Epileptogenic Network Formation

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KEYWORDS

• Epilepsy surgery • Epileptogenic network • Epileptogenesis • Propagation network

KEY POINTS

- Epilepsy surgery is based mainly on the recognition of the epileptogenic lesion and their removal, leading at best to a 70% to 80% postsurgical seizure freedom state.
- The epileptogenic network usually alters connectivity measures well beyond the lesion itself.
- Understanding of the main parameters that are altered by the epileptogenic process will lead to a better knowledge of surgical failures and comorbidities.
- New machine learning tools that integrate altered network parameters may better define postsurgical outcome.

INTRODUCTION

Nowadays, modern neuroscience indicates that complex cognition and goal-directed behaviors arise from the spatiotemporal integration of parallel and interconnected large-scale distributed neural networks forming the central nervous system.[1] Moreover, those networks are characterized by specific properties, including shortest path length, clustered connectivity, modular organization, and rich-club organization.[2] In pathologic conditions, such as epilepsy, several adaptive and maladaptive responses are undertaken. The extent and the degree of alterations depend on the specific type of brain insult and the related epoch of neurologic development during which the damage occurs.[3] In this perspective, there is growing agreement that epilepsy should be considered a network disease, resulting from altered interregional anatomo-functional relationships among brain areas.[4]

Concerning the pathophysiology of epilepsy, 2 main processes have been distinguished. The first mechanism, epileptogenesis, consists of the development, within a given brain region, of abnormal spontaneous electrical activity that underlies seizures.[5] Although the exact mechanism of epileptogenesis is not fully understood, it implies a first hit (eg, MTOR mutation in the case of focal cortical dysplasia [FCD] type II), which causes a structural lesion associated with specific electrical abnormalities, leading to clinically evident epilepsy.[6] The delay between lesion formation and epilepsy onset depends on the time of epileptogenic network formation. The second mechanism, ictogenesis, is characterized by the pathologic synchronization of functionally altered groups of neurons.[7]

The epileptogenic network includes both the concepts of epileptogenesis and ictogenesis and refers to anatomic distribution of involved brain region and temporal dynamic course of the seizure itself.[8] Two different networks are recognized: the epileptogenic zone network, where the ictal discharge start and organize, and the propagation zone network, characterized by a delayed electroencephalographic

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(EEG) discharge.[8] In epileptic patients, seizure persistence is associated with maladaptive responses that lead to a less integrated and more segregated organization of whole-brain networks in comparison with healthy subjects.[9]

Moreover, it has been demonstrated that network alterations may evolve with the epilepsy history,[10–12] can be associated with progressive structural alterations,[13] and also may be found in unaffected siblings, especially in cases of some specific etiologies.[14] Finally, several different epilepsies share common alterations in functional and structural connectivity.[12,15]

EPILEPTOGENIC NETWORK FORMATION

Studies of the anatomo-functional basis of epileptogenesis are advancing consistently, thanks to continuous technological development of several techniques, including diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), magnetoencephalography, and electrocorticography.[16] These methods are useful to identify the structural components of brain network and their functional properties, to characterize quantitative differences of neural synchronization at the level of both local circuits and the whole brain, and to highlight the pathologic modifications at the basis of epilepsy.[16–22] Evidence suggests that brain networks in epilepsy patients are characterized by an enhanced network segregation and reduced global anatomo-functional integration, in comparison with healthy controls.[23] Moreover, a progressively more regular network configuration has been demonstrated during the ictal phase, followed by gradual postictal decrease toward the baseline. In contrast, a recent meta-analysis showed that, during the interictal phase of focal epilepsies, whole-brain networks are characterized by a less integrated and more segregated organization.[9,16]

Different possible mechanisms participate in altering normal interneural synchronization that is the basis of epileptogenic network formation, and these modifications also can persist after epilepsy remission.[23]

In summary, the main parameters identified include

1. Alteration of cortical thickness[17,24–26]
2. Development of pathologic hubs[18,27–29]
3. Modification of hubs distribution[30]
4. White matter (WM) alterations[31–35]

