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A critical review of the different conceptual hypotheses framing human focal epilepsy

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ABSTRACT – In the attempt to understand the processes affecting human focal epilepsy, various models that have been proposed as a back drop to which current observations of the clinical manifestations and therapies in this disorder can be tested. There are three main models that are reviewed. The notion of epileptogenicity as described by Penfield and Jasper's epileptogenic zone model postulates that specific regions of cerebral cortex have varying degrees of importance in the generation of focal epilepsy. A variation of this hypothesis comprises the second model put forth by Talairach and Bancaud. In this view the notion of the epileptogenic zone is expanded to incorporate a larger regions of cerebral cortex involved in the seizure propagation. A third concept and more separate hypothesis suggests that all components of the neural network involved in focal epilepsy are equally importance in the initiation and maintenance of the seizure. The various concepts underlying these models are reviewed in this paper and data from clinical and neurophysiologic observations are discussed in the context of these models. We suggest in this paper that the data best supports the epileptogenic zone hypothesis put forth by Penfield and Jasper.

KEY WORDS: focal epilepsy, networks, epileptogenic zone, seizure, localization-related epilepsy, ictal-onset zone

Different concepts have been used to explain the generation and propagation of focal seizures. The notion posited by the regional conceptualization of epileptogencity is that there exits a theoretical "epileptogenic zone" which, if removed, would result in cessation of the seizure generation. Opinions differ as to the regions of importance that should be included in this "epileptogenic zone". To estimate the epileptogenic zone, Penfield and Jasper [1], hypothesized that only the initial ictal-onset zones, as defined by neurophysiology, is important. On the other hand, Tailarach and Bancaud [2], conceptualized a slightly more extended epileptogenic zone that included the initial ictal-zone and the regions of immediate seizure propagation. In contrast, the "large network" hypothesis, recently described by S. Spencer [3], holds that focal epilepsy is based on an organization of a neural network in which the epileptogencity is distributed throughout the entire network. This concept of a network is a significant departure from the regional concept. The "large network" model would suggests that the entire

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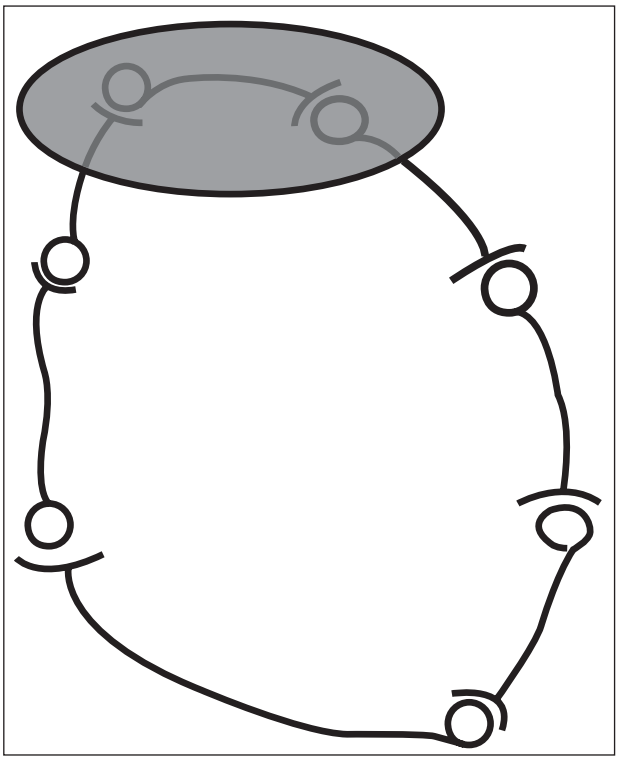

Figure 1. *Penfield/Jasper concept of epileptogenic zone*
Seizure-freedom is achieved by resection of the actual (and potential) seizure-onset zone. "Early" seizure spread zone is not part of the epileptogenic zone.

