

The concept of the epileptogenic zone: a modern look at Penfield and Jasper's views on the role of interictal spikes

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ABSTRACT – In modern times, the determination of the epileptogenic zone demands a sophisticated combination of neurophysiological and neuroimaging tools. Historically however, the concept of the epileptogenic zone was based on and has evolved from the recording of interictal spikes, both in the scalp electroencephalogram (EEG) and, particularly, in the acute electrocorticogram (ECoG). Because the role of interictal spikes is still not always clear in the decision-making process of epilepsy surgery, the relevance of these spikes in the definition of the epileptogenic zone is reviewed here, starting with the pioneering work of the Montreal school.

Keywords: interictal spikes, epileptogenic zone, epileptogenic lesion, Wilder Penfield, Herbert Jasper, Montreal School

If a newcomer to the field of epilepsy surgery were to list, in hierarchical order, the most relevant tools with which to delineate the epileptogenic zone in these modern times, he or she would probably rate magnetic resonance imaging (MRI) and ictal (scalp or intracranial) EEG as more important than seizure semiology and interictal EEG. High resolution structural and functional imaging modalities now have established roles in the identification of epileptogenic lesions and their spatial relationships with eloquent cortex, and multi-channel video-EEG recording systems often provide some degree of localization of the cortical area from where seizures start (Rosenow and Lüders, 2002). Nevertheless, experienced epileptologists would not dispense with detailed

descriptions or video reviews of seizure semiology, or with careful analysis of the distribution of interictal spikes. Not infrequently, these more simple tools help contextualize the findings obtained through more sophisticated imaging and neurophysiological modalities within the perspective of each individual patient.

Conceptual and technological advances in the field of epilepsy surgery have made the presurgical evaluation of patients with refractory seizures increasingly systematic and sophisticated (Carreno and Lüders, 2000, Rosenow and Lüders, 2004). These presurgical protocols can be thought of as topographical journeys throughout the cortex, searching for more or less specific regions related to seizure generation and neuronal dys-

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function. Thus, with the ultimate goal of localizing the epileptogenic zone – that is, the area of cortex indispensable for the generation of epileptic seizures – these protocols attempt to localize the symptomatogenic zone, the seizure-onset zone, the irritative zone, the epileptogenic lesion, and the functional-deficit zone. A detailed description of these «topographical markers» is dealt with elsewhere in this volume. Here, we will revisit the concept of epileptogenic zone as proposed in the beginnings of epilepsy surgery by Wilder Penfield and Herbert Jasper. In doing that, we will necessarily focus on the role of interictal spikes in the determination of the cortical regions to be resected at surgery, since localization and interpretation of the relevance of these spikes had a pivotal role in the presurgical protocol at the Montreal Neurological Institute (MNI) (Penfield and Jasper, 1954; Penfield, 1956; Penfield, 1958; Jasper *et al.* 1961). Throughout this text we will try to link topographical concepts at the time of Penfield and Jasper with the modern conceptualization of our times.

Determination of the extent of cortical tissue to be resected at surgery in Penfield and Jasper's era

From the 40s, the MNI school had a comprehensive pre- and intra-surgical protocol to determine the extent of tissue resection at epilepsy surgery (Penfield, 1956; Penfield, 1958). Detailed descriptions of seizure semiology were obtained, with particular attention to auras and early motor phenomena. These semiological elements were regarded as most significant not only because they indicated the likely sites of seizure-onset, but also because attempts were made to reproduce the aura and these early motor manifestations during the operations, under local anesthesia (see below). In addition, the distribution, frequency, and morphology of interictal spikes were evaluated. Because prolonged video-EEG facilities were not available, ictal recordings were only rarely obtained. Thus, presurgical information was basically synonymous with semiological descriptions and interictal spikes on the scalp/sphenoidal EEGs (reliable imaging came in much later).

The limitations of presurgical data were partially circumvented by intra-operative clinical and neurophysiological information. At the time, the mapping of interictal spikes in the acute pre- and post-resection electrocorticography (ECoG) was regarded as indispensable for planning the resection (see below) (Jasper, 1941, Jasper *et al.* 1961). Furthermore, as alluded to above, attempts were made to reproduce the aura or other initial ictal manifestations as an additional step towards a refinement in localization. Finally, eloquent cortex was localized through acute electrical cortical stimulation (Penfield and Rasmussen, 1950, Penfield and Jasper, 1954).

As can be inferred from such an interictally-based approach, no explicit efforts were made to establish with certainty anatomo-clinical correlations regarding the origin and evolution of epileptic seizures. For such a dynamic perspective, ictal EEG recordings – often with intracranial electrodes – are crucial.

