Definition and localization of the epileptogenic zone

The Bancaud and Talairach view on the epileptogenic zone: a working hypothesis

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ABSTRACT – The definition of the epileptogenic zone, as proposed by Talairach and Bancaud, is an ictal electro-clinical definition based on the results of stereotactic intracerebral EEG (SEEG) recordings. It takes into account not only the anatomical location of the “site of the beginning and of the primary organization” of the epileptic discharge, but also how this discharge gives rise to the accompanying clinical symptoms. This definition is different from the North American view since, for the French authors, the epileptogenic zone is not synonymous with what can be called the “what-to-remove area”. In fact, it is above all a conceptual definition which emphasizes the importance of studying the spatio-temporal dynamics of seizure discharges, and not only their starting point.

Key words: epileptogenic zone, neuroimaging, seizure

During the last 50 years, epilepsy surgery has largely benefited from the modern neuroimaging and other non-invasive, localizing techniques, thus increasing safety, accuracy, and efficacy of presurgical investigations and surgical treatment. As a matter of fact, the concept of the epileptogenic zone has also evolved over time, and other additional definitions have emerged to account for the different information provided by all the newly available diagnostic techniques (Rosenow and Lüders 2001, Lüders et al. 2006). Thus, according to Carreno and Lüders (2001), five cortical zones can be actually determined during the presurgical evaluation: the irritative zone, the seizure onset zone, the symptomatic zone, the epileptogenic lesion, and the functional deficit zone. The epileptogenic zone, defined as “the minimum amount of cortex that must be resected (inactivated or completely disconnected) to produce seizure freedom”, is an unmeasurable cortical area, the location and extent of which is deduced from the information coming from the delimitation of the other five zones, independently from the technique used to determine the extent of surgical resection (Lüders et al. 2006). Thus, this definition of the epileptogenic zone is a theoretical one which, in every case, must be validated post-surgery. The seizure-free status of the patient after surgery however, only confirms that the epileptogenic zone has been included in the resected cortex (surgery was sufficient), but this does not mean that the epileptogenic zone necessarily matched closely with the extent of the resection. Yet, such a surgical definition is given at the end of the whole presurgical evaluation process and, as such, it cannot be applied easily in the out-patient setting.
In contrast, the concept of the epileptogenic zone, as proposed during the sixties by Talairach and Bancaud (Talairach and Bancaud, 1966), derived primarily from a working hypothesis: since the seizure was the symptom to be cured, it was the region of cortex generating the epileptic seizures that had to be determined electrophysiologically, and then translated into anatomical terms. In other words, the idea was to use electro-clinical information obtained during seizure recordings, rather than findings coming from the study of interictal spikes (Bancaud, 1959, Bancaud and Dell, 1959). At that time indeed, presurgical evaluation of focal epilepsies remained the province of electrocorticography, the aim of which was to define the “epileptogenic focus” both on the basis of the extent of “stationary” interictal spikes, and on the results of cortical electrical stimulation (Penfield and Jasper, 1954). The principal guide of the French approach consisted, conversely, of a careful analysis of ictal clinical symptoms, the “syndromic” organisation of which made it possible to “visualize mentally” the spatial trajectory of the epileptic discharge within the cortex. Therefore, Bancaud and Talairach elaborated a comprehensive methodology, the stereo-electro-encephalography (SEEG), the aim of which was to study, in each individual case, the anatomical structures from which seizures originated (Bancaud et al. 1965, Bancaud et al. 1973, Talairach and Bancaud, 1973, Talairach et al. 1974). This intracerebral recording of ictal activity required a new definition with respect to the brain area to be resected: the term epileptogenic zone was proposed, and defined as the “site of the beginning and of the primary organization of the epileptic seizures” (Munari and Bancaud, 1987). From a surgical perspective however, this so-defined epileptogenic zone did not serve as the only guide for planning the surgical excision. It is clear, when looking at the work of Talairach and Bancaud, that the French investigators also took into consideration the topography of what they named the irritative and lesional zones (Talairach and Bancaud, 1966), as well the results of intracerebral electrical stimulation. We will see, in the following paragraphs, how the new concept developed by Talairach and Bancaud (the epileptogenic zone) directly derives from the innovative approach they proposed at that time for studying partial epilepsies (the anatomo-electro-clinical correlations), and from the new method they then elaborated for validating it (the SEEG).

