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INVITED REVIEW

Presurgical evaluation of epilepsy

Felix Rosenow[1] and Hans Lüders[2]

[1]*Department of Neurology, Philipps University, Marburg, Germany and* [2]*Department of Neurology, The Cleveland Clinic Foundation, Cleveland, Ohio, USA*

Correspondence to: Hans O. Lüders, MD, Department of Neurology S90, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA
E-mail: scolarc@ccf.org

Summary

An overview of the following six cortical zones that have been defined in the presurgical evaluation of candidates for epilepsy surgery is given: the symptomatogenic zone; the irritative zone; the seizure onset zone; the epileptogenic lesion; the epileptogenic zone; and the eloquent cortex. The stepwise historical evolution of these different zones is described. The current diagnostic techniques used in the definition of these cortical zones, such as video-EEG monitoring, MRI and ictal single photon emission computed tomography, are discussed. Established diagnostic tests are set apart from procedures that should still be regarded as experimental, such as magnetoencephalography, dipole source localization and spike-triggered functional MRI. Possible future developments that might lead to a more direct definition of the epileptogenic zone are presented.

Keywords: epilepsy surgery; diagnostic procedures; concept of cortical zones; ECoG; FLAIR

Abbreviations: ECoG = electrocorticography; FDG-PET = [^{18}F]fluorodeoxyglucose–PET; FLAIR = fluid attenuation inversion recovery; fMRI = functional magnetic resonance imaging; MEG = magnetoencephalography; MRS = magnetic resonance spectroscopy; SPECT = single photon emission computed tomography

Introduction

The purpose of this review is to give an overview of the currently established diagnostic tools and strategies used in epilepsy surgery. We will start by clarifying the concepts underlying epilepsy surgery and their historical development, and we will then compare the relative values of the currently available diagnostic standard methods in determining the location and extent of the epileptogenic zone.

Aims and concepts in surgery for epilepsy

Approximately 60% of all patients with epilepsy (0.4% of the population of industrialized countries) suffer from focal epilepsy syndromes. In ~15% of these patients, the condition is not adequately controlled with anticonvulsive drugs. Under the conservative assumption that 50% of such patients are potential candidates for surgical epilepsy treatment, 4.5% of all patients with epilepsy (0.03% of the population) could potentially profit from epilepsy surgery (Engel, 1993). Depending on the epilepsy syndrome and the ability to define clearly and resect completely the epileptogenic zone, 30–85% of epilepsy patients operated on remain seizure-free. The larger epilepsy centres report average seizure-free rates of ~60% (Engel, 1993). Therefore, considering the severity of the epilepsy in the population operated on, epilepsy surgery can be considered a very successful therapy.

The objective of resective epilepsy surgery is the complete resection or complete disconnection of the epileptogenic zone, which is defined as the area of cortex indispensable for the generation of clinical seizures. This aim is to be achieved with preservation of the 'eloquent' cortex. Modern epileptologists use a variety of diagnostic tools, such as analysis of seizure semiology, electrophysiological recordings, functional testing and neuroimaging techniques to define the location and boundaries of the epileptogenic zone. These diagnostic methods define different cortical zones (symptomatogenic zone, irritative zone, ictal onset zone, functional deficit zone and the epileptogenic lesion), each of which is a more or less precise index of the location and extent of the epileptogenic zone (Table 1). Our ability to define the epileptogenic zone precisely is essentially a function of the sensitivities and specificities of our diagnostic methods. In this first section, we will describe the historical development of the five zones used to define the epileptogenic

zone and of the different diagnostic techniques necessary to define them.

Definition of cortical zones

The symptomatogenic zone

The symptomatogenic zone is the area of cortex which, when activated by an epileptiform discharge, produces the ictal symptoms. It is defined by careful analysis of the ictal symptomatology, with either a thorough seizure history or an analysis of ictal video recordings. The precision with which we can define the location and extent of the symptomatogenic zone depends on the specific ictal symptoms. For example, a highly localized somatosensory aura, such as paraesthesias of one or two fingers at the beginning of a seizure, clearly localizes the symptomatogenic zone to the corresponding primary sensory area. On the other hand, a poorly defined body sensation has little localizing or lateralizing value. There are many other ictal signs or symptoms whose localizing/lateralizing value falls between these two extremes.

It is important to stress here that there is frequently no overlap between the symptomatogenic zone and the epileptogenic zone. The best method of defining the symptomatogenic zones of the brain is direct cortical electrical stimulation, which produces conditions closely resembling activation of the cortex by an epileptiform discharge. Electrical stimulation reveals that the majority of the human cortex is symptomatically silent, strongly suggesting that its activation by an epileptiform discharge will not produce any symptoms unless the electrical activity spreads to the adjacent eloquent cortex. The presence of ictal symptoms may be caused by the generation of the seizure from a zone of eloquent cortex. Usually, however, the initial ictal 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.

Electrical stimulation studies have also demonstrated that symptoms can be elicited from the eloquent cortex only if the stimulus parameters are 'strong' enough. This requires that the stimulus has appropriate frequency, the individual stimuli are of sufficient duration and intensity, and the duration of the stimulus train is adequate. We would not expect any symptoms from an epileptiform discharge unless it fulfils these criteria. This explains the observation that an epileptiform discharge recorded from a symptomatogenic zone frequently may not produce the corresponding symptoms. All the limitations outlined above have to be considered when trying to define the epileptogenic zone by a careful analysis of ictal symptoms.

The irritative zone

The irritative zone is defined as the area of cortical tissue that generates interictal electrographic spikes. The irritative zone is measured by EEG (scalp or invasive), magnetoencephalography (MEG) or functional MRI (fMRI) triggered by interictal spikes. These can be considered as 'mini-seizures'. If they are of sufficient 'strength' and are generated within an eloquent cortical area, spikes can give rise to clinical symptoms. A typical example is the localized myoclonic jerks that can be seen in patients with spikes in the primary motor cortex (Fig. 1). In general, however, isolated, independent spikes will not generate any clinical symptoms regardless of whether they are located in silent or eloquent cortex. To produce symptoms, spikes usually have to give rise to runs of epileptiform discharges (afterdischarges) that have sufficient strength to induce symptoms when they invade a symptomatogenic zone.

