The epileptogenic zone: general principles

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Sir Victor Horsley, a British neurosurgeon, pioneered epilepsy surgery and, in 1886, published the reports of successful cortical resections that resulted in a significant reduction in epileptic seizures in three patients (Horsley, 1886). At that time, V. Horsley assisted by J.H. Jackson (epileptologist) and D. Ferrier (neurophysiologist), identified the region to be resected by the location of either a structural lesion and/or the area of cortex which, on stimulation, reproduced the initial symptoms of the clinical seizure. As J.H. Jackson indicated, they hoped that surgery would result in "cutting out the discharging lesion" that they believed was "the very local cause of the fits". In other words, in the 19th century, the so-called "discharging lesion", defined by the location of the macroscopic cortical lesion and/or clinical ictal semiology, was equivalent to the epileptogenic zone of modern epileptology.

In 1929, H. Berger (Berger, 1929) published the first report of EEG recordings in humans, and in 1934 O. Foerster (Foerster and Altenburger 1934) reported the first electrocorticogram. However, the extent of the "epileptogenic zone" was defined almost exclusively by the limits of the macroscopical cortical lesion until the early 1950s. At that time, Bailey and Gibbs (Bailey and Gibbs 1951) and Penfield and Jasper (Penfield and Jasper 1954) also used complementary **interictal scalp EEG and interictal corticography** to establish the limits of the epileptogenic zone. For the next 10-20 years these techniques remained the essential armamentarium used to define the epileptogenic zone, even if researchers realized the limitations and lack of precision intrinsic to the interictal epileptiform activity as an index of the epileptogenic zone. A new breakthrough was the introduction of the stereo-electroencephalography (SEEG) by Jean Talairach and Jean Bancaud that revolutionized our concept of the epileptogenic zone (Bancaud *et al.* 1962a, Bancaud and Chauvel 1987, Buser *et al.* 1973, Talairach and Bancaud 1973, Talairach and Bancaud 1974). The French investigators assumed that "*stereoencephalographie*" would actually provide the ideal methodology to define, with extreme precision, what they defined as the **epileptogenic zone**.

Since the pioneer work of Talairach and Bancaud in the 1960s, extensive surgical experience and the emergence of new, powerful diagnostic techniques have led to the redefinition of the epileptogenic zone, clearly distinctive from that originally described by Talairach and Bancaud (Lüders *et al.* 1993). The approach of this definition was significantly more **abstract** and allowed the inclusion of modern diagnostic techniques and possible future technological advances. For example, the epileptogenic zone in Talairach and Bancaud definition was determined by the results of the stereo-EEG evaluation and therefore was primarily an ictal EEG concept. On the other hand, the modern/practical "epileptogenic zone" is de-

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fined as the "minimal area of cortex that must be resected to produce seizure-freedom" (see below), independent of the technique used to determine the extent of the surgical resection.

Definition of epileptogenic zone

In 1993, we defined the epileptogenic zone as the "area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures" (Lüders *et al.* 1993). Without deviating significantly from this definition, we would like to propose the following, simplified definition of the epileptogenic zone as "the minimum amount of cortex that must be resected (inactivated or completely disconnected) to produce seizure freedom". This definition of the epileptogenic zone has a number of assumptions and shortcomings that should be considered:

1. It assumes that seizures can only be controlled surgically by either removing or completely disconnecting the seizure-onset zone. In other words, disconnection of seizure-spread pathways could modify the expression of the seizures but would not result in seizure-freedom. There is evidence in the literature that surgical disconnection strategies have been unsuccessful in the control of epileptic seizures (Kinay *et al.* 2004). This is not surprising considering that cortical connections spread in all directions from any given cortical point, including cortico-cortical and extensive subcortical connections. Even if seizures tend to have preferential spreading patterns, disconnection of any given spread pathway will not prevent the evolution of the seizure using alternative spread pathways. This may result in some modification of the seizure symptomatology but will not prevent the occurrence of an epileptic seizure. The only way to avoid seizure occurrence is removal of the seizure-onset zone or what is equivalent to its *complete disconnection* that may not be possible in most situations. A good example of a *complete disconnection* is functional hemispherectomy (Rasmussen 1983), which replaced the more traditional anatomical hemispherectomy (Krynauw 1950) because it was assumed that the hemosiderosis observed following anatomical hemispherectomy was due to removal of a large amount of brain tissue. In the context of the present discussion it is interesting to notice that functional hemispherectomy (= total *disconnection* of the epileptogenic zone) is as effective as anatomical hemispherectomy (= total *removal* of the epileptogenic zone) as long as the *disconnection* is complete (Delalande *et al.* 2000). On the other hand, seizures invariably persist if the surgeon does not succeed in cutting all of the connections between the abnormal hemisphere and the rest of the brain. It is also interesting to observe that even in patients with complete agenesis of the corpus callosum, seizures eventually