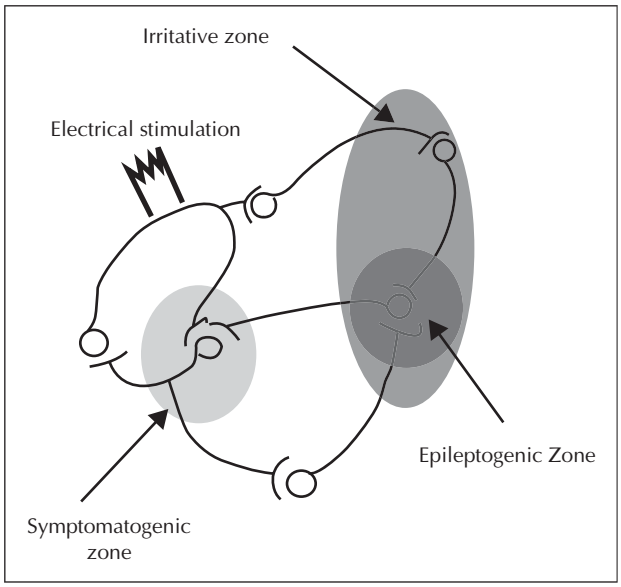

Figure 2. *Illustration of various regions in an epileptic network*
This figure illustrates the Penfield/Jasper "epileptogenic zone", the "symptomatogenic zone" and a "large neuronal network". In the Penfield/Jasper epileptogenic zone hypothesis, resection of the relatively small epileptogenic zone results in seizure-freedom. In the "Large Network" hypothesis, discharges in the neurons of the whole network can modulate the excitability of the epileptogenic zone, which can trigger a seizure or be used to suppress seizures by resection of any part of the network or electrical stimulation of the epileptic network.

system is equally important in not only initiating, but also propagating and maintaining the seizure.

It has always been appealing to look for a new and alternative conceptual framework for epilepsy, especially in light of the recent advances in molecular biology and genetics. Shifting from old to new paradigms has often led to a better scientific understanding of disease processes. However, for a new paradigm to be successful, it must not only explain all of the observations already understood within the old conceptual framework, but must also be useful to explain, and even to predict, new observations.

The more restricted Penfield and Jasper's view of the epileptogenic-zone postulates that a specific region of the cerebral cortex gives rise to seizures [1], and different [4] regions of the brain have different degrees of importance. The salient consequence of the Penfield/Jasper epileptogenic-zone concept is that seizure-freedom can be achieved by resection of the area of cortex generating the seizure, namely the actual (or potential) ictal-onset zones *(figure 1)*. It also follows that other regions involved in the early or late seizure-spread patterns are not a part of the Penfield/Jasper epileptogenic zone *(figure 2)*. An important therapeutic corollary of this concept therefore, is that surgical resection of brain regions outside the epileptogenic zone, (i.e. including those involved in early seizure propagation) will only modify the seizure spread (i.e. the seizure semiologic expression), but will not prevent the generation of seizures.

Another concept, an expansion of the idea of regional epileptogenicity put forth by Tailarach and Bancaud, incorporates not only the "epileptogenic zone" but also the areas of cortex involved in early seizure-spread. Their conclusion from this hypothesis is that to achieve seizure-freedom the surgical resection must be expanded to include those cortical areas responsible for "early" propagation of seizures [2] *(figure 3)*.

The large network hypothesis on the other hand suggests that all the parts of the neural network are equally important for the generation of seizures. It suggests that seizure-freedom can be achieved by the interruption of the network at any level *(figure 4)*. The concept of a neural network organization in epilepsy and the suggestion that epileptogenicity requires an intact network is not new [5], and has been described by other authors [2]. Although networks are clearly involved during seizure propagation, it does not necessarily follow that all parts of the network are equally important in the generation of seizures. The large network hypothesis makes no distinction between the importance of local and distant regions of a neural network for the generation of epileptic seizures.