The seizure onset zone

The seizure onset zone is the area of the cortex from which clinical seizures are (actually) generated, as opposed to the epileptogenic zone, which is the area of the cortex that is indispensable for the generation of epileptic seizures (see also the section 'The epileptogenic zone', below). The seizure onset zone is most commonly localized by either scalp or invasive EEG techniques. Unlike the irritative zone, however, the location of the seizure onset zone can also be determined by ictal single photon emission computed tomography (SPECT). It is usually the portion of the irritative zone that generates spikes capable of producing afterdischarges. These consist of repetitive spikes that have enough strength to produce clinical ictal symptoms when invading eloquent cortex. It has been thought that precise definition of the seizure onset zone should provide an accurate definition of the epileptogenic zone. However, this is not always true. Not infrequently, the epileptogenic zone is more extensive than the seizure onset zone (see below) and there is no method that permits precise definition of the seizure onset zone. Scalp electrodes give us an excellent overview of the electrical activity of the brain and frequently suggest the side and approximate location of the seizure onset. Using these electrodes, we are able to obtain broad coverage of the brain surface. However, scalp EEG has relatively low sensitivity for the detection of the seizure onset because 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, afterdischarges generated locally at the seizure onset zone are too small to be detected by scalp electrodes and, therefore, scalp electrodes are only capable of detecting a seizure discharge after it has spread considerably. Invasive cortical surface electrodes, on the other hand, record activity from an extremely limited region of the brain. By eliminating distance and the insulating barriers, each electrode records the cortical area covered by only that electrode. Invasive electrodes are, therefore, inherently very sensitive for the detection of afterdischarges but will only be able to define the seizure origin accurately

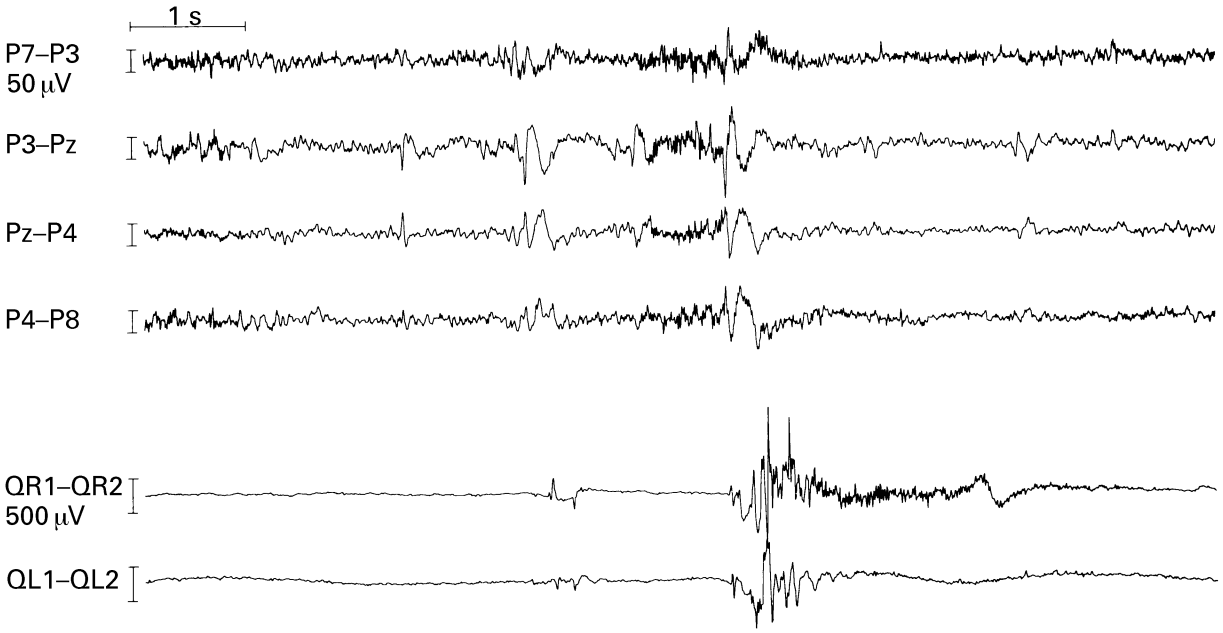

Fig. 1 Single spikes causing clinical (myoclonic) seizures. Ten seconds of EEG of a patient with a left parietal focal cortical dysplasia and left parietal lobe epilepsy is shown. Repetitive spikes with a maximum at Pz were recorded. Small spikes (first second) are not followed by any motor phenomenon. With increasing amplitude (second and third seconds), the spikes are associated with bilateral asymmetrical (right > left) myoclonic seizures of increasing strength and duration. Recording parameters: International 10-10 system, transverse bipolar montage with surface EMG recording from the right (QR1–QR2) and left quadriceps femoris muscles (QL1–QL2).

if they cover the seizure onset zone directly. Unfortunately, due to the difficulties in obtaining broad cortical coverage, it is unusual that invasive electrodes are located over the entire seizure onset zone. Instead, the invasive recording is typically limited to a zone near the seizure onset zone or covers only a portion of this zone.

As already mentioned above, the other problem to consider is that the extent of the seizure onset zone may not correspond with the epileptogenic zone (cortical area from which clinical seizures may arise). In other words, the epileptogenic zone may be either more or less extensive than the seizure onset zone. When the epileptogenic zone is smaller than the seizure onset zone, partial resection of the seizure onset zone may lead to seizure-freedom because the remaining seizure onset zone is no longer capable of generating further seizures. Conversely, when the epileptogenic zone is greater than the seizure onset zone, even total resection of the seizure onset zone will not result in seizure-freedom. This phenomenon occurs when a patient has seizure onset zones of different thresholds within a single epileptogenic zone. The seizure onset zone of lowest threshold will generate all the usual seizures and is, therefore, the only one we can directly measure before surgery. Once this zone has been resected, however, another seizure onset zone of higher threshold may become clinically evident. There is no way to predict, even with the most modern technology, if additional, higher threshold seizure onset zones exist. The cortical area of interest now becomes a 'potential epileptogenic zone' containing one or more seizure onset zones. Summarizing, there are almost insurmountable practical barriers to defining the exact boundaries of the seizure onset zone. Even as our abilities in this regard improve, there are reasons to believe that in many cases no accurate definition of the correlation between the seizure onset zone and the epileptogenic zone will be possible.

The epileptogenic lesion

This is a radiographic lesion that is the cause of the epileptic seizures. The best way to define this today is by high-resolution MRI. However, not all lesions seen in a patient with epileptic seizures are epileptogenic. Some radiographic lesions may be unrelated to the clinical seizures. For this reason, even when we 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 radiographic lesion is indeed responsible for the patient's seizures. A related problem is the definition of epileptogenicity in cases with dual or multiple pathology. Here again, additional testing is necessary to define which of the lesions are epileptogenic. In those cases in which two or more lesions are in close spatial proximity, the problem of attributing epileptogenicity to one lesion or another can frequently only be resolved with the use of invasive EEG technology.

The spatial relationship of the epileptogenic zone with the epileptogenic lesion is similar to its relationship with the seizure onset zone that was discussed above. It has been thought that complete resection of the radiographic

epileptogenic lesion is necessary to obtain seizure-freedom. This is not always true, however, as evidenced by cases in which only partial lesion resection was possible (because of its location in eloquent cortex), with resultant complete seizure-freedom. This implies that the remainder of the radiographic lesion was either never epileptogenic or was dependent on the resected tissue to elicit seizures. A more common clinical scenario, however, occurs when seizures persist in spite of complete resection of the lesion visible on MRI. This is frequently the case in patients with cortical dysplasia or post-traumatic epilepsy. There are two possible explanations for this phenomenon. Many lesions are not intrinsically epileptogenic but induce seizures by generating reactions in the surrounding brain tissue with which they are in contact. Some of these lesions may induce microchanges in the brain tissue located at a significant distance from the epileptogenic lesion visible on MRI. These microchanges are epileptogenic and, therefore, in these cases selective resection of the MRI-visible epileptogenic lesion will frequently not be sufficient to abolish all the seizures. Another explanation addresses the sensitivity of MRI in detecting the complete lesion. Brain tissue adjacent to a radiographic lesion may consist of lesional tissue of lesser pathological severity. This tissue, while being potentially epileptogenic, may remain invisible on MRI. This is frequently the situation with cortical dysplasia in which only the 'tip of the iceberg' is visible on MRI. Failure to resect these MRI-invisible lesions can lead to persistence of seizures after epilepsy surgery. This is the most likely explanation for the relatively high frequency of surgical failure in patients with neocortical dysplasia.