spread to the opposite hemisphere. In these cases, the seizures must spread to subcortical structures, cross the midline and then return to the opposite cortex. This is illustrated in *figures 1, 2 and 3*, that show a case of corpus callosum agenesis in which the seizure activity spread from one hemisphere to the other along subcortical pathways.

2. This again illustrates the powerful tendency for epileptogenic cortex to spread through whatever cortical or subcortical pathways that are available.

3. Talairach and Bancaud assumed that what they named the epileptogenic zone could be defined with precision with depth electrodes as long as invasive electrodes were placed directly in the seizure-onset area as well as in the region(s) in which seizures spread (Talairach and Bancaud 1966). This conviction led them to the development of stereoelectroencephalography (Talairach and Bancaud 1973, Talairach and Bancaud 1974). This is also the basis of the position held by some epileptologists that the epileptogenic zone is primarily an electroencephalographic (EEG) concept. There is no right or wrong answer to this situation. It all depends on definitions. However, it is important to stress that in the definition we adopted in this manuscript, the *epileptogenic zone is not equivalent to the seizure-onset zone.* Besides, in the concepts discussed here, the *seizure-onset zone can be defined by different techniques* including depth electroencephalography (EEG). These two concepts will be discussed in detail below.

4. The concept of the epileptogenic zone as "the minimum amount of cortex that must be resected (or completely disconnected) surgically to produce seizure freedom" apparently provides an objective definition of this zone. However, the definition does not consider the time factor. There is conclusive evidence in the literature that the epileptogenic zone is not static over time. Indeed, on the contrary, the epileptogenic zone is a dynamic concept that changes continuously over time. The typical example are the benign focal epilepsies of childhood in which there is a tendency for the epileptogenic zones to appear first in the occipital areas and then to "migrate" anteriorly to the centro-temporal region, and finally to disappear at puberty (Lüders *et al.* 2004). Another example is the cortical dysplasias. In a not insignificant percentage of cases, seizures only appear after 10-20 yrs of "maturation" and then frequently tend to become progressively more active with time (Fish 1999). Finally, the "running down phenomenon" (Andermann *et al.* 1993) and the recurrence of seizures many months or years following epilepsy surgery, are clear examples of epileptogenic zones which change over time. To simplify the following discussion however, we will start by assuming that we are dealing with static epileptogenic zones. At the end of the review, we will then discuss how an epileptogenic zone that changes over time would influence the concepts we have developed.
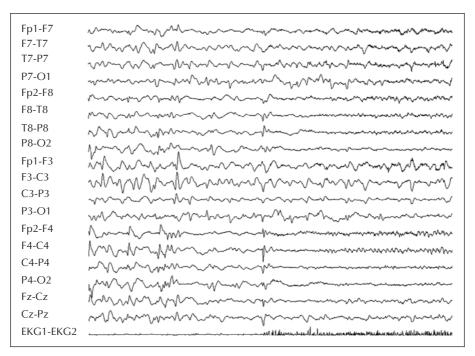
Figure 1. Ten-year-old girl with seizure onset at one month of age, characterized by unresponsiveness and left-sided clonic movements followed by right-sided clonic movements. The pregnancy was complicated by bleeding at seven weeks. She was born at 38 weeks by vacuum and forceps and with Apgar scores of 1 and 5. The EEG shows the seizure-onset with an electrodecremental pattern in the right hemisphere. At this time, the left hemisphere is not involved; the preictal left-sided background activity continues without any significant change. The patient had left clonic seizures during the initial part of the seizure.