An important additional aspect was that many of the operations in the earlier decades were on patients who had suffered unequivocal brain insults. As a corollary, most of these patients had lesions visible to the naked eye of the surgeon. The visualization of these post-traumatic scars, tumors, and atrophic convolutions was, of course, a major intraoperative guide, and helped to contextualize the findings from the ECoG and reproduction of auras (Penfield, 1956). Less obvious in this respect – but «more obvious» in EEG and ECoG terms – were operations for temporal lobe epilepsy due to mesial pathology. Indeed, the identification of basal/mesial temporal foci in patients with partial seizures characterized by unresponsiveness and automatisms was perhaps the first great contribution of scalp/sphenoidal EEG to epilepsy surgery. Even nowadays, amidst the impressive advances in neuroimaging, scalp/sphenoidal EEG continues to be highly relevant for the confirmation of the irritative and ictal-onset zones and for prognostic purposes in the syndrome of mesial temporal lobe epilepsy due to hippocampal sclerosis (Paglioli *et al.* 2004).

Lesions and spikes: old and important lessons

A critical issue, at a time when the extent of resection was determined intraoperatively on the basis of acute ECoG and the presence of cortical scars and other types of lesions was, the relationship between epileptogenic cortex and epileptogenic lesions, *i.e.*, structural abnormalities interfering with normal cortical physiology and giving rise to epileptiform discharges and seizures. In a sense, the concepts of epileptogenic cortex and epileptogenic lesions complement each other, although intersecting in different ways and to different degrees. A clear understanding of these intersections demands a brief review of historical, factual, and conceptual issues.

As mentioned above, in the beginning there was no cortical imaging, and the relationships between spikes and structural abnormalities were determined intraoperatively, through direct observation of the cortex and the recording of acute ECoG discharges. From the start, Penfield and Jasper demonstrated that spikes were to be expected in the cortex surrounding the structural lesions, particularly those lesions without neuronal components, such as glial tumors or cysts (Penfield, 1956). These surrounding regions – as well as atrophic cortical lesions – were thought to be «injured areas of gray matter». Thus, the early history of the relations between epileptogenic

lesions and epileptogenic cortex was based on the concept of abnormal gray matter within atrophic scars or surrounding foreign tissue lesions. An interesting historical landmark is the letter Penfield wrote to Lennox in 1940 (Penfield, 1956), where he adamantly expresses his views that by epileptogenic lesion one should not mean «the foreign tissue lesion itself», but rather the structurally and functionally disturbed but still viable surrounding gray matter. These concepts were further supported by pathological examination of this surrounding tissue, which usually demonstrated some degree of gliosis.

However, as the understanding of the genetic bases of certain forms of epilepsies grew, it became clear that epileptiform spikes could be recorded from structurally normal cortex, as epitomized by the very frequent spikes seen in benign rolandic epilepsy (Berroya *et al.* 2005). Furthermore, the studies of Frank Morrell (Morrell and de Toledo-Morrell, 1999), among others, showed that epileptiform spikes could be recorded at a distance from a foreign tissue lesion, in regions which were synaptically connected with the area harboring the lesion. This evidence also indicated that not all epileptiform spikes meant the same, namely, that the underlying cortex is structurally abnormal. Actually, this latter observation had already been made at the MNI, as a logical consequence of routinely performing acute ECoGs. Penfield, Jasper, and later Theodore Rasmussen often recorded acute ECoG spikes not only in abnormal cortical regions surrounding a structural lesion, but also at variable distances from the lesional border. These observations prompted the terminology «red» versus «green» spikes, pointing respectively to epileptiform discharges recorded from abnormal cortical tissue – that could be related to seizure generation – and to discharges recorded from structurally normal, underlying cortex (Rasmussen, 1983). The latter was regarded as not relevant for the production of seizures. Nevertheless, in a detailed follow-up study published in the early 60s, Jasper and colleagues demonstrated a significant (albeit not absolute) correlation between completeness of excision of the cortex displaying interictal spikes, both surrounding and at some distance from the lesion, and surgical outcome, suggesting that cortically-recorded spikes were, more often than not, relevant for the overall «epileptogenic proneness» (Jasper *et al.* 1961).

More recently, MRI has confirmed these two historical, conceptual views and has added new insight into the relations between lesions and spikes (or epileptogenic cortex). The incorporation of MRI in the presurgical evaluation of refractory epilepsies, leading to a frequent identification of structural lesions, made clear that the generation of interictal spikes in lesional epilepsies behaves along a spectrum: one end of which being represented by those patients in whom discharges are restricted to the cortical area containing the lesion, and the other end by patients whose interictal discharges are distributed over

much larger regions of one or both hemispheres. The intermediate situation is exemplified by regional spikes, that is, spikes recorded from cortical regions which are more extensive than the «surroundings» of a lesion, but are still contained, for instance, in a single lobe or «quadrant» of the brain.