How can we predict if, in any given patient, total resection of a lesion will lead to seizure-freedom? There is no direct method to determine if an additional, epileptogenic zone that is invisible on MRI surrounds any given epileptogenic lesion. However, we can try to predict the presence of a perilesional epileptogenic rim by understanding the nature of the MRI-visible lesion. We know, for example, that well delineated brain tumours and cavernous angiomas tend to produce epileptogenicity only in the MRI-visible lesion and its immediate surroundings. Therefore, lesionectomy is usually successful in these cases. On the other hand, as mentioned above, cases with cortical dysplasia or post-traumatic epilepsy typically require more extensive resection for a successful outcome. In these cases, exact definition of the irritative and seizure onset zones may also help in determining if the epileptogenic zone extends outside the limits of the epileptogenic lesion

The functional deficit zone

This is defined as the area of cortex that is functionally abnormal in the interictal period. This dysfunction may be a direct result of the destructive effect of the lesion or may be functionally mediated, i.e. abnormal neuronal transmission that may affect brain function either locally or at a considerable distance from the epileptogenic tissue. There are a variety of methods that can be used to measure the functional deficit zone. Neurological examination, neuropsychological testing, EEG, [^{18}F]fluorodeoxyglucose-PET (FDG-PET) scanning and interictal SPECT are some examples.

What is the relationship between the functional deficit zone defined by these different tests and the location of the epileptogenic zone? Unfortunately, it is very complex and difficult to establish even in individual cases. This is related to the fact that these tests measure parameters, such as global brain function (general neurological examination) and brain physiology (local glucose metabolism or blood perfusion), which are not necessarily directly related to epileptogenesis. Some of these changes may be the result of a non-epileptogenic lesion or may occur at a considerable distance from the primary seizure focus. For this reason, the value of defining the functional deficit zone presurgically is relatively limited compared with the measurement of zones that are related more directly to epileptogenesis. A typical example of this is seen in patients with pure mesial temporal sclerosis. FDG-PET studies often reveal extensive hypometabolic regions outside the mesial temporal structures. We know, however, that the epileptogenic zone is usually limited to the mesial temporal region and seizure-freedom is often achieved with resection of this tissue alone. Another example is seen in patients with extensive non-epileptogenic lesions in addition to a more limited epileptogenic lesion. Both types of lesions may produce a widespread functional deficit zone, as defined by neurological testing, neuropsychological testing, FDG-PET and interictal SPECT.

In spite of all these limitations, good correlation of the functional deficit zone with the other zones defined above gives us additional supportive information regarding the lateralization or location of the epileptogenic zone. On the other hand, clear discrepancies between the results obtained in the tests used to define the different cortical zones makes accurate definition of the epileptogenic zone very difficult and is frequently a reason to request more sensitive, specific tests, such as invasive monitoring.

The epileptogenic zone

The epileptogenic zone is the area of cortex that is indispensable for the generation of epileptic seizures. It may include an actual epileptogenic zone, which is the cortical area generating seizures before surgery (see above; it is equivalent to or smaller than the actual seizure onset zone), and a 'potential epileptogenic zone', which is an area of cortex that may generate seizures after the presurgical seizure onset zone has been resected. There is no diagnostic modality currently available that can be used to measure the entire epileptogenic zone directly. This is because we cannot exclude the existence of a potential epileptogenic zone that would only become clinically apparent postoperatively. The epileptogenic zone, therefore, is a theoretical concept. If the patient is seizure-free after surgery we conclude that the epileptogenic zone must have been included in the resected cortex.

Since we cannot measure the epileptogenic zone directly, we must infer its location indirectly by defining the other zones discussed above. When all of these data are concordant, the determination is easy. Unfortunately, these cases are rare. In most cases there is some degree of discrepancy between the five different zones. Attempts should then be made to find a plausible explanation for these discrepancies, taking into consideration the basic principles outlined above. It is difficult to define accurately the epileptogenic zone when no adequate explanation for the discrepant location and/or extent of the different zones is found. In these cases, surgery should be deferred while more precise testing, such as invasive video-EEG, is performed. As discussed earlier, however, invasive recordings are limited by the extent of their cortical coverage. They should only be used in those cases in which there is a clear hypothesis regarding the location of seizure onset and in which 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?).

On the basis of meticulous investigations of epilepsy patients using multiple depth-electrodes (stereoelectroencephalography), Talairach and Bancaud developed a somewhat different concept of the epileptogenic zone, emphasizing that it involves not only a single region but also a distinct set of directly interconnected regions. The concepts of Talairach and Bancaud were further developed by their most prominent pupils, P. Chauvel and the late C. Munari, and are now widely represented by the French and Italian school of epilepsy surgery. In this school, the epileptogenic zone is considered a complex structure composed of a separate pacemaker and relay and subrelay areas essential for producing individual ictal symptoms and signs (Buser and Bancaud, 1983; Isnard *et al.*, 2000; Chauvel, 2001). This definition, in which corticocortical facilitatory connections are of major importance, led, for example, to the concept of frontotemporal epilepsy (Bancaud and Talairach, 1992) and geared surgical strategy towards larger resections and more extensive disconnections. Contemporary presurgical diagnosis in France and Italy still relies more heavily on the use of stereoelectroencephalography in an attempt to define with precision the relatively more extensive epileptogenic zone defined above (Isnard *et al.*, 2000). Detailed anecdotal evidence to support the Talairach/Bancaud concept of the epileptogenic zone has been provided in the literature but no systematic study has verified their hypothesis.

'Eloquent' cortex

Epilepsy surgery is usually an elective procedure. Whereas the complete resection of the epileptogenic zone is of paramount importance, this aim is limited by one major restriction: the sparing of eloquent cortex in order to avoid new, unacceptable deficits for the patient. Eloquent cortex is cortex related reproducibly to a given function. Methods commonly used to detect such functions 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. Especially invasive methods, such as subdural electrodes, are nowadays most frequently used when the location and extent of the seizure onset zone and of adjacent eloquent cortex are to be defined.

