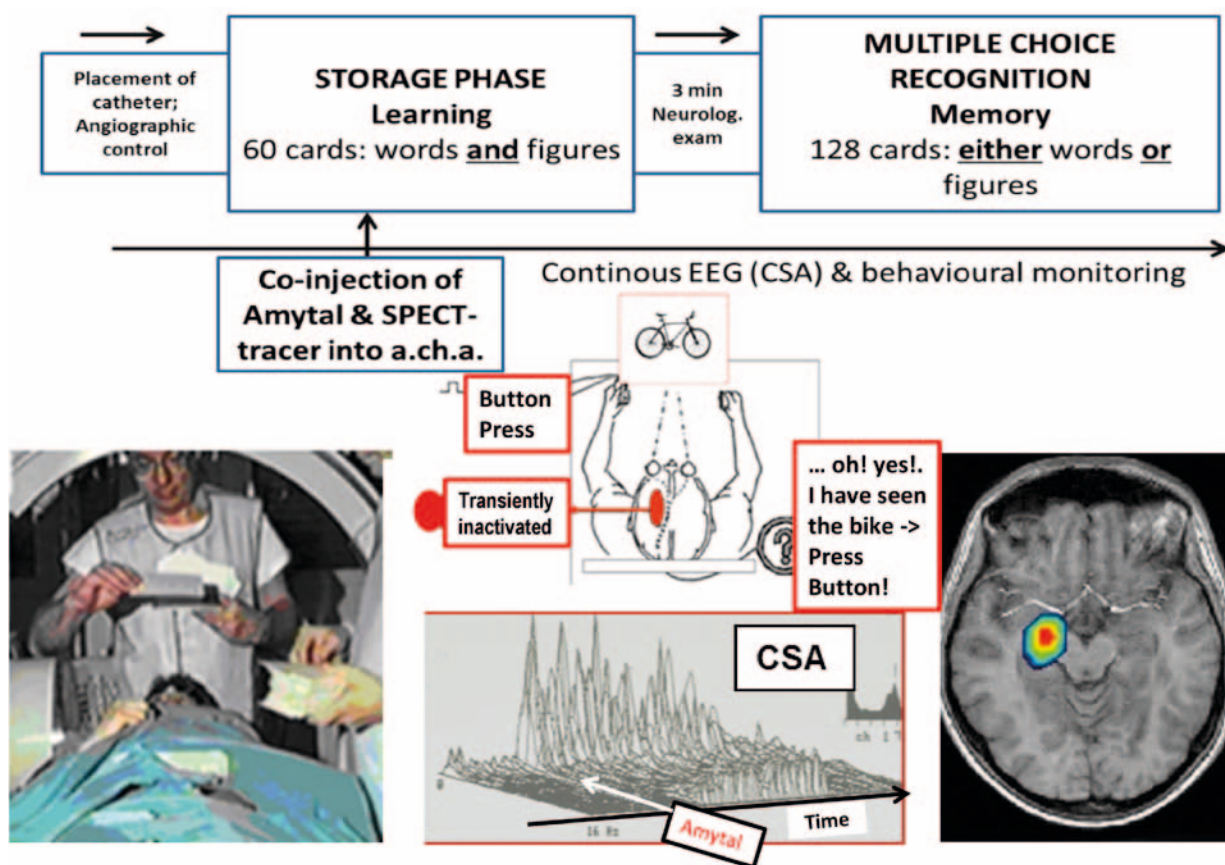
*High Frequency Oscillations (HFOs* – figure 10) has emerged as a new biomarker for epileptogenic tissue, which holds the promise to improve understanding of the pathophysiology of epilepsy and to develop new clinical diagnostic methods. Higher resolution EEG and/or magnetoencephalography (MEG) can identify HFOs. This biomarker can be found in brief intracranial EEG recordings and possibly even in extracranial

MEG or EEG. HFOs above 80 Hz require the EEG to be sampled at a frequency above the usual 200 Hz or 500 Hz. To reliably record HFOs, the intracranial EEG needs to be sampled at least at 2000 Hz. The oscillatory events can be visualized by applying a high-pass filter and increasing the time and amplitude scales, or EEG time-frequency maps can show the amount of high-frequency activity.