Cortical Thickness

Several studies showed that axonally connected regions have trophic, developmental, and maturational concordances, underlying the so-called structural covariance network.[25] In children and adults with epilepsy, it has been demonstrated that interregional variations of cortical thickness are related to epilepsy severity, including seizure duration, lifetime number of focal to bilateral tonic-clonic seizures, age at onset, drug load, and cognitive performance.[25,36,37]

Moreover, alterations of cortical morphology have been demonstrated far from the seizure-onset zone, reflecting the existence of an interregional network formed by anatomically correlated territories.[26,30,38–40] For example, comparison between patients with sleep and awake seizures revealed larger volumes of insular, orbitofrontal, and superior temporal cortices; hippocampus; amygdala; and basal ganglia, in patients with seizures arising from sleep. These cortical and subcortical structural differences may alter the normal topological organization of brain networks at the root of epileptogenesis. Moreover, patients with sleep seizures show a more integrated network than patients with awake seizures. This might be attributed to the tendency of reorganizing the aberrant local circuit and compensating for the loss of topological flexibility.[24]

In subjects with childhood absence epilepsy, increased cortical thickness connectivity was found in frontotemporal regions in comparison with control subjects, in which the greatest connectivity was found in occipital regions. This abnormal cortical organization persisted after seizure resolution and may depend on genetically determined alterations occurring during the normal structural development of connectivity. Gray matter thinning, for instance, involves processes, such as synaptic pruning, use-dependent plasticity, apoptosis, and myelination.[36] Moreover, in another common childhood-onset epilepsy syndrome, benign epilepsy with centrotemporal spikes, voxel-based morphometry analysis revealed a bilateral regional increase of cortical thickness and gray matter volume, especially at the level of the superior frontal gyrus, the insula, and the right inferior frontal gyrus regions. The rate of these differences progressively normalized with age, in parallel with resolution of the clinical epilepsy syndrome.[41]

Finally, whole-brain morphometry also has been applied in cases with symptomatic epilepsy. For example, comparison between patients with FCD type I and FCD type II revealed specific multilobar patterns of cortical thinning and cortical folding. These data provide further evidence of different pathophysiologies in FCD subtypes and open the door for the development of pattern-learning techniques, useful for automated lesion detection,

preoperative classification, and postsurgical outcome prediction.[42]

Pathologic Hubs

The general anatomo-functional configuration of the human brain reflects a typical property of many natural systems, the so-called small-world topology. According to this framework, the central nervous system consists of a large number of neural circuits (hubs of the network) with a grade of interconnection that is inversely proportional to their distance and with a level of intrinsic order intermediate between fully regular and completely random.[43,44] This architecture has been shown correlated with a lower degree of total energy expenditure.

Network analysis in patients with partial temporal and extratemporal epilepsy has revealed the existence of abnormal organization, including local clusters of hypersynchronous neurons and noncontiguous regions distributed in multiple lobes.[27,29]

The hippocampus is a good example of a well-connected, small-world network. End-folium sclerosis is a disease characterized by alterations that occur in the dentate gyrus, including hilar cell loss and mossy fiber (granule cell axon) sprouting. It was observed that even the most severe forms of epilepsy depend on few newly formed or existing highly interconnected cells. These cells would play the role of aberrant hubs, modifying neural microcircuit topology, by increasing neural hyperexcitability.[45] Moreover, it has been hypothesized that these relatively small groups of cells act as microscopic epileptic foci, in controlling and coordinating microcircuits and recruiting larger macrocircuits, leading to generalized seizure activity. Also, in nonlesional epilepsy, interictal intracranial EEG analysis has shown that network disfunction not only derives from localized reorganization within the epileptogenic zone but also may extend beyond the source of epileptogenic activity.[27]

More recently, it has been shown that brain areas with high local synchronization have the smallest temporal variability. These areas, also called local stable synchronization areas, may be distributed either focal or widely, and consequently not correlated to classical seizure-onset zones. Resection of these stable areas was associated with a favorable surgery outcome.[28] Growing similar results suggest that the characterization of an individual's epilepsy syndrome based on the epileptogenic network allows for an innovative therapeutic approach based on either removing or disconnecting the crucial nodes of the network instead of only classical seizure-onset zone.[27,28]