Historical evolution of the cortical zones and current standards of their definition

The era of the symptomatogenic zone (1884–1935)

When epilepsy surgery was first introduced, the location of the epileptogenic zone was determined almost exclusively by trying to locate the symptomatogenic zone. The concept that the symptomatogenic zone is a good estimate of the location of the epileptogenic zone was a by-product of the pioneering 19th-century works of John Hughlings Jackson in clinical epilepsy. At that time Hughlings Jackson started to use ictal symptomatology for cerebral localization in patients with partial epilepsies. Hughlings Jackson first wrote about epilepsy in 1861 when he published an article entitled 'Cases of epilepsy associated with syphilis' (Jackson, 1861). In this article, he discussed seizures which are incomplete, unilateral 'epileptiform convulsions' without loss of consciousness. Hughlings Jackson initially held to the popular view of the 1860s that the corpus striatum was the highest point in the motor tract and at first he believed the pathology of focal motor epilepsy to be located in the basal ganglia (Eadie, 1992; Finger, 1994). In 1863, however, Hughlings Jackson began to recognize that the hemispheres were frequently involved in the generation of motor seizures. He wrote that 'as autopsies of patients who have died after syphilitic epilepsy appear to show, the cause is obvious organic disease on the side of the brain, opposite to the side of the body convulsed, frequently on the surface of the hemisphere' (Jackson, 1863). From 1863 to 1870, Hughlings Jackson provided additional clinical evidence that led him to recognize the role of the cerebral cortex in motor function and in epilepsy.

In 1870, experimental studies by Gustav Theodor Fritsch and Eduard Hitzig provided experimental proof that electrical stimulation of the dog's frontal cortex could cause movement in the body on the opposite side. Hitzig later stated that these experiments confirmed physiologically 'that which Hughlings Jackson had concluded from clinical fact' (Hitzig, 1900). David Ferrier confirmed these studies in London through electrical stimulation and ablation studies in animals. In 1873 he stated 'The proximate causes of the different epilepsies are, as Hughlings Jackson supposes, 'discharging lesions' of the different centres in the cerebral hemispheres' (Ferrier, 1873). By 1873 Hughlings Jackson had made his conclusive definition of epilepsy, which still stands today, that 'epilepsy

Table 1 *Descriptions of zones and lesions of the cortex (adapted from Lüders and Awad, 1992)*

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

is the name for occasional, sudden, excessive, rapid and local discharges of grey matter' (Jackson, 1873).

The belief that the epileptogenic zone could be localized solely on the basis of symptomatology paved the way for epilepsy surgery. The work of Jackson, Ferrier, Victor Horsley and William Gowers was taking place at a time when a new trend in neuroscience recognized that certain somatic functions were attributable to specific locations in the brain. This led to concepts of cortical localization in epilepsy that revolutionized the way in which neuroscientists examined this disease process. In 1879, using such localization principles, William Macewen, a neurosurgeon working in Glasgow, correctly determined the location of a patient's frontal meningioma and resected the lesion. The patient survived and was cured of his seizures (Macewen, 1979). In 1884, Alexander Hughes Bennet, with the help of Hughlings Jackson, had in his care a patient who had seizures of increasing frequency involving his left side and leading to loss of consciousness and generalized seizures. Primarily on the basis of this clinical observation, they localized the presumed lesion and, on November 25, 1884, Rickman Godlee found and resected a tumour from this site (Bennett and Godlee, 1884; Green, 1985). Over the next several years, Victor Horsley, working with Hughlings Jackson and Ferrier, would perform several operations for the treatment of epilepsy, basing the localization of the resected tissue on the symptoms (Horsley, 1887). Until the introduction of the electroencephalogram by Berger, localization in epilepsy surgery was based almost solely on determination of the symptomatogenic zone.

Current standards in the definition of the symptomatogenic zone

With regard to the symptomatogenic zone, most of the advances in the last 20 years have concerned the better understanding we now have of the location of different symptomatogenic zones and their relationships with the location of the epileptogenic zone (Lüders, 2000; Wieser, 2000). Definition of the location of the symptomatogenic zones was achieved mainly by detailed cortical stimulation studies using subdural grid electrodes in wake patients (Bracht and Kramer, 2000; De Graaf *et al.*, 2000; Dinner *et al.*, 2000; Dinner and Lüders, 2000; Ebner and Baier, 2000; Ebner and Kerdar, 2000; Foldvary and Morris, 2000; Geller *et al.*, 2000; Lüders *et al.*, 2000; Schulz and Lüders, 2000; Winkler *et al.*, 2000).

The relationships between the symptomatogenic zones and the epileptogenic zone were clarified by investigating ictal symptoms in patients who became seizure-free after epilepsy surgery, i.e. patients with a known location of the epileptogenic zone. In these studies, the ictal symptoms were analysed in detail by reviewing ictal video recordings. The introduction of closed-circuit video-EEG monitoring has provided a tool that allows repeated careful analysis of the ictal and postictal symptoms independently by different epileptologists blinded to other information relevant to the case. If applied to patient populations in which postoperative seizure-freedom indicates that the epileptogenic zone was included within the resection, the lateralizing or localizing value of ictal and postictal clinical symptoms can be investigated. Furthermore, for a given defined symptom, the frequency in the population of interest, i.e. patients with mesial temporal lobe epilepsy, the specificity for the laterality, lobar or intralobar location of the epileptogenic zone and the inter-rater reliability (κ score) can be calculated. This kind of research leads to the identification of single ictal and postictal symptoms and clusters or evolutions of symptoms that indicate the laterality or localization of the epileptogenic zone. Postresective seizure-freedom should be used as the 'gold standard' for the localization of the epileptogenic zone in clinical studies.

As mentioned above, some of these associations of symptoms and the location of the epileptogenic zone have been known since the time of Hughlings Jackson. One example is the correlation of clonic seizures of the left hand with an epileptogenic zone in the hand area of the right precentral gyrus. The highly specific lateralizing value of unilateral clonic seizures and of auras arising from primary cortical areas, such as visual or localized somatosensory auras, is obvious. Other lateralizing signs have only been

Table 2 *Lateralizing ictal and postictal symptoms in patients with temporal lobe or extratemporal epilepsy*

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

ETE = extratemporal epilepsy; FLE = frontal lobe epilepsy; sGTCSs = secondary generalized tonic–clonic seizures; TLE = temporal lobe epilepsy.

evaluated through the kind of meticulous clinical research described above. Table 2 gives a list of these lateralizing symptoms.

Besides the lateralizing signs listed in Table 2, several localizing ictal symptoms or evolutions of symptoms have been established, e.g. version was found to occur significantly earlier during a seizure evolution in patients with extratemporal compared with temporal lobe epilepsy (Bleasel *et al.*, 1997). Auras are frequently localizing and can be lateralizing. Olfactory auras, for instance, localize the epileptogenic zone to the amygdala and were found to be associated with tumorous lesions involving the amygdala in >60% of epilepsy surgery candidates (Acharya *et al.*, 1998). Visual auras are usually localizing and lateralizing.