Terminology of HFOs is varied and includes gamma (30–80 Hz), ripple (80–250 Hz), and fast ripple (FRs; > 250 Hz) oscillations. HFOs in the 80–200 Hz range can be recorded from normal hippocampus and parahippocampal structures of both humans and animals. They are believed to reflect inhibitory field potentials, which facilitate information transfer by synchronizing neuronal activity over long distances. FRs are pathologic and are readily recorded from hippocampus and parahippocampal structures of patients with MTLE, as well as rodent models of this disorder. Some slower oscillations in the “ripple” frequency may also be abnormal epileptiform events with a similar significance with respect to epileptogenicity. Since these epileptiform HFOs occur early after an epileptogenic insult, long before seizures begin, HFOs appear to be putative surrogate markers not only for epileptogenicity, but also for *epileptogenesis* (Engel et al., 2009; Andrade-Valenca et al., 2011).

Removal of brain tissue generating HFOs has been related to better postsurgical outcome than removing the seizure onset zone, indicating that HFOs may mark cortex that needs to be removed to achieve seizure control. The existence of an interictal, electrophysiological biomarker of epileptogenic brain has the potential to significantly advance epilepsy surgery by potentially eliminating the reliance on chronic intracranial EEG monitoring (Worrell and Gotman., 2011). The correlation between removal of HFO-generating areas and good surgical outcome indicates that HFOs could be used as a marker of endogenous epileptogenicity (Jacobs et al., 2010) and may be more accurate than spike-generating areas or the seizure onset zone. In patients in whom the majority of HFO-generating tissue remained, a poor surgical outcome occurred (Zijlmans et al., 2012).

Spatially, fast ripples are recorded in small areas of the cortex, whereas ripples are more widespread, which might explain different findings among electrode sizes. Several studies with microelectrodes conclude that fast ripples are most specific for the epileptogenic zone, but in clinical studies with macroelectrodes it is useful to



**Figure 9.** Illustration of the selective temporal lobe Amytal test with nonverbal motor response to predict memory in a candidate for selective amygdalohippocampectomy. The mixture of Amytal and SPECT-tracer is injected into the territory of the anterior choroidal artery (a.ch.a.). Amytal produces slow waves in the depth EEG recorded from amygdala and hippocampus. Compressed spectral analysis (CSA) quantifies the amount and duration of the slow wave activity as a measure of inactivation. SPECT-MRI fusion (lower right) delineates the inactivated structures, which are identical with the planned resection. The type of stimulus material is shown in figure 8. In the storage phase 60 cards with words (e.g. OVER) and figures (e.g. bicycle) are presented, providing a baseline and the performance after inactivation. In the recognition task 128 cards are presented containing either words or figures. The patients respond with button press (non-verbal motor response) if they believe to recognize an item. This way correct and false positive answers can be counted for verbal and non-verbal (figural) material (adapted from Wieser et al., 2007).

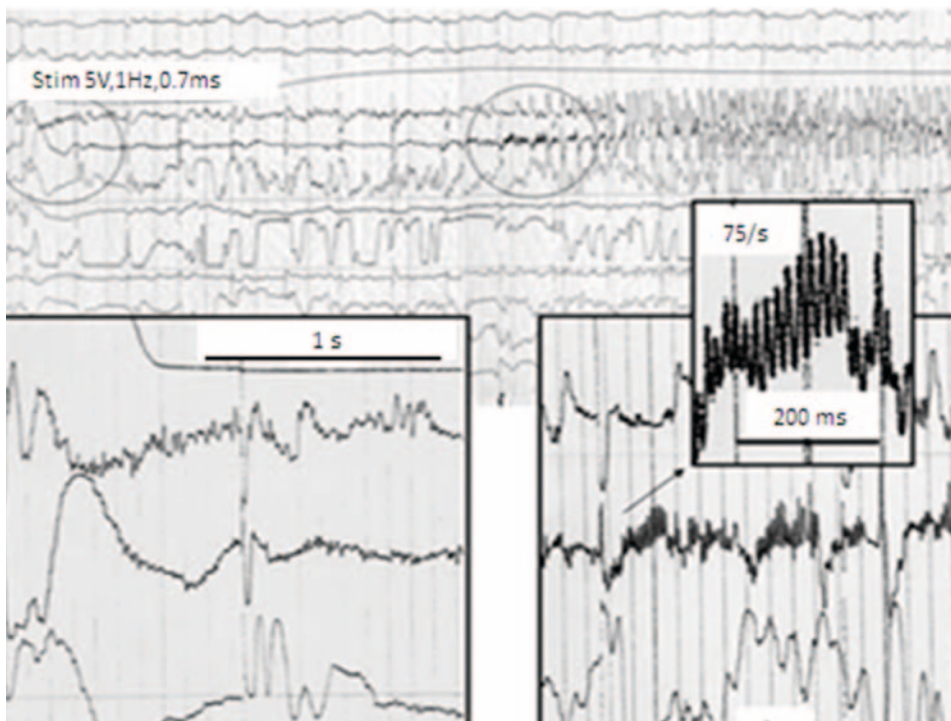
Neurol. exam. – neurological examination; SPECT – single-photon emission computed tomography