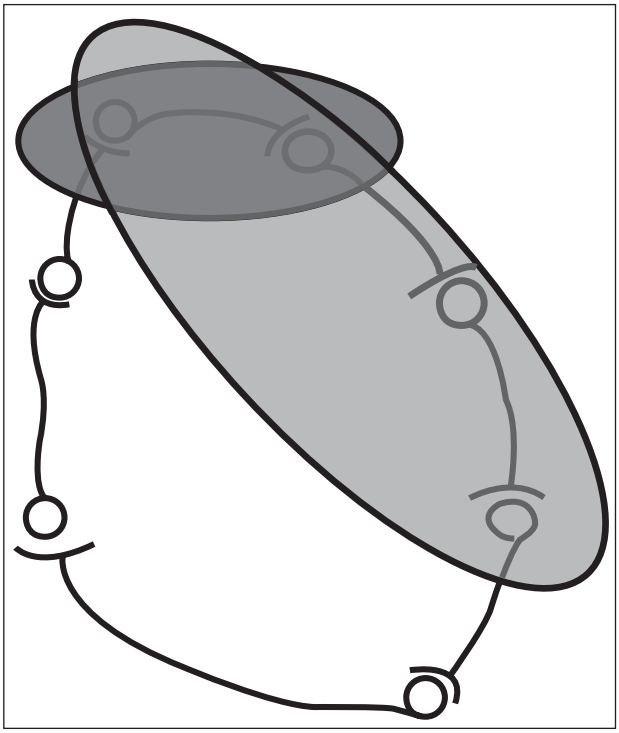

Figure 3. *Tailarch/Bancaud concept of epileptogenic zone*
This figure illustrates the seizure-onset zones (darkly shaded area) and the "early" seizure-spread zone (lightly shaded area). The Tailarch/Bancaud hypothesis suggests that seizure-freedom requires resection of the seizure-onset zone and "early" seizure-spread zone.

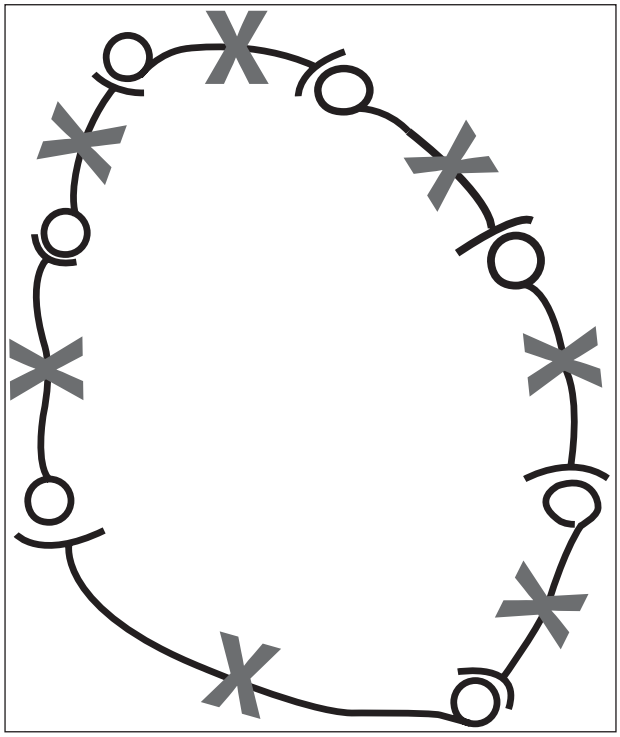

Figure 4. *Concept of Large Network Hypothesis*
All parts of the neuronal network are equally important for the generation of seizures. Seizure-freedom can be achieved by interruption of the network at any level (noted by "X").

The cornerstones of the large network hypothesis include the following: 1) seizures are a disease of large neural networks and not of discrete cortical regions; 2) interference with any part of the network will alter or stop seizure generation i.e. all regions of the network are potential sites of treatment; 3) seizures may propagate through the network or outside the network. While the Penfield/Jasper and Tailarch/Bancaud epileptogenic zone hypothesis certainly supports the third point, it does not support the first two *(figure 2)*.