Even in young infants, who cannot report on auras and who frequently display seizure symptoms different from those of adults (Brockhaus *et al.*, 1995; Nordli *et al.*, 1997; Hamer *et al.*, 1999*b*), the seizure semiology correlates with the lateralization of the epileptogenic zone. The main seizure types seen in children under 3 years of age are epileptic spasms, hypomotor seizures (characterized by decreased behavioural motor activity with an indeterminate level of consciousness), clonic seizures and tonic seizures. Focal motor seizures and versive seizures indicate an epileptogenic zone (and seizure onset) in the contralateral hemisphere (Hamer *et al.*, 1999*b*), frequently in the frontal lobes (Acharya *et al.*, 1997). Hypomotor seizures frequently arise in the temporal, temporo-parietal or temporo-occipital lobes (Acharya *et al.*, 1997). Generalized motor seizures and the other seizure types mentioned can be associated with generalized or focal seizure onset and are not of lateralizing value (Hamer *et al.*, 1999*b*).

This kind of research has provided the clinician with a number of frequent and highly specific signs which can be applied in the out-patient setting as well as in presurgical diagnosis for more accurate localization of the epileptogenic zone. The diagnostic value of seizure symptoms independent of any other signs or symptoms has also led to the development of a semiological classification of seizures based exclusively on seizure symptoms (Lüders *et al.*, 1998; Noachtar *et al.*, 1998; Bautista and Lüders, 2000).

Era of the irritative and ictal onset zones (beginning 1935)

The concepts of the irritative zone and the ictal onset zone are dependent on the ability to record interictal and ictal epileptiform discharges. Richard Caton in 1875 was the first to record electrical activity from the brains of rabbits and monkeys (Caton, 1875; Swartz and Goldensohn, 1998) and P. Y. Kaufmann was the first to record seizures induced in dogs by electrical stimulation of the cortex (Kaufmann, 1912).

However, the greatest advance in electroencephalography came in 1929, when Hans Berger published his work on scalp recordings of the human EEG (Berger, 1929; Swartz, 1998). Berger mentioned his findings on interictal EEG activity as early as 1933 (Berger, 1933). Initially, his work met with scepticism, but it was finally confirmed by Adrian and Matthews, as reported in *Brain* in 1934 (Adrian and

Matthews, 1934) and soon afterwards by Jasper and Carmichael in *Science* (Jasper and Carmichael, 1935). Both Jasper and Gibbs described the interictal spike as the hallmark of epilepsy in 1936 (Gibbs *et al.*, 1936; Jasper, 1936). In 1949, Jasper and Hunter published their method of simultaneously recording both EEG tracing and the patient using a single camera (Hunter and Jasper, 1949) and in 1962 Goldensohn started using a closed-circuit television system (Goldensohn, 1966).

The first report of measuring electrical activity directly from the human cerebral cortex was in 1935 by Foerster and Altenburger (Foerster and Altenburger, 1935), and by the early 1950s electrocorticography (ECoG) was playing an essential role in the surgical treatment of temporal lobe epilepsy. In the 1950s the use of chronic intracranial electrodes was also introduced (Ajmone-Marsan and VanBuren, 1958), allowing ictal EEG recordings to be performed without skull artefact. Besides the clinical findings and ictal symptoms that had been used previously to localize the symptomatogenic cortex, EEG and ECoG were now used routinely to define the irritative zone and ictal onset zones in candidates for epilepsy surgery. The use of EEG also influenced the classification of seizures, which were now seen as electroclinical syndromes (Commission on Classification and Terminology, 1981). The evolution of MEG over the last 35 years has provided additional data for the definition of the irritative and functional deficit zones. The development of MEG began in the 1960s with the work of David Cohen, a physicist at the Massachusetts Institute of Technology (Cohen, 1968). Over the next two decades, interest in this modality grew with the publication of several important papers from researchers at New York University (Okada *et al.*, 1982; Williamson and Kaufman, 1987). In 1982, researchers at the University of California at Los Angeles, USA, first described the use of MEG to localize epileptiform discharges in human subjects, leading to the first consideration of this technique for clinical use (Barth *et al.*, 1982). Today, MEG is used in the diagnosis of epilepsy for two primary tasks: (i) localization of the irritative zone; and (ii) functional mapping of normal cortical areas (Rowley and Roberts, 1995).

Current standards in the definition of the irritative and ictal onset zones

In the definition of the irritative zone and the seizure onset zone, video-EEG monitoring remains the gold standard. During monitoring, sufficient interictal EEG is usually sampled when the subject is awake and during all sleep stages to allow definition of the irritative zone. Spatial distributions and amplitude maxima of all spike and sharp waves detected and their relative frequencies should be documented, as there is evidence that multifocal and especially epileptiform activity contralateral to the suspected location of the epileptogenic zone correlates with a poorer outcome (Hufnagel *et al.*, 1994; Pataraia *et al.*, 1998; Janszky *et al.*, 2000). Regarding 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. The use of sphenoidal electrodes is controversial. This is considered the most unpleasant experience during non-invasive monitoring by some patients. Besides, it is rare that anterior temporal sharp waves are missed completely by anterior temporal electrodes when no sphenoidal electrodes are used. However, the relative amplitudes of sharp waves at anterior temporal and sphenoidal electrodes can be misjudged. This is important, because the relative amplitude distribution of spikes helps to localize their origin to the mesial temporal versus lateral temporal region. Furthermore, Pacia and colleagues reported that seizure onset with a maximum at the sphenoidal electrode occurred only in mesial and never in lateral temporal lobe epilepsy (Pacia *et al*., 1998). Finally, Hamer and colleagues found that, in mesial temporal lobe epilepsy, an amplitude maximum at the sphenoidal electrode alone was significantly more frequent in patients with hippocampal sclerosis than in patients with a tumour as the underlying pathology (88.1 versus 24.8%; $P < 0.001$) (Hamer *et al.*, 1999*a*).

In the majority of the patients at most centres, the use of anticonvulsive drugs is reduced during monitoring in order to make the occurrence of seizures and epileptiform discharges more likely and frequent. Potential seizure onset zones may be unmasked by this procedure. This practice helps to shorten the monitoring sessions considerably but has several drawbacks which need consideration. The withdrawal of medication increases the risk of status epilepticus and of generalized tonic–clonic seizures associated with a risk of injury. Furthermore, there is a risk of activating epileptiform activity or withdrawal seizures in cortical areas that otherwise do not produce such discharges. In other words, the extent of the irritative and seizure onset zones may be overestimated.

With regard to the irritative/seizure onset zone, some significant advances have been made. Analogue electroencephalography 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 (Gotman, 1990; Blum, 1998; Swartz, 1998). This technology has removed significant constraints from EEG data collection. Now the technologist only needs to be concerned with collecting an artefact-free record with good notation. If the interpreter is unsatisfied with the montage, it can easily be reformatted to produce a new montage. Changing the variables, such as chart speed, gain and filters, is simple and can enhance the interpretation of individual electrographic events (Swartz, 1998). Furthermore, digital technology allows automatic spike and seizure detection, computer-based surface mapping of EEG voltages and source localization of EEG generators (Duffy *et al.*, 1979).