include both ripples and fast ripples in the evaluation of the potential epileptogenic region and future studies are needed to explore the importance of discriminating between the two.

Whereas most studies have concentrated on brief ripple events, recently, however, Mooij et al. (2016) showed that background activity in the ripple band also has some ability to discriminate epileptic channels. In line with this, Ferrari-Marinho et al. (2016) demonstrated that distinct seizure-onset patterns correlate with specific interictal and ictal HFO profiles confirming that seizures with different morphological patterns likely have different mechanisms of generation.

*Magnetic resonance spectroscopy (MRS)* is used to detect abnormalities (decreases) in the *N*-acetyl-acetate/choline or the *N*-acetyl-acetate/creatine quotient. *N*-acetyl-acetate is a marker mainly of neuronal membranes. A decrease in the quotients mentioned correlates with structural or functional changes. A functional decrease has been reported to be reversible after contralateral selAHE in patients with mesial temporal sclerosis and bilateral MRS abnormalities (Duc et al., 1998). MRS has been applied primarily to the investigation of mesial temporal structures, with promising results. However, it still cannot be considered a technique of established diagnostic value.





**Figure 10.** High frequency oscillations of about 75/s (see enlarged inserts) in the anterior hippocampus recorded with depth EEG macroelectrodes in close proximity to the stimulated ipsilateral amygdala.

*Functional magnetic resonance imaging (fMRI)* visualizes the area of hyperperfusion associated with EEG spikes as an indication of which brain tissue is generating epileptiform discharges (Coan et al., 2016). The combination of simultaneously acquired EEG-fMRI has recently become possible thanks to MRI-compatible EEG systems. Subsequently, powerful artifact removal algorithms for the EEG-signals have been developed that now allow to recover the EEG despite the high amplitude MR-artifacts during scanning. EEG-fMRI combination has become of particular interest for the localization of epileptogenic foci (Seeck et al., 2010). Kesavadas et al. (2007) showed that the results of real-time fMRI matched those of off-line processing using the well-accepted standard technique of statistical parametric mapping. Coregistration of the fMRI data on a 3-D FLAIR sequence, rather than a  $T_1$ -weighted image, provided better information regarding the relationship of the lesion to the area of activation. The results of intraoperative cortical stimulation and fMRI matched in all six patients. In a recent study Coan et al. (2016) showed that the presence of significant BOLD changes in the area of resection on interictal EEG-fMRI

in patients with TLE retrospectively confirmed the epileptogenic zone. These authors conclude that surgical resection including regions of haemodynamic changes in the TL may lead to better postoperative outcome.

*EEG spike-triggered fMRI averaging* provides hope that the fMRI image produced by spikes originating in primary epileptogenic regions will be different from those that are propagated, or originate in secondary epileptogenic regions, i.e. there is hope that fMRI might be able to detect the metabolic consequences of the "red" spikes.

In the study of Fernández et al. (2003) *language fMRI* proved sufficiently reliable for the determination of global and regional lateralization of language representation in individual unselected patients with epilepsy. Worthington et al. (1997) compared the results of standard intracarotid speech amytal testing and echoplanar blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI), in patients undergoing presurgical evaluation for intractable epilepsy. Of the 15 patients entered in the study, all had fMRIs while performing a verbal fluency task. Twelve of these patients also underwent standard intracarot-

id sodium amytal testing (IAT) for speech and memory. There was only poor concordance between the results of these two methods. The authors discuss possible reasons, including complexity of the verbal fluency task, and motion and technical issues in MRI scan acquisition and data analysis.

Janecek et al. (2013) tried to more definitively characterize Wada/fMRI language dominance discordance rates with a large sample of 209 patients and examined demographic, clinical, and methodologic predictors of discordance. In this prospective study language laterality indices were computed for each test using automated and double-blind methods, and Wada/fMRI discordance rates were calculated using objective criteria for discordance.