As discussed elsewhere in this and other publications, the relations between the cortical regions generating interictal spikes - «the irritative zone» - and the area harboring the lesion and the injured, surrounding cortex - «the epileptogenic lesion» – lead with more or less precision to an approximation of the vital anatomical construct represented by the actual cortical regions from where the seizures arise. This «ictal-onset zone» may be more or less spatially congruent with the irritative zone, the epileptogenic lesion or both. A major challenge of the presurgical evaluation in patients with refractory partial epilepsies is to disentangle these relationships and determine the ictal-onset zone.

The classical MNI approach to localize (to infer would be a more appropriate terminology) the ictal-onset zone, was already partially discussed above. Penfield and Jasper performed large craniotomies, exposing extensive areas of the cortex. This allowed (i) identification of visually «abnormal convolutions»; (ii) detailed recording of the ECoG over large portions of the convexity; (iii) electrical cortical stimulation to localize functionally eloquent cortex and its boundaries; and (iv) an attempt at reproducing the habitual seizures, particularly the aura. Thus, intra-operative structural and neurophysiological findings were used to determine the most relevant irritative zone, but also, to a certain extent, the lesional cortex and the ictal-onset zone (that could, at times, well have been what is nowadays known as the “symptomogenic” zone). The extent of resection was tailored by these findings, coupled with preservation of eloquent functional cortex.

An interesting set of concepts began to be nurtured at that time that would flourish decades later, based on the application of advanced technology to the localization of relevant epileptogenic cortex. One of these concerned the existence of regions of variable epileptogenic thresholds within a larger area of injured or epileptogenic cortex. Penfield proposed that within an area of epileptogenic cortex identified by ECoG, seizures would originate in a given subregion and propagate through facilitated pathways (Penfield, 1956; Penfield, 1958). These pathways could thus be considered as a common denominator for electrical seizures originating in different subregions of a larger area of epileptogenic cortex. This, in turn, would lead to similar semiology, irrespective of the exact subregion of seizure origin. Interestingly, this concept of variability of seizure thresholds (or variability of thresholds of the seizure-onset zones) within an area of epileptogenic cortex has been recently revisited. Rosenow and Ludders have properly renamed this whole area as “potential epi-

leptogenic zone", containing one or more seizure-onset zones of variable thresholds (Rosenow and Lüders, 2002; Rosenow and Lüders, 2004). Indeed, this explains those situations where a seizure-onset zone is identified with a high degree of precision – even through the judicious use of intracranial electrodes – yet seizures recur nevertheless. These are scenarios in which the epileptogenic zone (or the "potential epileptogenic zone") is more extensive than the (any single) seizure-onset zone, justifying the individualization of these concepts. It is to be expected that incomplete resection of this "potential epileptogenic zone", with "preservation" of «higher threshold seizure-onset zones», may be associated with later seizure recurrence after resection of the lowest threshold ictal-onset zone (Palmini *et al.* 1997).

A modern look at old concepts

The two most significant advances in the presurgical evaluation of refractory partial epilepsies over the years have been the advent of MRI and multichannel video-EEG recordings – including detailed, chronic intracranial recordings with intracerebral or subdural electrodes. Whereas Penfield and Jasper usually operated on macroscopically visible, injured cortex and used acute ECoG to determine the extent of epileptogenic tissue, modern approaches use MRI to identify even small structural epileptogenic lesions and have a wide range of neurophysiological tools to determine the extent of epileptogenic tissue. It is important to note, however, that the ability to identify small lesions by MRI has, in a sense, rekindled the issue of the relationships between structural epileptogenic lesions and interictal spikes. Although there are spatio-temporal differences in the distribution and amount of interictal spikes recorded from intracerebral depth electrodes, subdural grids and strips, and acute ECoG, all methods systematically identify cortical regions displaying interictal spikes that extend beyond both the lesion margins and the boundaries of the seizure-onset zone (Rosenow *et al.* 2004). The significance of these spikes is then the crucial issue. These relationships are not fully understood, and the practical point is that if one assumes that a given cortical region displaying interictal spikes can produce seizures, it should be resected for seizure control. On the other hand, if it were possible to identify patterns or other variables related to interictal spikes that were not indicative of a potential for seizure generation, cortical regions displaying such spikes could be safely spared.

Even though some progress has been made, we believe that there is still work to be done to specify the role (functional intersections) of the type of lesion associated with the spikes, the cortical region where the spikes are distributed, the duration and severity of the epilepsy, and genetic tendencies of the individual patient. It is possible that the «epileptic» relevance of interictal spikes vary

according to each, or a combination, of these (or even other) factors.