The surface EEG is attenuated and may be distorted by the meninges, skull and scalp, especially after a prior

craniotomy. It 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, and EEG localization is less reliable after a craniotomy (Williamson *et al.*, 1991; Cuffin, 1993). Some of these problems of surface EEG can be overcome by MEG. MEG relies on the detection of magnetic fields generated by epileptiform discharges. In MEG, signal attenuation occurs to a degree equal to the third power of the distance between generator and sensor, and it is estimated that, as in EEG, 6–8 cm^2 of cortex needs to discharge synchronously to generate a detectable potential (Ebersole, 1998). MEG signals are, however, not subject to distortion by the dura, skull and scalp and are independent of a reference. This gives MEG a theoretical advantage in localization over EEG, which, in at least some comparisons between these two techniques (Cohen *et al.*, 1990; Balish *et al.*, 1991; Hari *et al.*, 1991; Rose *et al*., 1991; Williamson *et al.*, 1991), has been confirmed experimentally. On the other hand, the measurement of magnetic fluxes from the cortical surface is dependent on the orientation of the measured neuronal population with respect to the detector, when the MEG is recording only tangential vector components. For this reason, MEG is only capable of sampling those neurones lining the sulci and is unable to detect discharges from the gyral surfaces (Hari and Kaukoranta, 1985). In this regard, EEG is able to provide a more global representation of cortical neuronal activity. MEG detectors need cooling with liquid helium, and only calm, cooperative, quietly resting patients can be studied. Therefore, it is impossible to record seizures routinely (Ishibashi *et al.*, 1998), which restricts the use of MEG to the definition of the irritative zone. In conclusion, it appears that EEG and MEG provide complementary data in the work-up of epilepsy surgery candidates (Wheless *et al.*, 1999). EEG yields a more global picture of cortical electrical activity, whereas MEG tends to give more precise localization of a subset of sources. Furthermore, large-array MEG systems are able to obtain data faster and in a more standardized fashion than modern EEG systems (Rowley and Roberts, 1995). Because of the limitations and high cost of MEG, this method is currently still considered experimental.

For the localization of MEG potentials, dipole source modelling is usually performed. The same can be done for EEG potentials. On the assumption of a 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, 1998). The results of these procedures have been verified by simultaneous intracranial recordings (Mikuni *et al.*, 1997; Minassian *et al.*, 1999; Morioka *et al.*, 1999; Otsubo *et al.*, 1999) and postoperative results (Wheless *et al.*, 1999). Unfortunately, dipole source modelling also has significant limitations because the assumptions of the model are usually not correct.

Recently, spike-triggered fMRI has been established (Ives *et al.*, 1993; Allen *et al.*, 1998; Seeck *et al.*, 1998; Krakow *et al.*, 1999; Symms *et al.*, 1999) and shown to be safe (Lemieux *et al.*, 1997). This method visualizes the area of hyperperfusion associated with EEG spikes as an indication of which brain tissue is generating epileptiform discharges. Spike-triggered fMRI is still an experimental tool of uncertain reliability.

For the definition of the seizure onset zone by video-EEG monitoring, all seizure types (at least the initial evolution of all seizure types) reported by the patient and his or her relatives or care-givers should be recorded in order to ensure that all seizure onset zones are documented. Usually a minimum of three to five seizures are recorded (Sirven *et al.*, 1997). Seizure onset can be regional, lateralized or non-localizing. Bilateral seizure onset zones and a bilateral, asymmetrical (in frequency) seizure evolution, or a switch of lateralization of the ictal activity, indicate a poorer postsurgical seizure outcome (Schulz *et al.*, 2000).

If the scalp EEG does not allow the localization or even the lateralization of the seizure onset zone, other tests are frequently needed. Ictal SPECT is a standard procedure in this situation in many centres nowadays. Victor Horsley, in 1892, was the first to observe hyperaemic cortical changes during a patient's intraoperative seizure (Horsley, 1892). The use of SPECT to demonstrate ictal hyperperfusion was first described in 1983 (Uren *et al.*, 1983) and has since been refined in multiple studies (Stefan *et al.*, 1990). Characteristic and diagnostic patterns of blood flow in the postictal period have been shown to aid in seizure localization in patients with temporal lobe epilepsy (Rowe *et al.*, 1991*a*, *b*, 1989) and extratemporal epilepsy (O'Brien *et al.*, 1998; Brinkmann *et al.*, 1999). In certain settings, it is a sensitive and accurate diagnostic method. However, early injection of the tracer, usually technetium-99m ECD (ethyl cysteinate dimer) or technetium-99m HMPAO (hexamethylpropylene amine oxime), is of paramount importance (Avery *et al.*, 1999). Ho and colleagues showed that the presence of an atypical pattern of hyperperfusion in patients with temporal lobe epilepsy was associated with a poorer seizure outcome after surgery (Ho *et al.*, 1997). The relative sensitivity and specificity of ictal SPECT for the side and lobe of the epileptogenic zone, compared with other diagnostic tools, has been investigated by several authors (Stefan *et al.*, 1987; Spencer, 1994; Markand *et al.*, 1997; Won *et al.*, 1999). Ictal SPECT and interictal PET were found to have similar sensitivities, which were higher in temporal lobe epilepsy (75–95%) than in extratemporal epilepsies (~60%). The sensitivity of ictal SPECT can be improved further by comparison with interictal SPECT images. This effect appears to be more pronounced when the subtraction of ictal and interictal SPECT scans is coregistered with the MRI of the patient (O'Brien *et al.*, 1998). The same reportedly applies to postictal versus interictal SPECT images (O'Brien *et al.*, 1999).

False localization has been reported in ictal SPECT and appears to be particularly common in parieto-occipital lobe

epilepsy (Noachtar *et al.*, 1998), unfortunately a syndrome in which scalp EEG is frequently not highly localizing either (Salanova *et al.*, 1992). Thus, ictal SPECT is not exclusively a marker of the seizure onset zone but may mark tissue hyperperfused because of propagated seizure activity (Arnold *et al.*, 2000). Furthermore, the results of ictal SPECT need to be seen in the context of the ictal EEG and other localizing information to allow the detection of false localization.

Invasive studies

Intraoperative ECoG is frequently used to tailor resections, i.e. to modify the exact extent of a resection according to the ECoG findings. There is some 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 (Wennberg *et al.*, 1998, 1999). These results have led some to the conclusion that the use of intraoperative ECoG is justified in many lesional cases and in particular when MRI-negative epileptogenic tissue is suspected (Palmini *et al.*, 1995). One exception to this rule is mesial temporal lobe epilepsy associated with hippocampal sclerosis. In a prospective study, Tran and colleagues did not find a correlation between residual spiking on ECoG and outcome in this setting (Tran *et al.*, 1995). 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 poorly defined influence of anaesthetics, the shorter recording time, which does not usually allow the recording of seizures and the reproduction of the results of cortical stimulation. 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 (Lüders *et al.*, 1987).

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 (Lüders *et al.*, 1987; Jayakar, 1999). Jayakar proposed the following relative indications for an evaluation with chronic subdural electrodes: normal structural imaging, extratemporal location, divergent non-invasive data, encroachment on eloquent cortex, tuberous sclerosis and cortical dysplasia. As invasive electrodes carry considerable costs and complications (Hamer *et al.*, 1999*c*), their use 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 electrodes that are placed should be formulated. It is important to be aware that inadequate spatial sampling with invasive electrodes is by no means rare; it was reported to prevent the localization of the seizure onset zone in 13 of 110 patients in one recent study (Siegel *et al.*, 2000). Furthermore, the very need for invasive recordings is reportedly predictive of a poorer seizure outcome (Hirabayashi *et al.*, 1993; Janszky *et al.*, 2000).