Distribution of Hubs

Several studies have demonstrated the existence of highly interconnected hubs, which may play a role in the initiation and propagation of the ictal activity by the epileptogenic networks.[45–47] Comparison between patients with drug-resistant temporal lobe epilepsy (TLE) and healthy subjects, based on graph-theoretical analysis, revealed modifications of distribution of hub regions, associated with increased path length and clustering, with consequent higher network vulnerability.[30] Moreover, it has been shown that altered topography of hub regions intensifies over time, reduces efficiency of global information transfer[48] and signal propagation speed to other extratemporal neocortical networks,[49] contributes to the decline in various cognitive domains,[50] and is directly related to postsurgical outcome.[30] Analysis of preoperative and postsurgical network activity based on causal relationships (betweenness centrality) indicated that the spatial distribution of activated nodes highly depends on the frequency of the analyzed network, with gamma band networks playing a significant role in epileptogenesis and propagation of the ictal activity.[18]

White Matter Alterations

Evidence coming from DTI and histopathology studies indicated a reliable correlation between different forms of focal epilepsy and alteration of structural network. For example, modifications of WM structure have been identified in patient with TLE. In these cases, structural WM damage was demonstrated not only within the temporal region[51,52] but also distant from the epileptogenic zone with possible widespread bilateral involvement.[52,53] Decreased axonal density of the fimbria-fornix was observed in a postmortem study of TLE associated with HS, with evidence of involvement of the fornix, bilaterally[54] or unilaterally.[35]

Moreover, a recent analysis based on an advanced diffusion magnetic resonance imaging (MRI)-based image technique allowed quantification of cytoarchitectonic changes, such as subtle pathologic denervation, in specific limbic WM pathways. These abnormalities were found to correlate with different seizure burden and trends between subjects with well-controlled TLE and not well-controlled TLE.[33] Abnormal WM connectivity also was demonstrated to be related to cognitive comorbidity in patients with chronic epilepsy with a temporal[52,55,56] or frontotemporal focus.[32] Different histologic anomalies have been identified as potentially related to WM changes, including neuronal cell death, axonal

demyelination, formation of axonal spines, replacement of axons with glial cells and astrocyte proliferation, and increase in interstitial fluid volume due to blood-brain barrier damage.[54,57–63]

Although the exact pathophysiology for these modifications are yet unknown, at least 2 mechanisms have been hypothesized. The first mechanism consists of a direct effect of axonal damage and associated secondary wallerian degeneration, due to repetitive seizure spread and propagation of interictal spikes to distal parts of network through WM fibers.[31,62,64] The other mechanism depends on diffuse WM abnormalities associated with hypoxia and vasoconstriction, antiepileptic drug treatment, altered brain development, and plasticity-related reorganization of local and global WM networks, leading to systemic effects of seizures.[31,65,66] Detailed DTI analysis identified progressive WM degeneration of the fornix after TLE surgery.[35] In particular, on the basis of different patterns of diffusivity modification, associated with axon and myelin alterations, 3 phases of histopathologic modifications, including hyperacute, acute, and chronic, were identified (**Table 1**).

EPILEPTOGENIC NETWORK AND EPILEPSY SURGERY

In epilepsy surgery, the key point is to identify the area involved in the beginning and early organization of the discharge,[67] because to the area involved in the beginning and early organizaion of the discharge removal allows the stabilization of the network and reduces the probability of new seizures.[4] Understanding of the mutual relationship between the anatomic lesion and the epileptogenic network is of paramount importance for the delimitation of the epileptogenic zone (**Fig. 1**). The pathologic substrate of symptomatic epilepsy is quite heterogenous, ranging from acquired structural morphologic alteration, such as hippocampal sclerosis[68] or inflammation, as Rasmussen encephalitis,[69] to genetically induced cortical malformation.[70] An MRI-evident lesion does not always represent the unique criterium leading to surgical indication. Other genetical focal epilepsies, such as FCD associated with PCDH19-related epilepsies[71] or WM alterations in epilepsy with centrotemporal spike,[72] contraindicate surgical treatment.