Figure 2. Ictal EEG recorded 80 seconds after the EEG shown in figure 1. At this point, the right hemisphere has returned to its baseline pattern and an electrodecremental pattern is now seen in the left hemisphere. During the latter part of this seizure, the patient had right clonic seizure activity. Figures 1, 2 and 3 illustrate the tendency of the brain to use any available pathways for seizure spread. This explains why attempts to block seizure spread by cutting pathways used for seizure spread will be unsuccessful unless the epileptogenic zone is *completely* isolated.
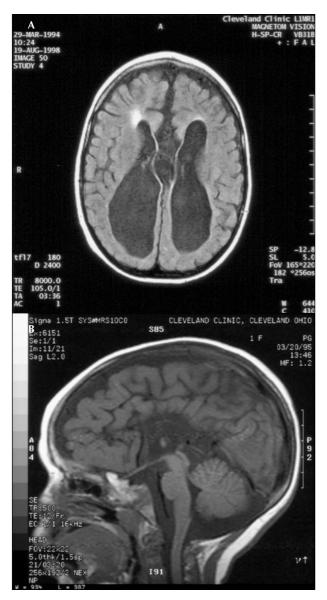
Figure 3. MRI of the patient whose EEGs are shown in figures 1 and 2. It shows marked ventriculomegaly and complete agenesis of the corpus callosum. The independent involvement of the left and right hemisphere illustrated in figures 1 and 2 is an expression of the absence of the pathways which are usually used to synchronize epileptiform activity in the two hemispheres. However, the eventual spread of the seizure activity from one hemisphere to the other illustrates the tendency of seizure activity to make use of *all available* pathways for seizure spread.

Cortical zones defined in the presurgical evaluation

During the presurgical evaluation, the following five areas (Carreño and Lüders 2001) are measured using different diagnostic techniques:
– Irritative zone ("area of cortex which generates interictal spikes"). This area is measured by EEG (invasive and

non-invasive), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI);
– Seizure-onset zone ("area of cortex that initiates clinical seizures"). This area is determined primarily by EEG (invasive and non-invasive), but can also be defined by ictal SPECT and to a lesser degree by fMRI and MEG;
– Symptomatogenic zone ("area of cortex which, when activated, produces the initial ictal symptoms or signs"). This area is determined by analyzing the initial seizure symptomatology;
– Epileptogenic lesion ("macroscopic lesion which is causative of the epileptic seizures because the lesion itself is epileptogenic (*e.g.* cortical dysplasia) or by secondary hyperexcitability of adjacent cortex"). This area of cortex is currently defined by anatomical imaging such as high resolution MRI. Further advances in imaging techniques will undoubtedly result in more accurate definition of the epileptogenic lesion and its cellular/molecular components: histo-molecular imaging;
– Functional deficit zone ("area of cortex that is not functioning normally in the interictal period"). This area can be defined by a number of tests including neurological examination, neuropsychological examination and functional imaging (interictal SPECT and PET).
These five zones are actually measured during the presurgical evaluation and then epileptologists use this information to deduce the location and extent of the epileptogenic zone.

Theoretical cortical zones and practical cortical zones

In the discussion of the different zones listed above, it is extremely important to differentiate between theoretical and practical cortical zones. The methods we currently use to measure the different zones have variable degrees of error, and certainly will never be able to define with 100% precision the cortical area they are intended to measure. However, no matter what the practical limitations, it is extremely important that we have a clear concept of the theoretical area we are trying to define and of its relationship with the other theoretical cortical zones. In the following paragraph, we will illustrate the difference between theoretical and practical cortical zones for the irritative zone.
As mentioned above, the theoretical "irritative zone" is the "area of cortex capable of generating interictal spikes". It can be measured by EEG (non-invasive or invasive) as also MEG or fMRI. Our previous experience suggests that the theoretical "irritative" zone is usually more extensive than the epileptogenic zone. This is best illustrated in patients with bilateral, independent, mesial temporal spikes who, not infrequently, can be rendered seizure-free by unilateral temporal lobectomy (Hamer *et al.* 1999, So 2001). In other words, in these cases the epileptogenic zone(s) is a