Regression analyses were used to explore a range of variables that might predict discordance, including subject variables, Wada quality indices, and fMRI quality indices. Discordant results were observed in 14% of patients. Discordance was highest among those categorized by either test as having bilateral language. In a multivariate model, the only factor that predicted discordance was the degree of atypical language dominance on fMRI.

Richardson et al. (2004) compared data for the prediction of post-operative verbal memory decline with a *fMRI assessment of verbal memory* encoding. In this study, multiple regression analyses showed that fMRI provided the strongest independent predictor of memory outcome after surgery. At the individual subject level, the fMRI data had high positive predictive value for memory decline. Powell et al. (2008) assessed the value of preoperative fMRI in the prediction of material specific memory deficits following both left- and right-sided anterior temporal lobe (ATL) resection. They concluded that preoperative memory fMRI may be a useful non-invasive predictor of postoperative memory change and that fMRI may provide additional information, over that provided by neuropsychology, for use in the prediction of postoperative memory decline.

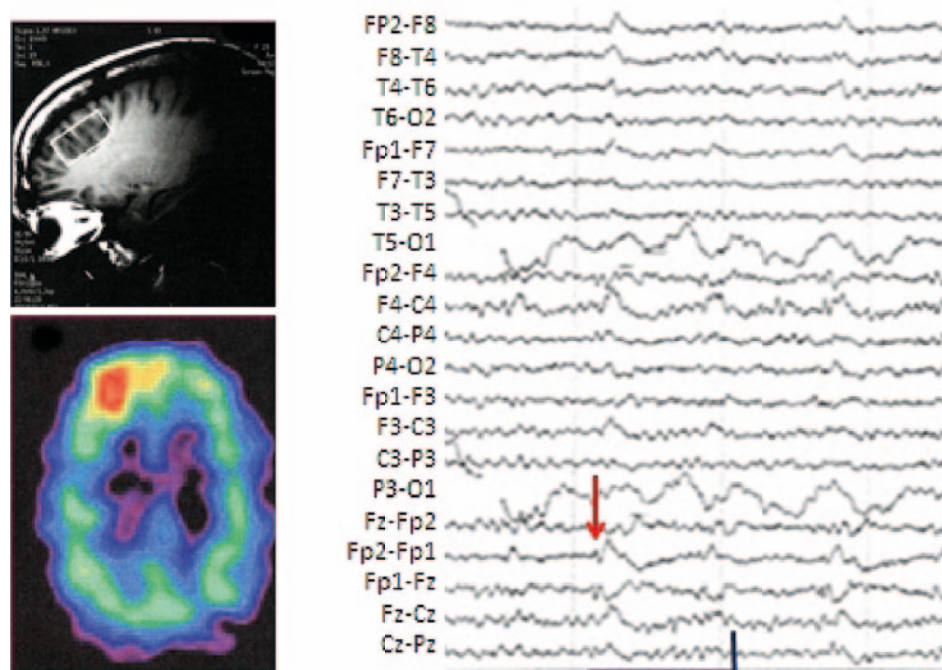
Binder et al. (2008) studied 60 left anterior temporal lobectomy patients and found that Wada memory testing is either insufficiently reliable or insufficiently material-specific to accurately localize verbal memory processes. In 2011 Binder concluded that the predictive power of fMRI appeared to be at least as good as the Wada memory test, making fMRI a viable noninvasive alternative to the Wada for preoperative assessment (Binder, 2011).

Bonelli et al. (2010) studied 72 patients with unilateral MTLE (41 left) and 20 healthy controls with a fMRI memory encoding paradigm for pictures, words and faces and found that event-related fMRI analysis revealed that activation asymmetry, language lateralization and performance on preoperative neuropsychological tests predicted clinically significant verbal memory decline in all patients who underwent left anterior temporal lobectomy, but were less able to predict visual memory decline after right anterior temporal lobectomy. Preoperative memory fMRI imaging was the strongest predictor of verbal and visual memory decline following left anterior temporal lobectomy. In addition these authors found that memory function in the ipsilateral posterior hippocampus may contribute to better preservation of memory after surgery.

