History of the Network Approach in Epilepsy Surgery

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KEYWORDS

• Epileptogenic network • Temporal lobe • Frontal lobe • Stereoelectroencephalography • Electrophysiology

KEY POINTS

- Different brain networks are engaged in the primary organization and spread of seizures.
- Recent approaches to epilepsy surgery capitalize on network models of epileptic foci.
- Further development of the network approach in epilepsy surgery will improve patient selection, surgical approaches, and patient outcomes.

INTRODUCTION

Numerous clinical studies demonstrate the efficacy of epilepsy surgery over continued medical management for patients with drug-resistant epilepsy.[1–3] Localization of the brain region(s) responsible for generating seizures is crucial for resective epilepsy surgery.[4] For the purpose of this article, we refer to that area of brain that, when removed, results in seizure freedom as the epileptogenic zone (EZ). Complete seizure freedom is often the goal of resective epilepsy surgery, which necessitates sufficient ablation of the seizure-generating cortex (ie, the EZ) to stop seizures. Concurrently, resection or ablation of as little brain tissue as is necessary is also important to maximize cognitive outcome and long-term quality of life.[5]

Theoretic models accounting for epileptic foci have evolved considerably over the past century.[6] The earliest forms of surgery for patients with seizures probably occurred during the Mesolithic era.[6,7] Trepanation, considered to be one of the earliest forms of epilepsy surgery, dates back to prehistory, with the earliest skeletal evidence of its use estimated to be between 2200 and 1720 BC.[8] In the 1870s, neurosurgical pioneer Paul Broca believed that trepanation could be used to treat convulsions in infants, which provided a basis for some of the most basic forms of epilepsy surgery.[9] However, by the late nineteenth century, it was recognized that seizures were frequently associated with focal brain pathology even in adults, resection of which was often associated with seizure control.[10] By the 1950s, Penfield and Jasper[11] recognized that lesionectomy did not always result in seizure freedom and that the EZ could extend beyond that lesion involving irritated (eg, spiking) cortical tissue. This idea of the EZ extending beyond the lesion would prove important in current models of the EZ.

In parallel to the work in North America, French groups led by Bancaud and Talairach developed their own model of the EZ based on seizure semiology and stereoelectroencephalography (SEEG) exploration, in which they defined the EZ as the site of seizure onset and primary organization of the ictal discharge.[12–14] In the 1990s, Hans Lüders

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introduced a theoretic model of the EZ as "the area of cortex that is necessary and sufficient for generating seizures and whose removal (or disconnection) is sufficient for complete abolition of seizures." Although a theoretic definition, the model of Lüders incorporates multiple measurable "zones" that can be considered when estimating the EZ. More recently, efforts to define and characterize the EZ have focused on the network properties of the EZ.[6,15] Thus, recent models take into account abnormal connectivity of epileptic cortex as measured by intracranial recordings and noninvasive functional neuroimaging. These complementary techniques can assess the interactions between epileptic activity and physiologic networks, which aids in the localization of the primary drivers of the overall epileptic network.[16]

A deeper and more accurate understanding of the network properties of the EZ will have a fundamental influence on future epilepsy therapeutics. Indeed, machine-learning analyses of thalamocortical connectivity have already shown potential for identifying patients who will respond to neuromodulation by vagus nerve stimulation.[17] Improved ability to characterize the EZ based on its network properties may lead to the ability to perform more targeted (ie, smaller) resections or ablations and also inform more effective use of neuromodulation strategies. Thus, in this article, we provide an overview of current models of the EZ and efforts to characterize network phenotypes of focal epilepsy. Finally, we provide an overview of how these models influence approaches to epilepsy surgery, focusing on emerging and future applications.

NETWORK MODELS IN EPILEPSY

Here, we provide an overview of current network models of the EZ. Although a complete review of these models is not possible here, please see the references for more in-depth accounts.