A new philosophy: the anatomo-electro-clinical correlations

The basic principle of Bancaud and Talairach’s approach to epilepsy surgery was to study the seizures themselves, through what they named the «anatomo-electro-clinical correlations». They regarded the chronological occurrence of ictal clinical signs as crucial, reflecting the spatio-temporal organization of the epileptic discharge within the brain. Their clinical analysis of ictal events, beyond a simple description, thus consisted, on one hand, of interpreting the symptoms according to documented cortical topology, and on the other hand, of analyzing them chronologically so as to imagine a logical spatial evolution of the intracerebral discharge. Such an approach depended on the current knowledge that they had of the anatomo-functional systems that underlay the clinical features of partial seizures, knowledge submitted to a systematic re-evaluation based on SEEG findings, thus leading to refinements in clinical seizure analysis. They proposed some elementary principles that were essential for a correct interpretation of the anatomo-electro-clinical correlations for temporal lobe seizures (Bancaud and Talairach, 1991):

1) classifying the ictal clinical symptoms with respect to the total duration of the epileptic discharge;
2) comparing each seizure with those that have similar clinical accompaniments (with digestive symptoms, with somato-motor signs...);
3) comparing each seizure with those that selectively involved different systems (vegetative system, emotional system, perceptual system...);
4) comparing ictal clinical signs related to the same – and then to a different - origin of the epileptic discharge;
5) correlating the occurrence of each sign (either at the same time, or at different times during seizure evolution) with the involvement of one preferential system or structure;
6) comparing the clinical pattern of seizures of temporal lobe origin, with those originating in juxta-temporal regions;
7) comparing the clinical symptomatology of seizures, the electrical pattern of which are different.

Today, evidence has accumulated on the diagnostic value of seizure symptoms, and many studies have been – and continue to be – conducted in this way. Most tend to attribute a lateralising or localization significance to isolated signs, as well as to clusters or evolution of a few signs (Rosenow and Lüders 2001). This kind of clinical analysis, although helpful, remains very different from the working method that Talairach and Bancaud emphasized since, for them, ictal clinical symptomatology must be viewed as a whole (this led to the notion of seizure pattern). In particular, it was clear for them that seizure symptoms (and more particularly the «signal-symptom»), when taken individually, could lead to erroneous interpretations (Bancaud et al. 1965, p.4).

The emergence of an identical clinical sign may result indeed, from the ictal disorganization of cortex regions which, even if different, may have common sub-cortical projections. For instance, an ascending epigastric sensation, «typically» of (mesio-)temporal lobe origin (Henkel et al. 2002), may also be a manifestation of an ictal involvement of the insular cortex (lsnard et al. 2004), or of the mesial prefrontal cortex (Munari et al. 1996), or indeed, be the first manifestation of a discharge circum-
A new method: stereo-electroencephalography