In their review Limotai and Mirsattari (2012) ask the question whether fMRI can replace the Intracarotid Amobarbital Test (IAT) for presurgical evaluation of memory function. They state that with optimal study paradigms and higher resolution MR scanners, fMRI has the potential to replace IAT to evaluate this risk noninvasively. They conclude that the role of language fMRI to predict postoperative decline in verbal memory is promising. The prognostic accuracy of fMRI to aid in prediction of postoperative memory changes is equal or even better than that of the IAT.

Answering the question of Limotai and Mirsattari (2012) Szaflarski et al. (2008) and Dupont (2015) concluded that numerous studies meanwhile demonstrate that the Wada procedure can be nowadays reliably replaced by fMRI activation studies, and that a vast majority of fMRI studies suggest that it is the functional adequacy of the resected hippocampus rather than the functional reserve of the contralateral hippocampus that determines the extent of postoperative memory decline. Furthermore, new functional neuroimaging procedures that explore more widespread network disruptions commonly found in MTLE, such as *diffusion-tensor imaging* (DTI), combined with fMRI activation studies, may significantly improve the prediction of postsurgical memory (Osipowicz et al., 2016).

A potentially exciting new development for fMRI is the use of *magnetized nanoparticles* (MNP). MNP are extremely small magnetized particles that are visible on MRI, and that can be attached to a wide variety of bioactive molecules. Consequently, MNP could be used to measure localized alterations in neurotransmitter activities that reflect brain excitation and inhibition. Re-



**Figure 11.** Concordance of MRI, ictal SPECT and localization of EEG spikes left frontal (Fp1, red arrow) in a patient with cortical dysplasia, seizure-free after the excision of the lesion. (Calibration: 1 sec, 50  $\mu$ V; please note the artifact in O1).

cently *in vitro* studies demonstrated rapid nanoparticle uptake that can target myeloid cells in epileptogenic brain tissue (Portnoy et al., 2016).

*Transcranial magnetic stimulation (TMS)* is currently being investigated as a possible diagnostic, as well as a therapeutic, tool for epilepsy. Particularly paired-pulse stimulation, can be used to measure cortical excitability, a potential surrogate marker of epileptogenicity (Boulogne et al., 2016).

*Gene microarray technology* is used to examine alterations in genetic profile of brain regions that may correlate with an epileptic disturbance.

*Optical intrinsic signal (OIS) imaging* is an invasive technique for measuring changes in brain associated with neuronal activity. Several investigators are applying this in patients during surgery. It is the hope that it may yield valuable results in future.

*Seizure Prediction:* The use of depth-recorded epileptiform EEG events to predict the onset of epileptic seizures and automatically activate seizure-aborting interventions has already a long history. Non-linear dynamic analysis of ongoing depth-recorded EEG activity can reliably identify changes in neuronal synchronization that precede epileptic seizure occurrence by several minutes. However, whether noninvasive sei-

zure prediction and automatic seizure abortion is feasible has yet to be shown.

Until then the concordance of the results of seizure semiology of habitual seizures, localization of epileptogenicity by EEG, MRI, and, when available, ictal SPECT remains the prerequisite for successful epilepsy surgery (figure 11). Some tools for modern epilepsy surgery are illustrated in figure 6abcdef. Besides mapping of seizure onset by SISCOM, and intraoperative electrocorticography and electrostimulation, the availability of intraoperative MRI constitutes an important element in modern successful epilepsy surgery.

## CONCLUSION AND PERSPECTIVES

Resective epilepsy surgery is a widely accepted and successful therapeutic approach, rendering up to 80% of selected patients seizure-free. Although other therapies, such as radiosurgery, and responsive neurostimulation will increasingly play a role in patients with unresectable lesion, it is unlikely that they will replace selective resective surgery.

Refinements of the currently available diagnostic techniques may increase the accuracy with which we define the different zones. The hope is that new diagnostic techniques will be developed that permit more



direct definition of the epileptogenic zone. Many diagnostic tools that have been considered “experimental”, i.e. being at the research level, have already been incorporated as standard care by advanced centres. Direct measurement of the epileptogenic zone is the ultimate goal of presurgical evaluation of the future and there is hope that direct imaging the distribution of neurotransmitters and receptors involved in the pathogenesis of epilepsy will become possible. Therefore it is believed that transmitter and receptor PET may play a major role in the definition of the epileptogenicity and epileptogenesis in the future.

Given the limitations of such a review, it is understood that the extent and complexity of this topic could neither be treated comprehensively nor all-embracing.

## CONFLICT OF INTEREST

The author declared no conflict of interests.

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