1. Talairach and Bancaud, the concept of epileptogenic circuits: The EZ, as defined by Talairach and Bancaud in the mid-twentieth century, is an ictal electro-clinical region identified by stereotactic intracerebral electroencephalogram (SEEG) recordings.[14] This region is not only defined by the anatomic location of the primary EZ, but also the network of brain regions activated by the seizure and associated clinical symptoms (ie, the spatio-temporal dynamics of seizure discharges, not only their starting point). Thus, the Talairach and Bancaud definition of the EZ represents the zone responsible for seizure generation and is transposed on an anatomic base, with the seizure recording being a primordial effect based on the technical limitations of the time.[13]
2. Hans Lüders, the epileptogenic zone and the ictal organization: Advances in diagnostic methods and improvements in epilepsy surgery techniques have resulted in a more comprehensive model of the EZ. Hans Lüders and the Cleveland Clinic group developed a new concept regarding the EZ and its correlation with other brain areas using invasive electroencephalogram (EEG) recording. Lüders and colleagues expanded Bancaud and Talairach's conception of the EZ to consider a total of 6 different zones, as follows:
   a. The irritative zone: The brain area responsible for the generation of interictal epileptiform discharges without clinical symptoms. Generative symptoms require runs of epileptiform discharges strong enough to activate the symptomatogenic zone.
   b. The seizure onset zone (SOZ): Described as the area responsible for seizure initiation, the SOZ is coincident with the symptomatogenic zone when clinical symptoms arrive at ictal onset. This area is the most important zone related to epilepsy surgery planning.
   c. The symptomatogenic zone: The cortical area which, when activated by an epileptiform discharge, can produce ictal clinical symptoms. This area could be related to the primary EZ. In epilepsies with a primary EZ located in a nonsymptomatogenic zone, symptoms could appear later during discharge spread in the epileptogenic network.
   d. The epileptogenic lesion: These lesions are directly or indirectly responsible for generating seizures due to their intrinsic ability to create electrical discharges either independently, or due to environmental changes. The concept of epileptogenic lesions grows with the radiologic developments and advances in brain MRI studies.
   e. Functional deficit zone: Described as the cortex area with abnormal function during the interictal period, potentially resulting from a structural brain abnormality. A competing hypothesis suggests that it could be dysfunctionally mediated as a disactivated area as a result of the epileptic discharges. These nonpermanent zones may be assessed by neurologic examination and can improve after successful epilepsy surgery.
   f. EZ: The EZ is a region of cortex responsible for seizure generation. It may encompass different zones or be limited to one area in

highly focal seizures responsible for multiple actions as described previously. Delimitation of the EZ is the crux of epilepsy surgery planning, the complete resection of which is necessary for achieving seizure freedom.

3. Modern concepts and assessment of the epileptogenic network: Despite new therapeutic and diagnostic technologies related to epilepsy surgery, outcomes have not changed substantially over time. Recently, new methods have been developed in an effort to increase the rate of seizure freedom and decrease postsurgical deficits through an improved understanding of the EZ and epileptic epileptogenic networks. We briefly describe 2 such efforts here.

EPILEPTOGENICITY INDEX

Bartolomei and The French Group of Marseille[18,19] published a series of articles about the epileptogenic network and several tools to measure those pathologic circuits using SEEG recordings, and in the same year, described the concept of the epileptogenic index as a new procedure to study epileptogenic networks in temporal lobe epilepsies. The epileptogenic index is based in the spectral (appearance of high frequency oscillation replacing the background activity) and temporal (delayed appearance with respect to seizure onset) properties of intracerebral EEG signals recorded during presurgical evaluation. This method can be helpful in difficult cases, mainly in negative MRI cases or cases with fast discharge diffusion during classic intracerebral recording analysis.[20]

CORTICOCORTICAL EVOKED POTENTIALS

In 2004, Matsumoto and The Cleveland Epilepsy Group[21] published the first of a series of articles based on connectivity using corticocortical evoked potentials (CCEPs) during invasive epilepsy investigation. This technique uses direct cortical stimulation during recording from other putative regions of the epileptic network to assess the connectivity of regions in the epileptic network.[22] Measures of connectivity include both response latency and magnitude. Using CCEPs, it is possible to quantify the probabilistic strength of brain networks or connections and make inferences about connectivity within the epileptic network.[22]

EPILEPSY NETWORK PHENOTYPES

Current models of focal epilepsy recognize the EZ as a network rather than a solitary anatomic region. Here we provide several examples of focal epilepsy network phenotypes.