Understanding the temporal dynamics of ictal symptoms with respect to brain anatomy implied that «ictal electroencephalographic changes must be evaluated at the very point where they occur (anatomo-electrical relationships), and that their initial or secondary reverberations on the clinical picture (electro-clinical relationships) must be evaluated as the discharge spread» (Talairach and Bancaud, 1973). Bancaud and Talairach therefore conceived a new method, the SEEG, aimed at the simultaneous investigation, in all planes of the intracranial space, of those structures, whose anatomical site and functional role implicate them as possible “generators” of the ictal clinical picture. Such an approach was rendered technically feasible due to the advent of atlases that provided the spatial coordinates of most telencephalic structures, as well as to the development of neurosurgical techniques that allowed such coordinates to be targeted and accessed (Talairach et al. 1958, Talairach et al. 1967). The selection of the structures to be explored was based on a very careful analysis of all the data – notably clinical – collected during the non-invasive, presurgical investigations in order to formulate one or more hypotheses concerning the site(s) of seizure onset, and the pathways of preferential ictal spread (Bancaud et al. 1965, Bancaud et al. 1973, Munari and Bancaud, 1987, Munari et al. 1986, Talairach and Bancaud, 1973, Talairach et al. 1974). Electrodes were then placed according to the prior hypotheses, in a way that enabled interpolation of intracerebral EEG activity within the interelectrode space. In this way, Bancaud and Talairach could study precisely the order in which symptoms accumulated as the epileptic discharge propagated into the different cortical structures and, in turn, confirm or not, their initial hypotheses (figure 1). The SEEG method has evolved with time: «acute» recordings have become «chronic» (for Bancaud and Talairach, this was a major advance for technical reasons, for the patient’s comfort, and for the reliability of the results), electrodes have been reduced in size, electro-clinical correlations have been improved thanks to the advent of audio-video-EEG monitoring system, and intracerebral targets are now assessed using MRI. Conceptually, «the song remains the same», as a SEEG study still cannot be performed without having previously hypothesized what the preferential origin and spread of the seizures could be (Chauvel et al. 1996, Cossu et al. 2005, Isnard, 2004, Kahane et al. 2004). As a rule, the position and number of intracerebral electrodes must then be designed to address the following issues:
• demonstrating that brain regions suspected of being involved in seizure-onset and early propagation (the «epileptogenic zone») show the expected ictal pattern. This requires the suspected brain regions to be implanted;
• considering the possibility that this pattern might in fact reflect the propagation of an ictal discharge generated elsewhere. This requires a comprehensive review of such alternative hypotheses, and the intracerebral evaluation of part or all of the corresponding brain structures (depending on the number and the likelihood of these hypotheses);
• delineating the border of the «epileptogenic zone» as precisely as possible, in order to perform the minimum cortical resection. This requires the placement of intracerebral electrodes in brain structures also located outside the borders of the suspected «epileptogenic zone»;
• assessing whether the removal of the cortical areas involved in seizure generation will be possible or not. This requires the investigation of the eloquent areas that are of interest, relatively to the hypothetical «epileptogenic zone», and with respect to the possible boundaries of the planned resection;
• evaluating the precise relationship between an anatomical lesion (when present) and the «epileptogenic zone». This requires investigation of, whenever possible, the epileptogenicity of the lesion itself and the surrounding cortex, the number of lesional’ electrodes that are needed depending on the morphology, extent and anatomical location of the lesion.

It is clear, when looking at this method, that if the pre-SEEG hypotheses are wrong, the placement of intracerebral electrodes will be inadequate, the interpretation of SEEG findings is likely to be erroneous, and surgical results will probably be poor (Bancaud, 1980). Conversely, if the pre-SEEG hypotheses are correct, the resulting implantation
strategy will facilitate the identification of the amount of brain tissue that must be resected, and the precise anticipation of the patient’s post-operative outcome according to the surgical possibilities and limits. Obviously, one problem linked to using intracerebral EEG recordings is that most of the brain volume remains unexplored (Halgren et al. 1998). This is likely to be true for what we could call “fishing expeditions”, i.e. implantation of electrodes conducted without any prior working hypothesis. Fortunately for the patients, the SEEG methodology allows this sampling necessity to be reduced, since electrodes are positioned to target specific functional systems, so that the spatial sampling accuracy is much higher within such systems. Additionally, utilisation of multi-lead electrodes provides an accurate coverage of all the structures that each electrode crosses along its trajectory, from its site of penetration to its final impact point. This allows simultaneous investigation of not only the mesial and lateral aspects of the different lobes, but also fissural and deep-seated cortices (figure 2). Also, judicious placement of a single electrode may give valuable information on anatomical structures pertaining to different subsystems. Therefore, by using a relatively limited number of electrodes (about 10 on average, resulting in 100 to 150
recording sites), insufficient spatial sampling appears rare, as has been indirectly suggested by an ictal PET study with simultaneous SEEG co-registration: of a total number of 120 regions studied by $\text{H}_2\text{O}^{15}\text{PET}$ in ten patients during electrically-induced seizures, 59 regions were not explored by intracerebral electrodes, and only 19 (24%) of these demonstrated ictal cerebral blood flow changes (Kahane et al. 1999).