Networks of neurons in the central nervous system have been conceptualized for the most part using various computational models, and there are analogies between the biological and biomathematical models of neural networks. While a branch of biomathematical techniques known formally as "Artificial Neural Networks" shares several, very simple properties with its namesake in clinical neuroscience, it is important not to let the semantic similarities prompt unwarranted conclusions. There do exist specialized mathematical network configurations optimized for efficient computer processing, but the majority of configurations employ quite different "connection weights" at each input and intermediate "neuron", thereby imparting very different significances to activities in various parts of the network [6]. In this sense, there is a clear differentiation between parts of a network in which particular components carry more importance in the operation of the network function than others. Similarly, the epileptogenic zone (as defined in the Penfield/Jasper and Tailarch/Bancaud model), which has a more crucial role in the generation of seizures, would carry higher "connection weights" than other parts of the network, such as the "irritative zone" or the "symptomatogenic zone". Although each of these zones is able to sustain epileptic activity, only the "epileptogenic zone" can initiate seizures.

An example of the workings of these zones is shown in *figure 5*. This is a case study of a patient with peri-rolandic epilepsy in whom the "symptomatogenic zone" included not only the post-rolandic primary sensory region of the hand (somatosensory aura), but also the ipsilateral supplementary motor area (asymmetric tonic seizures) as well. The patient had a somatosensory aura in the 2nd through 4th digits of the left hand followed, within seconds, by a asymmetric tonic seizure. Invasive recordings with subdural grids helped to identify a very small seizure onset zone in the primary sensory cortex, which was confirmed when the patient became seizure-free following resection of this small area of cortex. In this figure, we also make the