These relationships are illustrated by the following three examples. The first relates to the relevance of resecting temporal neocortical spikes in patients with temporal lobe epilepsies, and raises the issue of the relationships between topography and pathology. When the epilepsy is associated with neocortical lesions, there is some evidence that resecting the lesion and the cortical regions displaying spikes is the best strategy (Berger *et al.* 1993; Pilcher *et al.* 1993; Jooma *et al.* 1995). On the other hand, there seems to be a convergence of data and authoritative opinion (Cendes *et al.* 1993; Schwartz *et al.* 1997) that in patients with temporal lobe epilepsy due to mesial temporal sclerosis, there is no benefit in resecting neocortical spikes beyond the planned margins of resection. This, of course, is corroborated by the equally high rates of seizure-freedom in patients undergoing anterior temporal lobectomy (which resects neocortical tissue) and selective amygdalohippocampectomy (which does not) (Paglioli *et al.* 2006).

The second illustration also involves topography, combined with the presence of lesions, in a general sense, or in patients without identifiable macroscopic lesions. This refers to the work by Wennberg and colleagues at the MNI (Wennberg *et al.* 1998; Wennberg *et al.* 1999), who reviewed the historical series of frontal lobe epilepsy surgeries in that Institution. In patients with lesions, these authors showed that when acute ECoG spikes involved two or more gyri beyond the lesion, or when spikes persisted after the final resection, surgical outcome tended to be unfavorable. As expected, there was also a strong correlation between completeness of resection of the lesion and seizure control, which made it difficult to single out the specific role of the resection or persistence of ECoG spikes. The main positive message was the highly favorable outcome predicted by the combination of complete lesionectomy and complete resection of ECoG spikes, particularly when the latter were restricted to one or two gyri adjacent to the lesion. The same group reported on the role of resection of ECoG spikes in patients with nonlesional frontal lobe epilepsy, and showed that both the extent of the irritative ECoG zone and the post-resection data correlated with outcome. More specifically, they showed that widespread spike distribution (involving more than two gyri) and persistence of spikes at some distance from the margins of excision correlated with unfavorable outcome. The good news is that even in the context of nonlesional frontal lobe epilepsies, complete resection of spiking cortex, particularly if spatially restricted, may be associated with a good surgical outcome.

The final example focuses on the relation between a specific type of pathology and the relevance of interictal spikes. This particular example will deal with the focal cortical dysplasias, which are common neocortical epi-

leptogenic lesions. Perhaps in no other entity is the possibility that the cortical distribution of spikes indeed represent (and validate!) the concept of “potential epileptogenic zone” so strong as in the neocortical focal cortical dysplasias. Ongoing studies (Palmiini *et al.* in preparation) show that a number of patients do present seizure recurrence after up to 2 years of post-operative seizure-freedom. It is likely that at least some of these “late” or “delayed” failures may be due to persistence of higher threshold seizure onset zones, which independently began generating seizures after the initial resection. Several authors have independently confirmed the tendency of focal cortical dysplasias to display two distinct types of interictal epileptiform discharges on electrocorticography (Palmiini *et al.* 1995; Morioka *et al.* 1999, Binnie *et al.* 2000; Ferrier *et al.* 2001). The first type seems to be virtually specific for this pathological entity, namely a remarkable epileptiform pattern on acute ECoG manifesting as either continuous spiking, repetitive bursting of polyspikes, or recurrent electrographic seizures. These discharges are recorded from the lesions and their surroundings, in about 75% of cases with pathologically confirmed, focal cortical dysplasia (Palmiini *et al.* 2004). When cortical tissue, displaying such continuous or bursting spikes, is not included in the resection, seizures almost always recur after surgery (Palmiini *et al.* 1995; Chassoux *et al.* 2000; Francione *et al.* 2003). The second type are the more usual, discontinuous interictal spiking, more or less adjacent to the dysplastic lesion. A recent reanalysis of our data in Porto Alegre shows that complete resection of these discontinuous spikes is also relevant to complete seizure control (Palmiini *et al.* 2004). Caution however, must be exercised in this conclusion, because more often than not patients had incomplete resections not only of the cortical tissue displaying these spikes, but also of the dysplastic lesion itself. The role of these “discontinuous”, intermittent spikes at some distance from a dysplastic lesion, thus, is still open for discussion. Even prolonged recordings with depth electrodes failed to determine their role in the final post-surgical outcome of patients (Chassoux *et al.* 2000; Francione *et al.* 2003).

A final word

We have attempted to track the relevance over the decades, of interictal spikes in the definition of the epileptogenic zone, starting with the pioneering work of the Montreal school. Despite considerable technological advances both in terms of the recording of these spikes and our understanding in the context of detailed structural and functional imaging, research is still needed to fully integrate interictal data in the final decision regarding how much tissue to resect in individual patients. Perhaps a fruitful avenue of research has been opened by Rosenow and Lüders’ revisit of the issue of “potential epilepto-

genic zones” (Rosenow and Lüders, 2004). It may well be that the distribution of specific patterns of interictal epileptiform spikes will prove the only predictor of the full extent of these higher threshold, «potential» seizure-onset zones. □

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