A new concept: the epileptogenic zone

The SEEG definition of the epileptogenic zone is classically viewed as an ictal electrophysiological definition (figure 3). From the beginning however, Talairach and Bancaud emphasized that the topographic determination of the epileptogenic zone depended, above all, on the study of anatomo-electro-clinical correlations, the establishment of which necessitated «the simultaneous recording from a large number of structures, and the concomitant evaluation of the clinical symptoms» (Talairach and Bancaud, 1973). In other words, as far as they were concerned the epileptogenic zone was an **electro-clinical definition**: emphasis was put, not only on the precise anatomical location of the site of origin and early spread of the ictal discharges, but also on the importance of a careful analysis of their clinical correlates. This French approach to the epileptogenic zone, as we will see, agrees somewhat with some of the concepts further developed by Hans Lüders and collaborators (Lüders et al. 2006). It remains different however, from the North American view of the epileptogenic zone since, as already mentioned, it is not synonymous with what could be called the «what-to-remove area».

In SEEG terminology, the site of seizure-origin can be defined as the cortical area(s) from where the first, clear, ictal electrical change is recorded. It could then correspond to the North American «seizure-onset zone», which is defined as the «area of cortex that initiates clinical seizures» (this depends, obviously, on what «initiate» means). The SEEG assessment of this ictal onset zone however, depends on the spatial sampling of the SEEG investigation, so that caution is required to ascertain that the site of seizure origin has been unequivocally identified. Nevertheless, it is reasonable to attribute a reliable localizing significance to the first clear ictal electrical change, providing: (i) that this change occurs prior to the clinical onset of the seizure, and (ii) that it manifests by a fast synchronizing discharge (low-voltage fast activity or recruiting fast discharge of spikes), the pattern and frequency of which may differ from one region to another (Chabardès et al. 2005, Velasco et al. 2000, Wennberg et al. 2002). The lack of one of these two criteria means that the SEEG investigation hypothesis was wrong, so that the ictal onset zone, as well as the epileptogenic zone (which by definition should include the ictal onset zone), cannot be defined. In such conditions, success or failure of surgery, if eventually performed, will not provide any useful information. Conversely, the coincidence of clinical and relevant ictal electrical findings, and a fortiori the appearance of clinical onset after such ictal SEEG changes, both tend to indicate that the positioning of at least some electrodes was correct. It remains however, that depending on various factors, there may exist “a variability of the topographic origin of an epileptic discharge in the same patient” (Bancaud and Chauvel, 1986), thus justifi-
ing a relative large spatial sampling of the structures to explore, even in a single lobe.

The epileptogenic zone is the “site of the beginning of the epileptic seizures and of their primary organization”

The definition of the ictal onset zone, as assessed using SEEG, only helps in defining part of the epileptogenic zone, the main difficulty being then to evaluate “how much of the cortex contiguous to the site of origin is recruited into action to produce a clinical seizure” (Rasmussen, 1983). Bancaud and Talairach assumed that this issue could be answered, at least in part, by considering also the cortical areas participating in early seizure spread («the primary organization of the epileptic seizures»). This assumption derived from what they observed when they began to record seizures using intracerebral electrodes, i.e. that epileptic discharges that remained located within the structures where they had started was an uncommon finding, especially when the discharges were symptomatic. They noticed particularly, that discharges that remained confined to small territories were often subclinical, and that their identification did not preclude recording of the fully developed electro-clinical seizures, in which case the discharges recruited other cortical structures (Bancaud et al. 1975) (figure 4). Thus, one may assume that under the term “primary organization”, Talairach and Bancaud paid particular attention to the spatial extent of seizure discharges at the moment where the first clinical sign(s) occurred. In other words, this area could overlap, at least in part, the North American «symptomatogenic zone», which is defined as the «area of cortex which, when activated, produces the initial ictal symptoms or signs». Also, Talairach and Bancaud carefully considered and analysed the types of SEEG changes that occur during seizure evolution: once again, emphasis was put on cortex areas that were able to generate a fast synchronizing discharge, including not only those recruited successively from the ictal onset (figure 3), but also those exhibiting such a fast activity de novo during the course of the initial discharge (figure 5). What must be considered as an “early” or a “late” SEEG change therefore, cannot be assessed in terms of seconds, or tens of seconds, so the repertoire of ictal patterns are rich and the