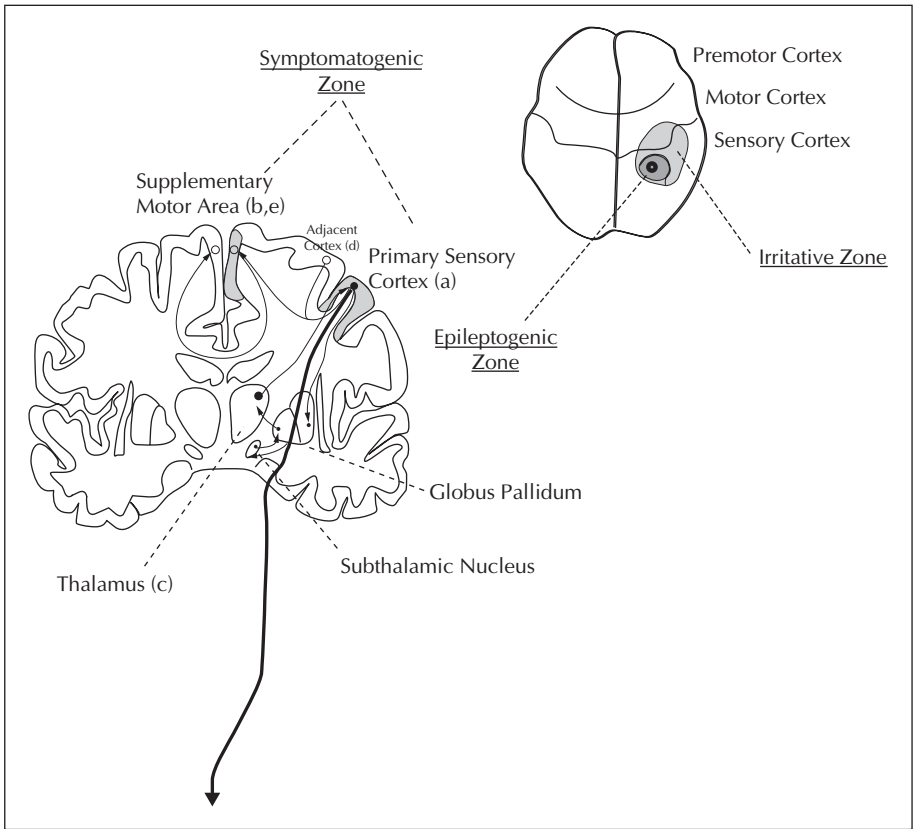

Figure 5. *A proposed network of perirolandic/supplementary motor area epilepsy*

distinction between the Penfield/Jasper epileptogenic zone, the Tailarch/Bancaud epileptogenic zone and the large network. All of the different parts of the network are important to produce the clinical symptomatology of the seizures, but the seizure-freedom after resection of the very limited Penfield/Jasper epileptogenic zone indicates that only that area of the cortex is essential for the generation of seizures.

This diagram shows the Penfield/Jasper epileptogenic zone, the symptomatogenic zone and "large networks" in a patient with epileptic seizures consisting of a somatosensory aura followed within seconds by a generalized asymmetric tonic seizure. The seizure onset zone was in the primary somatosensory area which represents the Penfield/Jasper epileptogenic zone. The Tailarch/Bancaud epileptogenic zone would also include the early spread of the seizure into the supplementary motor area. The limits of the large network hypothesis are more poorly defined but could include connections of the primary somatosensory area(a), supplementary motor area(b), thalamus(c), adjacent cortex(d), and even the contralateral cortex(e).

The first line of evidence in support of the large network hypothesis comes from intracranial recordings of stereotypical seizures [3]. It is argued that the electrographic variability of the seizures, recorded with intracranial electrodes in a patient with stereotypical clinical seizures, is due to a variation in the location of the seizure onset within a large network. We believe that the more likely explanation is that the "epileptogenic zone" consists of multiple, independent, small and potentially overlapping "seizure-onset zones" *(figure 6)*. Seizures, therefore, can start from any of the different small "seizure-onset zones", which may be closely connected. The propagation pathways may differ depending on which of the seizure onset zones start the seizure. Therefore, the notion that the pathways of seizure-spread vary, is highly consistent with the Penfield/Jasper epileptogenic zone hypothesis. It is important to remember here that even a large number of intracranial electrodes will usually cover only a fraction of the total surface area of cortex. If recording comes from only part of the ictal-onset zone, seizure propagation from different, but closely spaced epileptogenic zones, may have a variable electrographic appearance *(figure 6)*. The variable appearance or the implication of separate epileptogenic zones may be due to a) an absence of electrode coverage of the true epileptogenic zone, b) seizures generated from the depths of a sulcus, or c) other differences in the propagation patterns. In addition, electrical seizures can only avail themselves of a limited number of clinical manifestations since most parts of the cerebral cortex are