1. Temporal lobe epilepsy: The concept of a network involving the temporal lobe and surrounding regions is not new. However, the first article describing the concept of "temporal plus epilepsy" was published in 2015.[23] Using SEEG to explore temporal lobe epilepsies and related circuit areas, they defined temporal plus epilepsies (T + E) as an infrequent condition (only 27.5%) in patients with temporal lobe epilepsy. These epilepsies have an epileptogenic network that involves not only the temporal lobe and but also connected regions (ie, temporo-insular, temporo-orbito-frontal, occipital-temporal junction).[24] Importantly, T + E is a major determinant of treatment failure in temporal lobe epilepsy surgery, which illustrates the importance of recognizing T + E before surgical intervention.[24]
   a. Temporo-insular: The first anatomic description of the insular cortex, or Island of Reil, was made by Johann Christian Reil in 1809. It was described as an island of cortical tissue covered by the opercular cortex without clear function.[25] However, several years later, Penfield and Faulk[26] described their 1955 findings associated with intraoperative electrical stimulation of the insular cortex. They described vegetative functions, such as abdominal sensations and gastrointestinal movements.[26] Penfield followed the animal studies of Babkin between 1949 and 1951, when he defined these vegetative responses (eg, nausea, vomiting, hypersalivation) as a vagal "motor" center in the insular-orbital region responsible for feeding patterns, such as mastication, inhibition of respiration, salivation, swallowing, esophageal contraction, and inhibition of the pyloric antrum of the stomach.[27–29] In 1964, the Montreal Neurologic Institute team described differences in current practice between several epilepsy surgery centers for resection of insular cortex and application of intraoperative electrocorticography (ECoG) during temporal lobe epilepsy surgery.[30,31] They described similar rates of resection and ECoG usage between the groups of isolated temporal lobectomy (41.9%) and combined temporal and insular resection (39.5%), but the percentage of complications among insular resections was much higher (20.6%) compared with temporal lobectomy without insulectomy (2.8%).[32] In 2000, using the

concept of clinical ictal semiology associated with brain anatomic regions, Isnard and colleagues[33] related the role of the insular cortex in temporal lobe epilepsies using SEEG and direct electrical stimulation. They concluded that SEEG can distinguish between patients with pure temporal lobe epilepsy and those with temporo-insular epilepsy.

b. Temporal and orbitofrontal network: Epilepsies originating in the orbitofrontal cortex are rare, and there are few descriptions in the literature.[34] The orbitofrontal cortex has a complex cytoarchitectonic organization with more than 20 different network types, better based on the anatomy, cytoarchitecture, and network of that brain region.[35] There are inputs from gustatory, olfactory, visceral, somatosensory, auditory, and visual sensory areas with direct reciprocal connections with other limbic structures such as the amygdala, hippocampus, and cingulate cortex. In a review by Chibane and colleagues,[34] of 71 possible cases of orbitofrontal epilepsy, only 18.8% exhibited visceral auras, more reminiscent of temporal lobe seizures. Munari and colleagues[36] described a series of 8 patients with orbitofrontal epilepsy studied with SEEG and found a variety of symptoms attributed to anatomic spread patterns related to visceral symptoms, oral automatisms, and nonmotor phenomenon. Penfield and Jasper,[35,37] several years before, described the presence of interictal temporal discharges in frontal lobe epilepsies and focal ictal discharges in the temporal lobe. Some series of combined surgery for temporal plus orbitofrontal resection were described by a few groups in 1975 and 1995.[36,38]