The proportion of patients evaluated by invasive long-term monitoring has decreased over recent decades, mainly because of the inherent problems of these methods and because 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, especially when exact definition of the boundaries of the eloquent cortex versus the irritative zone and seizure onset zone is needed.

How do newer technologies designed to measure the seizure onset zone, such as ictal SPECT and fMRI, compare with scalp and/or invasive EEG? Both of these techniques measure blood flow changes (a relative increase in ictal blood flow with respect to the interictal state). This increase in blood flow is a direct autoregulatory response to the hyperactivity of neurones during epileptogenic activation. Given that these changes are seen in regions of neuronal excitation, SPECT and fMRI are expected to have the same theoretical limitations as EEG. We certainly would not expect that either of these two techniques would give us additional information about the potential epileptogenic zone if it has not reached its threshold of activation. What about the sensitivity of the techniques compared with scalp and invasive EEG? There is no clear evidence that these techniques are more sensitive or precise than scalp EEG. In a relatively high percentage of patients who have isolated auras, we do not detect significant EEG changes. Apparently, SPECT and fMRI are negative in an even higher percentage of such patients. On the other hand, invasive EEG with recording electrodes covering the seizure onset zone will always detect the seizure origin, often long before the initiation of clinical symptoms, indicating that, with regard to sensitivity, it is still the gold standard in detecting seizure onset. The advantage of ictal SPECT and fMRI is that they allow non-invasive evaluation of all areas of the brain with the same degree of accuracy. This includes deep regions of the grey matter that are inaccessible to monitoring by scalp EEG and subdural electrodes. Summarizing, it is clear that EEG and ictal SPECT are used to evaluate the same parameter but that both techniques have significant problems regarding sensitivity. The two techniques do not provide identical information and, therefore, should be considered to provide complementary data. The use of fMRI to evaluate the seizure onset zone requires that the patient should have a seizure while being scanned. In patients with motor seizures or impaired cooperation during seizures, movement and artefacts prevent meaningful data acquisition. This limitation makes the test practical only in patients who have very frequent seizures with retained consciousness and without motor symptoms. The use of imaging techniques to define the epileptogenic

lesion, the functional deficit zone and the eloquent cortex is discussed below.

Era of the epileptogenic lesion and functional deficit zone (1973 to present)

In 1973 the CT scan became available as a clinical tool. Initially, it had little impact on epilepsy surgery, where major structural lesions were detectable by the tools available at that time (clinical history, neurological examination, interictal EEG, CSF analysis and, in some cases, angiography or pneumencephalography). It was soon discovered, however, that CT scans could detect some lesions that were clinically silent. Eventually, it became a standard tool in most epilepsy centres. Patients who were candidates for epilepsy surgery were scanned in order to assure that prominent lesions were not missed.

The real impact of structural neuroimaging on the presurgical evaluation of patients undergoing epilepsy surgery came with the development of MRI. Studies using MRI were first performed on humans in the late 1970s (Gadian, 1982; Kuzniecky and Jackson, 1995). By the early 1980s, it had become available for routine clinical use and its role in evaluating epilepsy patients was becoming recognized (Oldendorf, 1984; Sostman *et al.*, 1984). With the introduction of high-resolution MRI in the mid-1980s, it had become established that this imaging modality is more sensitive than CT in detecting lesions that cause epilepsy (Laster *et al.*, 1985; Latack *et al.*, 1986; Ormson *et al.*, 1986; Schorner *et al.*, 1987; Heinz *et al.*, 1989).

The history of the development of anatomical imaging is closely linked in time with the development of functional neuroimaging techniques that permit the localization of eloquent cortex and the evaluation of the functional deficit zone in patients who are candidates for epilepsy surgery. Some evaluation of the functional deficit zone was, however, already possible before the introduction of neuroimaging. This began with the work of Franz Joseph Gall, who, more than any other scientist, put the concept of cortical localization into use in the early 19th century (Finger, 1994). By the mid-19th century, the standard neurological examination was understood well enough to allow the localization of functional deficits if they were severe and affected some of the highly eloquent areas of the brain, such as the primary afferent and efferent areas (hemiparesis, cortical sensory deficits, visual field defects, etc). However, such deficits typically affect only the minority of surgical candidates whose lesions do not involve eloquent cortical areas. In patients undergoing surgery in the late 19th century, this technique already had some influence on the decision regarding the location of the epileptogenic zone.

The second category of testing that helped in defining the functional deficit zone in patients with epilepsy was neuropsychological testing. With the availability at the Montreal Neurological Institute of large numbers of patients who had undergone anterior temporal resection, Brenda Milner and her group were able to attribute specialized functions to the left and right temporal lobes (Milner and Penfield, 1955; Milner, 1958, 1971). By the late 1950s, this had led to systematic pre- and post-surgical neuropsychological testing for all epilepsy surgery candidates. Milner's group was also the first to apply this test modality to the localization of the epileptogenic zone (Milner, 1975). By the early 1970s, extensive neuropsychological testing was considered an essential part of the work-up for epilepsy surgery (Lezak, 1983; Sass *et al.*, 1990; Rausch and Babb, 1993; Trenerry *et al.*, 1993). Historically, the three objectives of obtaining such data have been (i) the establishment of baseline function for comparison with future test results, (ii) the lateralization and localization of the seizure focus, and (iii) the prediction of postoperative cognitive outcome (Chelune, 1992). With the development of other, more powerful tests to evaluate cortical areas of functional deficit, however, the role of neuropsychological testing in the presurgical evaluation has changed. We now seldom rely on the results of neuropsychological testing to lateralize or localize the epileptogenic zone. In modern epileptology, neuropsychology only influences the decision regarding the location of the epileptogenic zone if it shows markedly discrepant findings with respect to other tests results, e.g. a striking verbal memory deficit in a right-handed patient with radiographic evidence of right mesial temporal sclerosis, electrographic evidence pointing to a right mesial epileptogenic zone, and no other factors to suggest dominance switching. Neuropsychological testing still remains, however, an indispensable tool for the prognosis of postsurgical neuropsychological deficits and for defining the potential for postsurgical neuropsychological rehabilitation.

The intracarotid amobarbital procedure or Wada test, which was first described in 1949 by Dr Juhn Wada, was used initially to lateralize only language function (Wada, 1949). Its introduction in North America took place in 1956 at the Montreal Neurological Institute (Wada and Rasmussen, 1960). In 1959, the use of the Wada test was expanded to the lateralization of memory function in an attempt to identify areas of functional deficit and to predict postsurgical outcome (Milner *et al.*, 1962; Blume *et al.*, 1973). In modern neuropsychology, the Wada test is used mainly to localize the eloquent cortex with regard to language and memory and is used only secondarily as a supplementary method of determining the localization of the epileptogenic zone. Its use varies between institutions, some centres testing all epilepsy surgery candidates and others selecting only a subset of these patients.