Figure 3. The Bancaud and Talairach definition of the epileptogenic zone includes the ictal onset zone (Amygdala, NA) and the zone of early spread (hippocampus, Hc; temporal pole, TP; parahippocampal gyrus, HcG). The temporal neocortex (TNcx) is only secondarily involved.
propagation times variable. This probably explains why Talairach and Bancaud preferred to use the term “primary organization of the epileptic seizure” than the term “early seizure spread”. Besides, they assumed that the term “early” was rather vague since “it mixed the concept of seizure spread with the concept of extent of the primary focus” (Bancaud and Talairach, 1991).

The epileptogenic zone is not the «what-to-remove area»

The epileptogenic zone of Bancaud and Talairach is a concept and, as such, it may be smaller, the same as, or larger than the cortical areas that have to be resected to cure the patient. Obviously, the determination of the “what-to-remove area” depends, above all, on the study of the anatomo-electro-clinical correlations demonstrated during the seizures themselves, and therefore on the extent of the epileptogenic zone. Nonetheless, the construction of the preoperative composite “drawing” of the brain area to be removed must also take into account the effects of electrical stimulation, the features of the interictal and postictal abnormalities, as well as the nature and topography of any possible lesion.

- Intracerebral electrical stimulations

They are part of the SEEG study, not only for localizing eloquent cortical area that have to be spared during surgery, but also for eliciting seizures (Bernier et al. 1987, Chauvel et al. 1993, Kahane et al. 1993, Landré et al. 2004, Munari et al. 1993). This latter aspect may provide very useful information, particularly when spontaneous ictal discharges are widely extended from the onset of the seizure, when they apparently arise “independently” from different brain structures, or when regions that are initially silent at seizure-onset abruptly activate in the course of the ictal discharge and further develop an ictal sequence that is different from the primary seizure discharge (figure 5A). In these cases, observation of a complete and habitual seizure sequence after stimulation is the main goal, and elicitation of such a fit clearly raises the issue of including the stimulated structure in the surgical resection (figure 5B). Elicitation of auras may also be helpful by identifying relay and subrelay areas that are essential for building up ictal clinical signs, particularly when auras have disappeared during the course of the disease, or occur only occasionally but have not been documented spontaneously. According to Talairach and Bancaud however, the correct interpretation of elicited auras has to take into account the possibility of the activation of regions (cortical and subcortical) remote from the stimulation site, so that caution is required when establishing a causal relationship between a stimulated structure and the occurrence of a given symptom, particularly when a local ictal discharge has not been concomitantly elicited (Talairach et al. 1974, p. 15). The term elicited ictal discharge was used by Bancaud and Talairach to make a clear distinction between an elicited “post- or after-discharge”, the epileptologic significance of which was much more controversial (Bancaud and Chauvel, 1986).

- Lesional zone

In SEEG terminology, the lesional zone refers to the brain area which is revealed by an abnormal slow-wave activity or, in some cases, by a major alteration of background activity or by an ‘electrical silence’. All these electrical features presume macroscopic alteration of the neural tissue, so that this area coincides, in many instances, with the “epileptogenic lesion”, which is currently the most
often revealed on MRI. The topographic distribution of the slow-waves however, does not always match with a lesion as assessed on pathological specimens, the extent and amplitude of such abnormalities are far from being homogeneous, and the relationships between the altered area and the origin of seizures vary widely from one case to another (Bancaud, 1980, Bancaud et al. 1973, Munari et al. 1983, Munari et al. 1986). However, although the significance of such non-paroxysmal events remains unclear, it seems legitimate to consider carefully the areas which exhibit continuous delta wave activity before the final surgical decision, even in the absence of a corresponding anatomical lesion on MRI.