On the other hand, FCDs and hippocampal sclerosis become surgical not only in cases of a positive MRI but also when their epileptogenic zone, namely the network involved in the production and early propagation of epileptic activities,[8] can be removed safely. In some specific etiologies, like FCD type II, the altered network seems to be correlated only to the MRI lesion[73] but even these patients could experience persistence of seizure after surgery,[74] suggesting a possible more complex epileptogenic zone organization (**Fig. 2**). For these reasons, an exhaustive characterization on abnormal neural network formation is as crucial as the study of genetic and morphologic alterations at the basis of epilepsy. In particular, studying the development of the epileptogenic network will enable better understanding of the relationship between a gene alteration or a cerebral malformation and its phenotype.

EPILEPTOGENIC NETWORK: FROM INTERICTAL TO ICTAL

Most studies reviewed up to now focused on recognizing the maladaptive responses that lead to epileptogenesis with poor correlation with surgical outcome. Neurophysiologic biomarkers on the other hand have the ability to investigate directly the altered network and evaluate the likelihood that a specific brain hub could cause of seizure generation.

Currently, the neurophysiologic investigations can be divided into 3 domains: (1) the study of the interictal periods aimed to find specific features linked to proepileptogenicity,[75] (2) the spectral EEG analysis of the transition from interictal to

Table 1
Stages of histopathologic modifications

Stage	Time	Modification	Diffusivity
Hyperacute	1–2 d	Axon swelling; increased axoplasmic viscosity; ischemia-induced cytotoxic edema and/or infiltration of inflammatory cells	Reduced perpendicular diffusivity
Acute	3–7 d	Pseudo-recovery	Reduced parallel diffusivity
Chronic	1–4 mo	Myelin degradation	Elevated perpendicular diffusivity

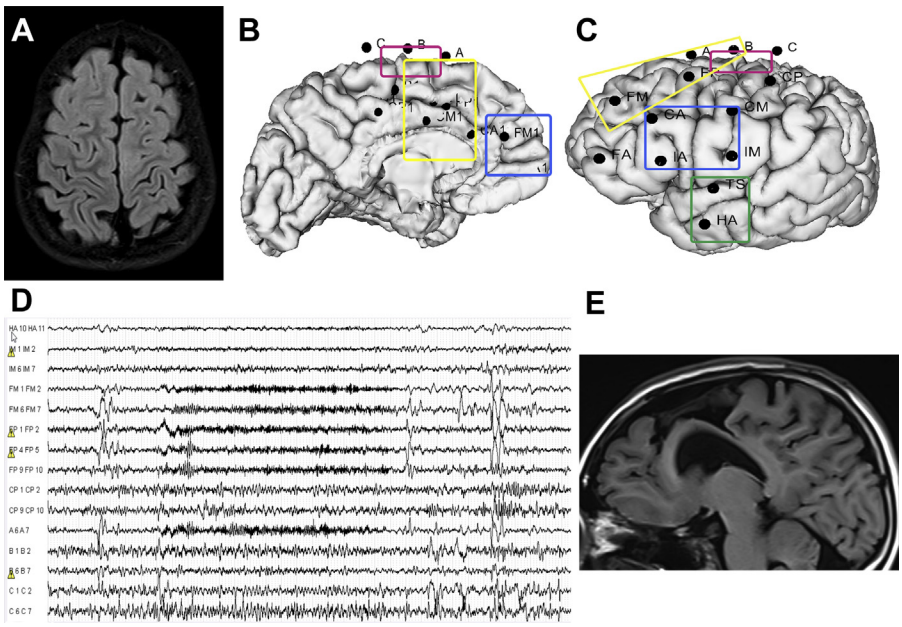

Fig. 1. Schematic representation of the complex interplay between different part of the epileptogenic network. A 10-year-old child with intellectual disability and autistic features; his epilepsy started at 18 months with focal stereotyped hyperkinetic and then tonic-asymmetric seizures. Pharmacoresistance rapidly developed. The scalp EEG showed an F3-C3-Fz discharge. (*A*) The MRI at age 6 years old showed evidence of a subcortical blurring at the level of the paracentral lobule associated with a more widespread volume reduction. (*B–D*) The SEEG evidenced a mesial discharge starting from A and B electrodes, going to FM1 (epileptogenic zone). IM showed a less tonic involvement (propagation zone). The temporal lobe was unaffected. (*E*) A resection sparing partially the most posterior border of the anatomic lesion (functional constraint) led the patient to a persistent seizure freedom state. The histology revealed an FCD type Ia also in the more anterior cortex.

ictal,[76] and (3) dynamic computational models that evaluate the possibility for a specific network to evolve from an interictal to ictal phase[4] (**Table 2**).