subset of the irritative zone(s). Understanding this *theoretical relationship* is extremely helpful because it defines the *theoretical limitations* of using the irritative zone as an index of the epileptogenic zone. In other words, measurements of the irritative zone, *independent of the precision of the methodology* used for its assessment and definition will not provide us with a precise index of the epileptogenic zone. A clear understanding of these theoretical limitations of the irritative zone is essential for the interpretation of the results of new techniques, such as MEG or fMRI, that are designed to measure with more precision, interictal spikes. Spikes localized with high precision will only identify better parts of the irritative zone which may or may not be part of the epileptogenic zone. Penfield and Jasper (Penfield and Jasper 1954), who, as stated above, used primarily, interictal spikes (recorded during electrocorticography) to define the epileptogenic zone, already realized that, very often, cortex outside the epileptogenic zone was capable of generating interictal spikes. In their terminology, they spoke of "red spikes" (originating from cortex that had to be resected = epileptogenic zone) and "green spikes" ("originating from cortex that did not have to be resected = irritative zone not overlapping with epileptogenic zone").

This discussion illustrates the importance of understanding the theoretical definition of the different zones and the *theoretical interrelationship* between the different zones including the epileptogenic zone itself. This theoretical understanding should be complemented by a clear assessment of the practical limitations of the methods used to define these theoretical zones. For example, the use of non-invasive scalp EEG to define the irritative zone is greatly limited by the relative insensitivity of scalp EEG for the detection of spikes generated in small areas of cortex. In general, spikes generated within less than 6 cm^2 are invisible on scalp recordings (Abraham and Ajmone-Marsan 2004, Cooper *et al.* 2004). We also know from invasive recordings, that a significant percentage of interictal spikes are generated in relatively small volumes of brain, and would therefore be undetected on scalp recordings. From these observations we can conclude that scalp recordings, very frequently will underestimate the extent of the irritative zone. On the other hand, it is also very difficult to estimate the real extent of the irritative zone with invasive recordings. Invasive electrodes, regardless of type, invariably cover only a small fraction of the brain. In addition, there are no generally recognized rules to identify epileptiform activity from invasive electrodes. As invasive recordings are carried out almost exclusively in patients with intractable epilepsy, there are no control studies in human that define physiological electrocorticographic or SEEG transients. Therefore, the specificity of invasive recordings for detection of epileptiform activity is very limited. The poor spatial coverage would lead to an underestimation of the irritative zone, and the poor specificity of the invasive recordings would lead to overestima-

tion of the irritative zone. These factors contribute to frequent mislocalization and lack of definition of the extent of the irritative zone using invasive recording techniques.

From this discussion we can see that, in addition, to significant practical problems related to the accuracy of our estimate of the location and extent of the irritative zone, there are major theoretical limitations when trying to use the irritative zone as an index of the epileptogenic zone. Both of these factors add to the unreliability of the any methodology that uses the irritative zone to define the location and limits of the epileptogenic zone.

The theoretical difference between the epileptogenic zone and the seizure-onset zone

Talairach and Bancaud assumed that direct, invasive, ictal recordings from the seizure-onset zone and the areas of brain into which the seizures spread would be a reliable index of the location and extent of the epileptogenic zone (Bancaud *et al.* 1962b, Bancaud and Chauvel 1987, Talairach and Bancaud 1966, Talairach and Bancaud 1973, Talairach and Bancaud 1974). In their terminology, the seizure-onset zone is identical to the epileptogenic zone. Extensive surgical experience has led us to regard the seizure-onset zone and the epileptogenic zone as two different concepts. In some cases, complete resection of the actual seizure-onset zone does not lead to seizure-freedom. In these cases, additional post-surgical recordings suggest that areas adjacent to the resection were now triggering epileptic seizures. These observations led to the concept of *potential seizure-onset zones (figure 4).*

In other words, we speculated that the epileptogenic zone consisted of an actual seizure onset zone and an additional, potential epileptogenic zone. Direct presurgical
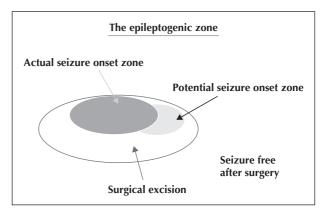

Figure 4. A diagram showing the actual seizure-onset zone, the potential seizure-onset zone, and a surgical resection that includes both seizure-onset zones. Complete resection of both seizure-onset zones should result in seizure-freedom.

measurements before resection would only be able to identify the actual seizure-onset zone. Talairach and Bancaud speculated that resection of cortex participating in "early" seizure spread should be included for better surgical results. Essentially, they speculated that cortex involved in "early" seizure spread was at least part of the potential seizure-onset zone. *figures 5 and 6* illustrate surgical resections that did not result in seizure-freedom either because of incomplete resection of the actual seizure-onset zone *(figure 5)* or incomplete resection of the potential seizure-onset zone *(figure 6)*.