c. Occipitotemporal circuit: Epilepsies with epileptogenic networks involving the temporal and occipital cortex have been described previously in the 1960s by the French as epilepsies with visual complex components.[39,40] Few descriptions were found before the 1980s and 1990s. In 1981, one of the first articles about occipitotemporal epilepsies described a single case of a young woman with clinical and electrographic seizures with occipital and temporal components explored by SEEG. They demonstrate, in that case, one circuit involving the occipital with fast diffusion to the temporal lobe and her treatment using a temporal lobectomy.[41] In 1993, Palmini and colleagues[42] demonstrated that this epilepsy group involved occipital or temporal origin with fast involvement of all circuits. The surgical decision was made in response to SEEG findings. The Cleveland Clinic published a few articles describing language involvement, such as alexia, classified as visual language disfunction related to the fusiform gyrus.[43] Maeda and Ogawa[44] described a case of dominant temporal lobe epilepsy as alexia with agraphia for Japanese ideograms with surface discharges beginning in the occipital region and with clear diffusion to the temporal region. In 2016, the French Group of Marseille described occipital and occipital plus epilepsy, demonstrating the most epileptogenic circuits related to the occipital lobe epilepsies as temporal (OT) and parietal (OP). The fusiform gyrus was considered the most pathologic region in both groups with surgery contraindicated in large circuits, mostly with eloquent cortical involvement.[45]

2. Occipital networks: The occipital lobe has intrinsic connection with several areas, such as temporal, parietal, and frontal lobes. Previously, we described the temporo-occipital network as part of temporal plus epilepsies; however, in this section we describe the occipito-parieto-frontal circuit.

   a. Occipito-parieto-frontal network: Cusmai and colleagues[46] described a series of infantile spams secondary to focal lesions. In some cases, spasms were associated with lesions in the Rolandic and temporo-occipital regions, demonstrating connections with frontal motor centers in this specific type of motor seizures. In 1996, Bullier and colleagues[47] described the network between the occipital cortex and frontal eye fields in this visual motor circuit of animal models. In the same year, Lekwuwa and Barnes[48] demonstrated the cerebral control of eye movement based on brain lesions and the occipito-parieto-frontal connection with the frontal eye field as the polymodal sensory association areas. Caminiti and colleagues[49] described the network involved in the occipto-parietal visual area coordination with hand motor areas in the frontal lobe for reaching mechanism. Ueno and colleagues[50] demonstrated the secondary synchronous occipito-frontopolar spikes in children with clear input from the posterior to anterior areas. However, there are limited data about epileptogenic networks in this specific brain circuit.[50]