The interictal period is the most studied. Several innovative features have been identified, including results from high-frequency oscillation (HFO),[75] connectivity measures,[77] source analysis using neurophysiologic data,[78] and EEG-fMRI.[83] Despite this huge amount of data, the value of the interictal period is debated and there are several limitations; the most important ones are that spikes,[84] HFO,[85] and connectivity measures[3] are sometimes difficult to differentiate from physiologic measurements and have lesion-specific patterns. Moreover, the only prospective study currently available evidenced how the application of such a promising tool like HFO could fail in providing reliable information on a single-patient level.[75]

The introduction by Kahane and colleagues[67] of extraoperative long-term electrical registration through intracranial electrodes (stereo-EEG [SEEG]) enabled to evidence that the fast discharge is the main hallmark of the transition from interictal to ictal electrical activity. Recent data have extended the original concept and evidenced an increase of spiking activity[84] followed by slow component reduction[81] and a fast discharge in the gamma band.[76] It is probable that each single component of the ictal discharge presents several confounding factors.[86] The exact relationship between specific ictal activity and related etiologies, however, is still debated.[87]

In recent years, more powerful mathematical analysis allowed focusing attention on the study of network dynamics with the aim of predicting the likelihood of some specific nodes to fluctuate from an interictal state to an ictal one.[4,82] The main possible applications are related to the prediction of seizure recurrence[82] or epilepsy surgery outcome.[4] Both approaches reached levels of sensitivity and specificity of up to 85% to 100% and 75%, respectively[82] (see **Table 2**).

EPILEPTOGENIC NETWORK AND PROPAGATION NETWORK

The relationship between the so-called epileptogenic zone and the propagation zone is even more elusive. During the interictal period, brain connectivity seems reinforced within both

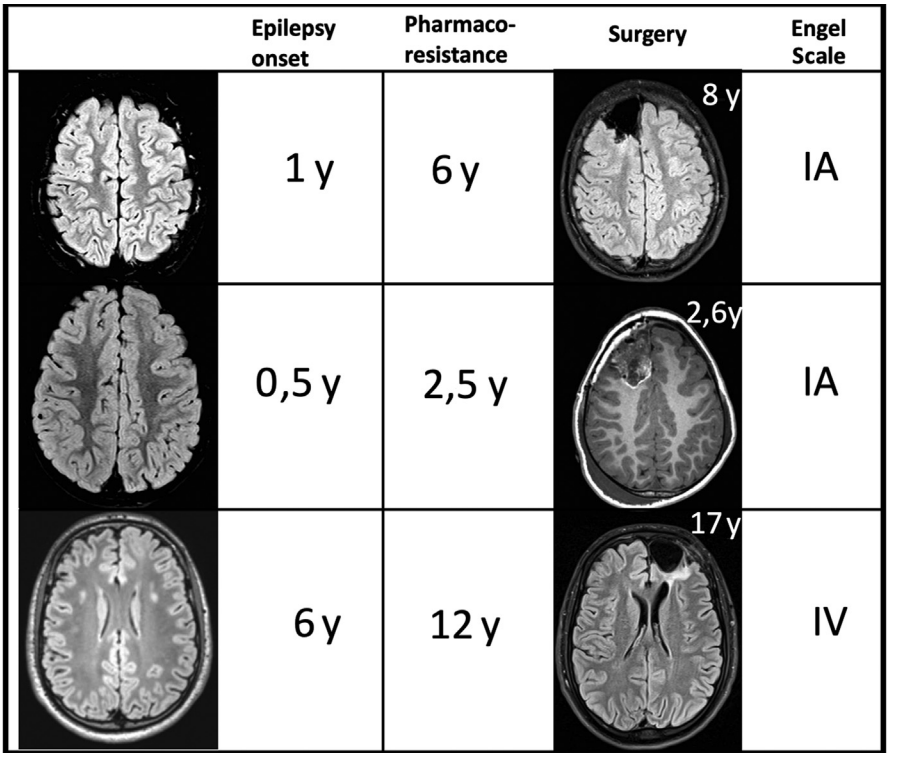

Fig. 2. Schematic representation of 3 patients, all with FCD type IIb on histopathology and similar localization and size of the malformed cortex. Despite these commonalities, they have different ages at onset (epileptogenesis), different times to pharmacoresistance, and different outcomes (engel scale) despite macroscopic complete resection.