Fundamental objectives of presurgical evaluation

The fundamental objective of presurgical evaluation is to define, with precision, the location and exact extent of the epileptogenic zone. Ideally, the surgical resection should take out the entire epileptogenic zone sparing any adjacent cortex that is not part of the epileptogenic zone
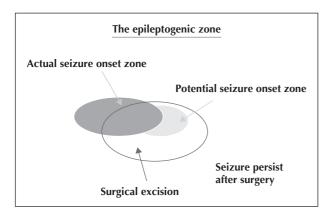

Figure 5. This diagram illustrates a surgical resection that did not result in seizure-freedom because of incomplete resection of the actual seizure-onset zone.
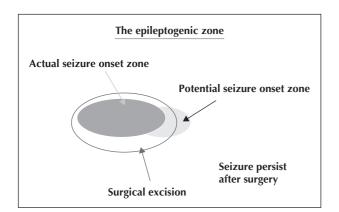

Figure 6. This figure illustrates a surgical resection that did not result in seizure-freedom because of incomplete resection of the potential seizure-onset zone.

(normal or abnormal). From the discussion above, it is clear that there are a number of problems that limit our ability to achieve this fundamental objective:
– We can only measure the actual seizure-onset zone. There is no proven methodology to define the potential seizure-onset zone. As mentioned above, Talairach and Bancaud assumed that cortex participating in "early" seizure spread was part of the potential seizure-onset zone. This belief is not shared by most North American epileptologists, who usually do not include in the surgical resection cortex activated by "early" seizure spread;
– All methods available to define the actual seizure-onset zone have significant limitations. The extensive presurgical evaluation, includes the measurement of many other zones (see list above) that are only indirect indices of the epileptogenic zone. This is a demonstration of our inability to measure precisely the actual and potential seizure-onset zone.

Differences between the theoretical actual seizure-onset zone and the practical ("measured") actual seizure-onset zone

As mentioned above, all the available methods to directly measure the actual seizure-onset zone have significant limitations.
Non-invasive surface electrodes give an excellent overview of the brain, but usually can not detect the actual seizure-onset zone. As we mentioned above, surface non-invasive recordings can only detect epileptiform activity that synchronizes at least 6 cm^2 of the cortex. In addition, surface recordings have even greater difficulty "seeing" seizure onsets occurring in cortical regions that are located relatively deep with respect to the scalp surface (interhemispheric, mesial temporal, etc.). This lack of sensitivity implies that surface recordings will only detect EEG seizures after they have spread to involve extensive areas of cortex. This explains why surface recordings are primarily useful to lateralize seizures, but are of limited value for precise localization of the actual seizure-onset zone. This clarifies why it is not unusual that, for example, patients with mesial temporal lobe epilepsy may have surface EEG seizure recordings that apparently start from frontal or temporo-occipital leads.
Invasive recordings also have major limitations in defining the precise seizure-onset zone. Invasive recording electrodes can only cover a very limited portion of the brain. In general, epileptologists perform a detailed, pre-surgical, non-invasive evaluation which provides them with some guidelines regarding the location of the epileptogenic zone. Using this information, they plan the implantation of invasive electrodes. Therefore the chances of accurately defining the location and extent of the seizure-onset zone will depend on the information gathered during the pre-surgical, non-invasive evaluation and the hypothesis that

the epileptologists formulated using this information. Unfortunately, only a finite number of invasive electrodes can be placed. Therefore, even if the hypothesis regarding the location and extent of the epileptogenic zone is correct, invasive recordings consistently only cover part of the actual seizure-onset zone.