From the beginning of epilepsy surgery, decisions regarding the location of the epileptogenic zone were influenced by tests whose goal was to define functional deficit areas. One of the tools used was the EEG, which can record intermittent or continuous slowing as a correlate of localized dysfunction. However, it was the development of modern functional neuroimaging techniques in the late 1970s that really ushered

in the functional deficit era. These developments centred on the field of nuclear medicine imaging. The two types of isotopic emission tomographic studies that were developed and refined during this time were PET and SPECT.

Brownell and Sweet recognized the potential of positron emission detection in imaging as early as 1953 (Early, 1995). The first positron scanner was developed at the Massachusetts General Hospital in 1970, but its clinical utility only became manifest with the technological advances made in instrumentation, cyclotrons and computational support (Early, 1995). In 1980, Kuhl and colleagues published the first report of the use of PET to aid in the cortical localization of seizures (Kuhl *et al.*, 1980). Engel and Kuhl then showed that areas of interictal cortical hypometabolism imaged by FDG-PET in patients with temporal lobe epilepsy correlated extremely well with the presumed lateralization of the epileptogenic zone, as defined by depth EEG (the gold standard at that time) (Engel *et al.*, 1982*a*, *b*). Later, the value of FDG-PET in the lateralization and even localization of extratemporal epilepsies was also demonstrated by a number of investigators (Theodore *et al.*, 1986; Swartz *et al.*, 1989; Henry *et al.*, 1991).

Parallel to the development of PET as a technique to define cortical areas of functional deficit, SPECT was introduced. Kuhl and Edwards first introduced the concept of SPECT imaging in the early 1960s (Kuhl and Edwards, 1963). Once again, the technique was seldom used until the 1970s, when technological developments, especially in digital computers, allowed its widespread clinical use. The use of SPECT in the presurgical diagnosis of epilepsy patients was introduced initially as an alternative, more affordable technique than PET to measure regional blood flow changes (usually a good reflection of regional metabolic changes). Indeed, a number of reports appeared suggesting that interictal SPECT alterations closely parallel the changes seen with PET technology (Biersack *et al.*, 1985, 1987; Podreka *et al.*, 1987; Ryding *et al.*, 1988). However, more detailed studies revealed that interictal SPECT was significantly less sensitive and specific than PET (Stefan *et al.*, 1987; Rowe *et al.*, 1991). Whereas SPECT technology has its place in the work-up of epilepsy surgery candidates (see above), interictal SPECT alone is seldom used to evaluate functional deficit zones. 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.

Current standards in the definition of the epileptogenic lesion, functional deficit zone and eloquent cortex

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. Most centres use a basic set of sequences and slice orientation and add appropriate sequences as need. Usually, T_1-weighted, T_2-weighted and fluid attenuation inversion recovery (FLAIR) sequences are used for the basic investigation. These sequences are highly ($<$99%) sensitive for tumorous epileptogenic lesions. As mesial temporal sclerosis is one of the most frequent epilepsy syndromes 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 (Kuzniecky *et al.*, 1997; Watson *et al.*, 1997; Cheon *et al.*, 1998). Volumetry relies on asymmetry and brain-volume-adjusted normal data derived from a control group at the same institution (Jack *et al.*, 1992; Chee *et al.*, 1997; Kuzniecky *et al.*, 1997). 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 (Woermann *et al.*, 1998). Currently, volumetry is an important research tool that permits the quantification of the degree of hippocampal asymmetry, but its direct impact on patient management is very limited.

Cortical dysgenesis as a frequent cause of medically intractable epilepsy is commonly not detected by the sequences used for the basic investigation; the dysgenesis is then referred to as 'MRI-negative'. 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 (Chan *et al.*, 1998; Lee *et al.*, 1998). Three-dimensional brain volume reconstruction is also helpful in visualizing the exact location of abnormalities of gyration in selected cases. However, the normal variability of the gyral architecture is great (Falk *et al.*, 1991; Maudgil *et al.*, 1998). Several attempts have been made to overcome these problems, e.g. by identification of reproducibly identifiable landmarks around the cortical surface in normal subjects (Maudgil *et al.*, 1998). Curvilinear reformatting was reported to be helpful in detecting subtle dysplastic lesions in otherwise MRI-negative cases (Bastos *et al.*, 1999). Automated segmentation and quantification of cerebral grey matter can identify subtle structural changes not otherwise detected in patients with cortical dysgenesis or hippocampal sclerosis, and even in those with generalized epilepsies (Richardson *et al.*, 1997; Woermann *et al.*, 1999). However, the value of these methods with respect to seizure outcome remains to be proven.

Special gradient echo sequences are the most sensitive sequences in the detection of cavernous angiomas (Brunereau *et al.*, 2000). Tumours and vascular malformations present the main indications for the application of contrast media in the MRI diagnosis of epilepsy (Duncan, 1997).

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 (Ng *et al.*, 1994). The decrease has been reported to be reversible after contralateral amygdalo-hippocampectomy in patients with mesial temporal sclerosis and bilateral MRS abnormalities (Cendes *et al.*, 1997). 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.

Recently, fMRI has also been used to localize the eloquent cortex. Considerable additional work will be necessary to define its practical value.

Future perspectives of epilepsy surgery and in the definition of the epileptogenic zone

As resective epilepsy surgery has proved to be an extremely successful therapeutic approach, rendering up to 80% of selected patients seizure-free, it will be used in the decades to come. Other destructive therapies, such as radiosurgery, will increasingly play a role, especially in patients unsuitable for operative procedures, i.e. those with unresectable lesion, such as some arteriovenous malformations (Eisenschenk *et al.*, 1998; Regis *et al.*, 1999). It appears unlikely that radiosurgery will replace selective amygdalo-hippocampectomy as the standard treatment for mesial temporal lobectomy. In patients in whom the epileptogenic zone cannot be resected, increasing use of the vagus nerve stimulator and other stimulation techniques, such as deep-brain stimulation, is likely in the future.

All these treatments require the definition of the epileptogenic zone, which is, as mentioned above, a theoretical concept. None of the available tests permits direct measurement of the epileptogenic zone. In the future, we will have to look for new diagnostic techniques that will permit more direct definition of the epileptogenic zone. It is very likely that these developments will be in functional neuroimaging. All widely available functional neuroimaging techniques (mainly FDG-PET and interictal SPECT) measure only non-specific brain physiology, such as regional metabolism and blood flow. On the other hand, further developments may make it possible to directly image the distribution of neurotransmitters involved in the pathogenesis of epilepsy. Not only may this allow us to define different types of epileptogenic lesions based on neurotransmitter and receptor physiology, but it may also give us a measurement of the potential epileptogenic zones that are currently undetectable preoperatively. Receptor PET may play a major role in the definition of the epileptogenic zone in the future. In addition, refinements of the currently available diagnostic techniques may increase the accuracy with which we define the different zones. This will give us some additional power even if it does not solve some of the essential theoretical limitations discussed above.

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