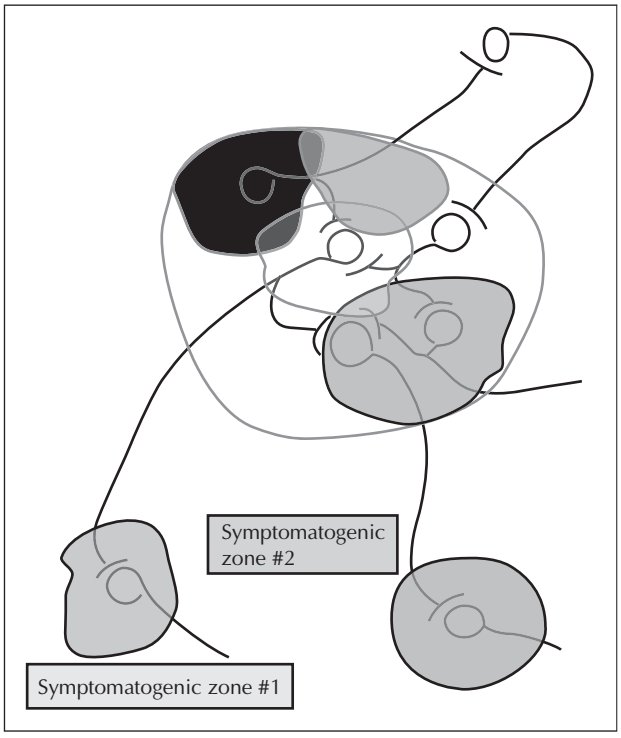

Figure 6. *The diagram illustrates four independent seizure-onset zones. Each of the zones can generate independent seizures. The Penfield/Jasper epileptogenic zone is the sum of the four small seizure-onset zones. The diagram also shows that seizures generated in different seizures-onset zones will propagate to different symptomtogenic zones and, therefore, will be associated with seizures of different symtomatology.*

"silent", i.e. cause no clinical changes as the electrical seizures propagate through them. Seizures arising from different, but closely situated epileptogenic zones, may extend to a common symptomatogenic zone, despite variability in the electrical spread of each seizure.

It is also argued that widespread interictal hypometabolism on FDG PET is evidence for the large network hypothesis of epilepsy at work [3]. However, this is contradicted by extensive evidence in the literature showing that resection of an epileptogenic zone much more restricted than the large region of PET hypometabolism, is frequently sufficient to eliminate seizures [7-9]. Moreover, after resection of a limited "epileptogenic zone", there is normalization of the more extensive PET hypometabolism area that had been observed before surgery [10], again validating [11-13] the "epileptogenic zone" concept that there are local regions of relatively greater importance in the neural network. Ictal PET scans can show a discrete focus of marked glucose hypermetabolism, as shown by the example in *figure 7*. This 30 year-old woman with temporal lobe seizures had undergone lateral temporal neocortical resection prior to presentation to our institution. The surgery had failed to alter her seizure frequency or semiology. The ictal FDG PET scan showed a discrete area of marked hypermetabolism in the remaining hippocampus. A second procedure removing only the relatively limited area of FDG PET hypermetabolism rendered the patient seizure-free. This suggests that there are important differences between local and distant areas of the network.

It is also unclear how the large network hypothesis in epilepsy would explain the results of lesionectomies that included only a limited resection of cerebral cortex and resulted in seizure-freedom [14-17]. Extensive experience with limited lesionectomies have established that the epileptogenic zone is frequently at or in the immediate environs of lesions recognizable on MRI. These observations also contradict the Tailarch/Bancaud hypothesis that "early" seizure spread pathways should be included in the surgical resection to obtain seizure-freedom. The case illustrated in *figure 5* illustrates a case in which an extremely limited resection rendered the patient seizure-free, even though EEG recordings showed that the seizure was spreading to the supplementary motor area immediately after seizure onset. Another example comes from experience with hypothalamic hamartomas where, if the resection includes only the recorded cortical ictal onsets zone, and the lesion is left behind, the seizure outcome is poor [18]. The large network hypothesis makes no clear distinction between local and distant regions of the network, suggesting that modification "in any part of the network will alter seizure expression or occurrence" [3]. It is true that both EEG seizures and seizure semiology can be altered by resection of areas outside of the epileptogenic zone, but this is simply a modification of seizure propagation and rarely achieves seizure-freedom [19, 20], therefore, in the example shown in *figure 5*, resection of the primary somatosensory cortex or of the somatosensory motor cortex should have been effective in modifying the seizures. It is universally recognized, for example, that patients with mesial temporal sclerosis who have lateral temporal neocortical or incomplete mesial temporal resections only, frequently continue to have seizures and often require further surgery. The variety of novel therapies that have been developed to affect outcome by interruption of the neural network, such as electrical stimulation (see *figure 1*), provide additional examples. To date, these modalities, including vagal nerve stimulation, have almost never achieved complete seizure-freedom [21]. In experiments with another therapeutic modality, animal research showed that the seizure termination effect of focal cooling of the cortex disappeared if the cortical area being cooled was moved just a few millimeters away from the epileptogenic zone [22]. In summary, treatment of seizures by an "interruption" of network pathways is frequently unsuccessful in controlling seizures, whereas lesionectomies have a 70-90 % chance of post-surgical seizure-freedom [23]. Indeed, even the removal of a tumor in cases showing a "mirror focus" of epileptic activity has resulted in good seizure outcomes [24].