There is another problem related to the EEG interpretation, particularly of seizure-onsets recorded with invasive electrodes. *Figure 7* shows a diagram of a seizure which actually started from brain cortex marked in orange. The seizure then spread progressively to the yellow → red → white and magenta coloured electrodes. Electroencephalographers would agree that the seizure starts at the yellow electrodes, but some would also include the red electrodes, others would include the red and white electrodes, and finally there are certainly electroencephalographers who would assume that the seizure-onset zone includes the yellow, red, white and magenta electrodes. EEG interpretation is thus a subjective "art", with no objective rules, and great variability between electroencephalographers exists. Notice also that in *figure 7*, the invasive electrodes were not covering the actual seizure-onset zone and therefore, the invasive EEG only identified seizure spread. As we mentioned before, Talairach and Bancaud assumed that "early" seizure spread (again with no clear definition of what "early" means) was part of the epileptogenic zone.

Another methodology used to define the actual seizure-onset zone is ictal SPECT. Unfortunately this technique also has major limitations. It is well recognized that during epileptic auras, ictal SPECT does not show areas of hyperperfusion. This implies, as would be expected, that ictal SPECT has limited sensitivity for the detection of small regions of hyperperfusion. Therefore, it is very likely that ictal SPECT may primarily detect ictal spread as opposed to accurately defining the actual seizure-onset zone.
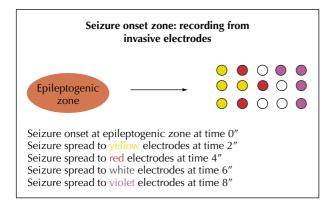

Seizure onset zone: recording from invasive electrodes

Seizure onset at epileptogenic zone at time 0"
Seizure spread to yellow electrodes at time 2"
Seizure spread to red electrodes at time 4"
Seizure spread to white electrodes at time 6"
Seizure spread to violet electrodes at time 8"

Figure 7. Diagram showing subdural electrodes placed at a short distance from the epileptogenic zone. There is a seizure discharge that spreads and progressively invades the yellow, red, white and magenta electrodes.

There are a number of features that either suggest or confirm that the invasive electrodes do not cover the epileptogenic zone (*i.e.* that the *apparent* initial seizure-onset zone is actually already an expression of seizure spread):
– clinical symptoms or signs preceding the EEG seizure-onset ;
– surface EEG recordings showing EEG seizure-onset before invasive electrodes ;
– seizure-onset zone is not, at least, a subset of the irritative zone.

Relationship between other zones with the seizure-onset zone and the epileptogenic zone

As mentioned above, detailed presurgical evaluation always requires the definition of various zones that have a variable spatial relationship with the epileptogenic zone:
1. *Irritative zone.* EEG and/or MEG are necessary to detect interictal spikes. fMRI can assist us in defining the exact volume of tissue that generates interictal spikes (= irritative zone). Interictal spikes essentially can be considered as extremely focal "EEG seizures" that do not spread and only infrequently are associated with clinical signs. To produce clinical signs, spikes have to be strong enough to activate the cortex and, since there is no spread, must be generated by eloquent cortex. In general, the seizure-onset zone is a subset of the irritative zone. From this observation derives also the assumption that the irritative zone not included in the actual seizure-onset zone is an index of the potential seizure-onset zone. There is no evidence that this assumption is correct. On the other hand, there is extensive evidence in the literature that the irritative zone is frequently more extensive than the epileptogenic zone (the typical example is patients with bitemporal spikes in which resection of one temporal lobe results in seizure freedom). This last observation clearly stresses the fact that even the most precise mapping of the irritative zone (with MEG, fMRI, or EEG source analysis) can be grossly misleading and points actually to brain regions that are not even included in the epileptogenic zone. There are also considerable difficulties of specificity, particularly when identifying spikes with invasive electrodes. Because of the lack of controls, electroencephalographers tend to label as epileptiform most sharply contoured, relatively outstanding waveforms. Contrary to surface recordings, in which we have extensive recordings from controls, there are no clear criteria that allow electroencephalographers to differentiate "real" spikes from physiological sharp transients. This greatly reduces the specificity of spikes identified in invasive recordings.
2. *Symptomatogenic zone.* Careful attention to the ictal semiology is extremely important because it usually provides a good index of the eloquent cortex that is involved

in the initial part of the seizure. However, the symptomatogenic zone rarely overlaps with the seizure-onset zone. In other words, seizures originate from the seizure-onset zone, which tends to be silent and then invades by electrical spread to eloquent cortex. This will give rise to the initial seizure symptomatology if the seizure activity that spread to the eloquent cortex was "strong" enough to activate the eloquent brain. In summary, identification of the initial seizure symptomatology only indicates that seizure-onset is in the neighborhood of (or directly connected to) the corresponding symptomatogenic zone. It certainly does not localize the exact seizure-onset zone and also gives no indication of the extent of the seizure-onset zone.