Table 2
Summary of sensitivity and specificity of published data on neurophysiologic biomarker of the epileptogenic zone

	Interictal			
	High-frequency Oscillation [75]	Connectivity[77]	Dipole analysis[78]	Electroencephalographic Functional Magnetic Resonance Imaging[79]
Sensitivity	67%	NA	90% TLE; 57% ETLE	69%
Specificity	NA	NA	NA	NA

	Ictal			
	Gamma Index[76]	Quantified Stereoencephalography[80]	Epileptogenicity index[8]	Fingerprint[81]
Sensitivity	NA	81%	NA	90%
Specificity	NA	90% (default)	NA	71%

	Network Dynamic	
	Computational Model of Epileptogenicity[4]	Prediction Error Cconnectivity[82]
Sensitivity	85%	96%–100%
Specificity	75%	8 false warning for each seizure

Abbreviation: ETLE, Extra-TLE

networks, and the more widespread the alterations are associated with worst postsurgical outcome.[77] The ictal onset zone is characterized by a predisposition to fluctuate from an interictal state to the ictal one.[4] The discharge then is organized within existing neural pathways[88,89] and propagates through large-scale networks.[8] As a consequence, it is likely that, if modularity and topological centrality of the starting point change, different strength and direction of discharge diffusion should be expected.[2]

Nonetheless, the implications of these results in the study of seizure spreading patterns is not well understood. For example, in the orbitofrontal regions, seizures are characterized by absence of motor signs and the tendency to involve rostral prefrontal network with propagation to amygdala and anterior temporal regions whereas in the premotor region seizures display significant involvement of the motor and parietal cortex.[90] This means that a seizure coming from the orbitofrontal cortex has a preferential spread within the limbic system more than using other networks, whereas a seizure arising from the motor system would diffuse through the motor network.

This is not always as clear, however, as in the case of insular seizures. The posterior insula is known to be involved in the somatosensory system[91] whereas the more anterior part is in the limbic system.[92] Nevertheless, the spreading pattern of insular epilepsy is not always is toward the motor system or the limbic system[93] but occurs mainly toward the opercular region or the frontal lobe,[94] independently from the respective onset sites. These difficulties in correlating brain networks to common patterns of epilepsy spread enhance the necessity of a methodological improvement to better characterize and predict the relationships between a given region and the trend of epileptic discharge.

For this aim, at least 2 approaches may be mentioned. The first tool is a probabilistic atlas of human cortico-cortical connection.[95,96] According to this approach, the connection strength is derived from the analysis of evoked potentials acquired during cortical stimulation in both SEEG and subdural recordings. Some preliminary data showed that the insula shows the highest connection strength toward the superior temporal, inferior parietal, and frontal and cingulate cortices. Although these results are promising, many limitations of this method are still present, including the small spatial brain sampling compared with DTI maps, and less information than DTI on contralateral connections. The second approach consists of the creation of a virtual epileptic brain derived from diffusion MRI that simulates seizure propagation patterns at the individual level. In other words, the knowledge of the single-patient connectome allows prediction of how a seizure can spread.[97]

SUMMARY

The concept of epilepsy as a network disease is now established. Several studies have attempted a better understanding of the dysfunctional network; nevertheless, limitations in their clinical applicability still exist. Today, numerous clinical, radiological, and neurophysiologic biomarkers of the epileptogenic zone have been tested retrospectively on a group level. None of them demonstrates superiority to morphologic MRI or visual SEEG analysis. But now, new advanced computational analyses may be able to predict surgical outcomes by taking into account several feature, balancing their predictive value at the single patient level. New prospective studies with larger populations have the potential to define the clinical usefulness of these algorithms and to redefine standard clinical practice.

DISCLOSURE

The authors have nothing to disclose.

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