• Interictal spikes

The SEEG identification of the cortical areas involved in producing interictal spikes – the “irritative zone” – is often complicated, since one is frequently faced with abundant paroxysmal activities, the firing pattern and location of which fluctuate greatly. As far as Talairach and Bancaud were concerned, the irritative zone thus had variable relationships with the epileptogenic zone and, on many occasions, the two zones were not overlapping (Bancaud, 1980). From a surgical perspective however, it would probably be a mistake to completely ignore the extent of the interictal spikes, whether they are focal or not. They can provide additional confirmation of localization, and may even prove of greater localizing value than the recording of seizures: this seems to be true for example, in focal cortical dysplasia of Taylor type, where the interictal spikes can be a good marker of the extent of dysplastic cortex that needs to be removed to abolish the seizures (Chassoux et al. 2000, Tassi et al. 2002, Francione et al. 2003). Also, particular attention must be paid to those spikes that do not disappear at seizure onset, since this might indirectly suggest that they do not depend on a common pathophysiological process related to the area(s).
from where the seizures arise, and therefore that they might be part of what Lüders and colleagues named the potential seizure-onset zone (Lüders et al. 2006).

Early post-ictal findings

Although not clearly specified in the work of Talairach and Bancaud, early post-ictal findings were part of the analysis of the seizures recorded during an SEEG investigation. Attention was paid, more particularly, to those from cortex areas that exhibited, at seizure termination, major attenuation and/or suppression of their background activity. Following this experience, the pupils of Talairach and Bancaud at the Sainte Anne Hospital have recently reported that, indeed, post-ictal SEEG suppression accurately localized the seizure-onset zone in a majority of frontal lobe cases, while it appeared more widespread in temporal lobe patients, involving areas of ictal onset and seizure propagation (Toussaint et al. 2005). Post-ictal spikes were of relatively poor localizing significance, in accordance with other studies (Gotman and Marciani, 1985). Certainly, post-ictal patterns have been neglected in the literature and further work is needed to investigate how to incorporate them into the surgical decision.

Conclusion

The SEEG definition of the epileptogenic zone is, above all, a conceptual definition, which emphasizes the importance of studying the spatio-temporal dynamics of seizure discharges, and not just their starting point. It cannot be viewed, as such, as the ideal definition of the cortical areas that have to be removed to cure a patient. This concept however, has greatly helped our understanding of the ictal clinical symptomatology of partial epileptic seizures, and it remains a reliable way of assessing the origin and extent of an epileptic discharge within the cortex, even in the absence of any neuroimaging abnormalities. The electro-physiological criteria used intracranially for defining the most epileptogenic region are, however, not clearly determined. Neuronal mechanisms associated with the emergence of epileptic seizures indeed, are still largely unknown, although certain evidence has suggested that the transition from the interictal state to the ictal state is not sudden, but due to a progressive increase in neuronal synchrony. Recent studies conducted in epileptic patients by means of intracranial macroelectrodes, have shown that epileptic seizures can begin with low amplitude, fast activities in the gamma frequencies range (60-120 Hz) (Allen et al. 1992, Fisher et al. 1992, Wendling et al. 2003), and that in the period between seizures, there are brief bursts of high frequency oscillations (60-100 Hz), which seem to have the same spectral characteristics as the seizure-onset activities (Worrell et al. 2004). These interictal fast oscillations seem to be recorded only in the seizure-onset zone, supporting the idea that they are pathological oscillations. Whether they have any relationship with fast ripples (250-500 Hz) recorded in humans using microelectrodes (Bragin et al. 2002, Staba et al. 2002a, Staba et al. 2002b) is a very important issue, since the latter could be the signature of the cortical regions capable of generating spontaneous seizures. □

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