3. *Epileptogenic lesion.* The development of high resolution MRI has greatly improved our ability to precisely define the epileptogenic zone. It is also generally accepted that in the great majority of the patients, the epileptogenic zone lies within the macroscopic lesion or in its immediate surrounding. North American investigators usually assume that the epileptogenic zone is more or less restricted to the macroscopic lesion and/or its immediate neighborhood except in those cases in which microscopic abnormalities (not necessarily visible in the MRI) extend relatively large distances from the macroscopic lesion. A typical example of this last situation is malformations of cortical development. In these cases, the macroscopic, MRI-visible lesion may be less epileptogenic than the surrounding microscopic, MRI-invisible lesion. The North American position contrasts with the French/Italian position that assumes that, for certain histological lesions, in addition to the lesion itself and its neighborhood, cortical areas of "early" spread are also part of the epileptogenic zone and have to be resected to assure post-surgical seizure-freedom.

4. *Functional deficit zone.* There are many tests to measure areas of cortex that in the interictal period are not functioning normally. This includes the neurological examination, neuropsychological testing, interictal PET and interictal SPECT. All of these tests point to cortex that is functioning abnormally in the interval between seizures. However, none of the tests are specific for an epileptic dysfunction of the cortex. Cortical dysfunctions uncovered by the tests mentioned above are frequently the expression of nonspecific, non-epileptic abnormalities. Besides, epileptic cortical lesions may not be associated with any interictal functional abnormality. An example are focal cortical malformations, which may be highly epileptogenic but do not necessarily result in interictal functional abnormalities. The area of functional cortical abnormality frequently extends outside the limits of the epileptogenic zone. For example, patients with temporal epilepsy due to hippocampal sclerosis very frequently show hypometabolism in fluorodeoxyglucose (FDG) PET studies that extends to large areas of the temporal lobe and at times, even to some extratemporal regions. All these limitations in the definition of the functional deficit zone greatly decrease its value in localizing and defining the extent of the epileptogenic zone.

Conclusion

Based on all the considerations as discussed above, the following conclusions can be drawn:

1. Defining the epileptogenic zone as the "the minimum amount of cortical tissue that must be resected to produce seizure-freedom" provides an objective and practical criterion for the testing of this theoretical concept. It means that seizure-freedom after surgery is evidence that the whole epileptogenic zone was included in the resected area. However, it does not mean that the complete area of excision had to be resected to produce seizure-freedom. In other words, very often the epileptogenic zone is a *subset* of the area of excision.

2. One of the limitations of the definition given above is its incorrect assumption that the epileptogenic zone is constant over time. We know that this is not the case. There are frequent examples of epileptogenic zones that shrink or disappear with maturation and also the opposite, namely a progressive extension of the epileptogenic zone over time can also be observed. In this manuscript, the complexity of variability of the epileptogenic zone over time was not taken into account.

3. The difference between "theoretical" and "practical" zones was discussed in detail. The importance of analyzing the theoretical zones and their spatial interrelationships was also stressed. In addition, we discussed the different methodologies and their limitations in defining the different presurgical zones (irritative zone, seizure-onset zone, symptomatogenic zone, epileptogenic lesion, functional deficit zone). The concept that the epileptogenic zone is the sum of the actual ictal-onset zone and the potential ictal-onset zone was explained. The location and extent of the actual ictal-onset zone can be estimated from (invasive or non-invasive) EEG recordings. Most North American investigators feel that there is no currently available method to measure the potential seizure-onset zone. French/Italian investigators assume that cortical areas involved in "early" seizure spread are part of the potential seizure-onset zone and therefore should be part of the surgically resected regions. There is no proof that this strategy leads to a higher percentage of successful resections. □

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