3. Insula:
   a. Operculum and insular circuit: In 1991, Bancaud and colleagues[51] described the role of operculo-insular circuitry in functional organization in man. In 2003, Frot and Mauguiere[52] described 2 distinct areas, one in the posterior opercular and another in the posterior insular cortex activated by pain stimulation using somatosensitive evoked potentials recorded in intracranial electrodes. Bouthillier and colleagues[53] described "The New Electrode" for intracranial exploration as operculo-insular for perisylvian/insular refractory epilepsies as a mix between depth and grid electrodes for recording those 2 regions based on the intimate relation of both. Bou Assi and colleagues[54] described the connectivity analysis in operculo-insular epilepsies using intracranial EEG (iEEG) and the spectrum weighted adaptive directed transfer function (swADTF) due to the intimate relationship between both and the difficultly in identifying the precise primary EZ with classic methods. In 2019, Peyron and Fachon[55] described the operculo-insular cortex as potentially the main region responsible for the thermic and nociceptive centers based on functional images, SEEG recordings, and direct brain stimulation.
   b. Insula and supplementary motor area (SMA) network: Several articles have described a relationship between the SMA and the insular cortex, which can both be involved in bilateral motor seizures. In 1937, Penfield and Boldrey described the motor and sensory areas and by responses elicited by electrical stimulation, which was one of the original descriptions of the motor homonculus.[56] In insular cortex and electrical stimulation elicited autonomic responses (ie, digestion, respiration, pupillary response, urination, etc.), which were associated with insular cortex.[57] In 1967, Bancaud and Talairach[56,58] described the functional organization of the SMA during SEEG and, subsequently described the role of the SMA in startle epilepsies. In 2016, connections between frontal (ie, SMA) and insular regions were described using CCEPs.[59] These connections between the anterior insular cortex and the SMA play in important role in the pathophysiology of seizures from these regions.[60]
4. Cingulate gyrus network: The cingulate gyrus, or cingulate cortex, has been previously described as part of the limbic network (ie, temporal lobe, anterior insula, posterior orbitofrontal cortex, anterior perforate substance, and the anterior cingulate gyrus). Lennox and colleagues[61] described similar effects in respiratory and arterial functions during stimulation in the animal model. In 1973, Talairach and colleagues[59] described their results in direct electrical stimulation of depth electrodes placed in the anterior cingulate gyrus, which showed primitive actions, such as touching, stretch, press, scratching, or sucking. Their results described integrative motor behaviors associated with the anterior cingulate gyrus. In 2001, Kremer and colleagues[62] of Grenoble described anterior cingulate gyrus involvement in the programming of movements for grasping. This phenomenon was described first in animal studies with monkeys. In 2009, the French group from Marseille described the neuronal network of temporal lobe hyperkinetic seizures involving the temporal pole, amygdala, and orbitofrontal cortex of the cingulate gyrus using an epileptogenic index.[63] The Cleveland Clinic, in 2013, described cortical to cortical-evoked potentials in an attempt to map the limbic system, during which hippocampal stimulation elicited responses in the posterior cingulate gyrus demonstrating a strong connection between those structures. In 2014, The Cleveland Clinic published a new article exclusively dedicated to posterior cingulate epilepsies concluding that the network of the posterior cingulate gyrus can involve the parietal lobe, temporal lobe, mesial occipital lobe, and frontal areas with motor manifestations when seizures evolve in the frontal lobe or dialeptic/automotor seizures which travel to the temporo-parietal region.[64]

In summary, as a general principle, focal epilepsy does not exist as an isolated anatomic region, but rather a distributed network that must be considered as a whole when planning epilepsy surgery interventions. Invasive monitoring, and perhaps neuroimaging in the future, are necessary to characterize the network characteristics of these focal epilepsies. The influence of focal epilepsy networks on surgical outcome is clear for T + E epilepsies, which demonstrates that understanding the network involved in focal epilepsies is important for planning surgical interventions.

SUMMARY

Accurate models of the EZ are crucial for accurate predictions about how a surgical intervention will influence seizure outcome, cognitive outcome, and subsequent quality of life. By these criteria,

current models of the EZ are limited because it is still not possible to make perfect predictions about surgical outcomes. Advancing network models of the EZ will potentially overcome the limitations of traditional models of the EZ, such as the model proposed by Penfield and Jasper, to enable more effective resection and neuromodulation strategies.

With regard to resection, stratifying temporal lobe epilepsies by network phenotype (eg, the temporopolar subtype), might more accurately inform whether to perform a cortico-amygdalohippocampectomy or a selective mesial resection/selective mesial laser ablation.[65,66] Although work describing different phenotypes of temporal lobe epilepsy suggest that different subtypes are associated with distinct clinical outcomes, it is unknown if there is any benefit to selecting specific resection strategies depending on temporal lobe epilepsy phenotype.[66] This would be an important area to explore in future work. More recent neuromodulation strategies will also benefit from advancing network concepts of the EZ. For example, responsive neurostimulation (RNS) provides the opportunity to record from multiple brain regions while simultaneously delivering therapeutic stimulation.[67–69] Furthermore, understanding changes in epileptogenic brain networks may inform patient selection for vagus nerve stimulation and various other neuromodulation strategies.[17]

In conclusion, the network approach to understanding the EZ has crucial implications for planning and predicting the outcome of interventions in epilepsy surgery. Future work should advance current understanding of abnormal connectivity of the EZ, how the EZ functions as a network, and how these characteristics influence surgical outcomes. Also, research into emerging surgical techniques (eg, RNS or laser ablation) should capitalize on network models of the EZ to maximize patient outcomes while minimizing the deleterious cognitive effects of both epilepsy and epilepsy surgery.

DISCLOSURE

The authors have nothing to disclose.

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