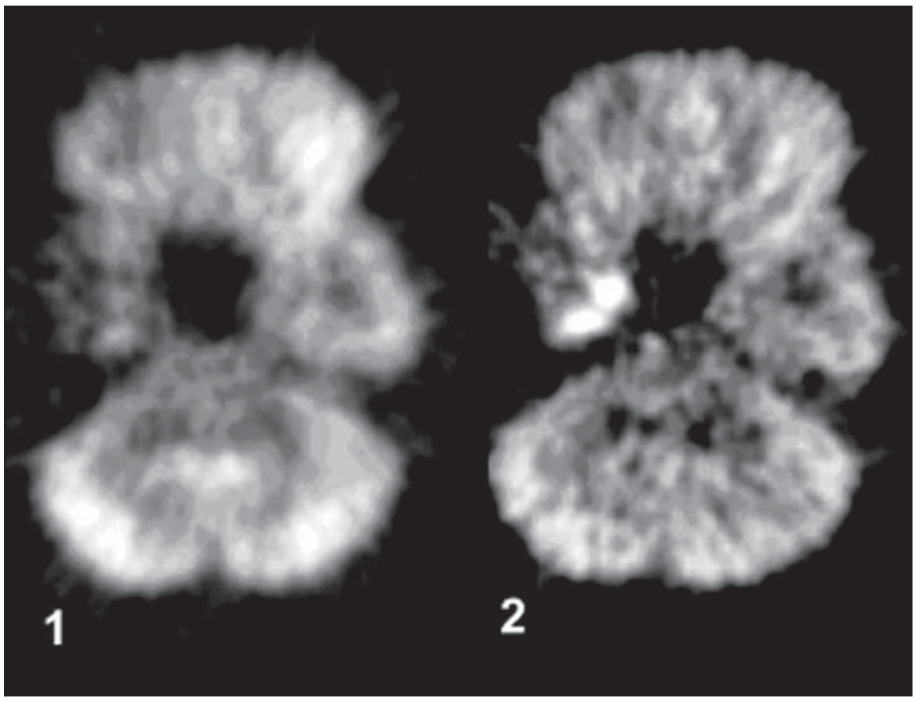

Figure 7. *Co-registered interictal (1) and ictal (2) FDG PET in a 30 year-old female with temporal lobe epilepsy who underwent right lateral temporal neocortical resection. There was no change in the frequency of her seizures or the seizure semiology. The ictal FDG PET shows a discrete focal area of markedly increased glucose metabolism in the hippocampus.*

In conclusion, there is no question of the importance of networks in epilepsy for determining patterns of seizure propagation, or that the alteration of these networks can modify seizures. However, we feel that the large network hypothesis offers little in exchange for the Penfield/Jasper epileptogenic zone hypothesis. There is no convincing neurophysiological evidence to suggest that all regions of a neural network have equal importance for the generation and maintenance of seizures. Nor is there any neurophysiological evidence to suggest that networks are required to sustain seizure activity via re-entrant or "circus movements" akin to cardiac neurophysiology. On the other hand, there is evidence that selective resection of the "initial" seizure-generating neurons is sufficient to produce seizure-freedom in patients with restricted epileptogenic zones. Even though detailed neurophysiological evaluations often reveal "early" seizure spread to widespread areas, there is no evidence that these "early" seizure spread regions (included in the Tailarch/Bancaud "epileptogenic zone") must be resected for successful epilepsy surgery.

Explorations based on the "epileptogenic zone" hypothesis continue to make significant contributions to development of new research insights and treatment paradigms. The Tailarch/Bancaud concept of an expanded "epileptogenic zone", and the "large network" hypothesis as it has been recently presented, do not stand as stable and consistent platforms for further investigations. □

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