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Presurgical epileptogenic network analysis: A way to enhance epilepsy surgery outcome

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Abstract

Accurate localization of the "epileptogenic zone (EZ)" is an important issue in epilepsy surgery. The EZ is not discrete and focal; in fact, the epileptogenic networks can spread ictal activity to different regions of the brain. Changes in network characteristics and functional connectivity are shown to be associated with epilepsy. Seizures are thought to represent a hyper-synchronous state and presumable changes in synchronization between different brain regions underlie the mechanisms of seizure spread. Although presurgical evaluation of the epileptogenic network analysis can be carried out using existing investigative techniques like electroencephalogram (EEG), video-EEG, magnetic resonance imaging, single-photon emission computed tomography, and magnetoencephalography, advanced imaging techniques such as optical intrinsic spectroscopy, auto-fluorescence imaging, voltage sensitive dye imaging, and calcium imaging have the advantage of better spatiotemporal resolution over a large area of cortex. Understanding the wide-scale dynamic networks by analyzing the changes in the synchronization patterns using advanced imaging techniques will be instrumental in the presurgical analysis of the epileptogenic network and better localization of the EZs in the future.

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Full Text

Introduction

Epilepsy that cannot be controlled with pharmacological management is referred as pharmacoresistant epilepsy (PRE). Patients suffering from PRE are recommended for epilepsy surgery.[1] However, about one-third of these patients continue to have their seizures even after surgical therapy.[2] Therefore, it is necessary to understand the underlying mechanisms of PRE to develop better paradigms in order to improve the surgical outcome. The commonality between various forms of epilepsy is the occurrence of recurrent seizures caused by an abnormal electrical activity in the form of synchronized discharges from neurons in the brain. This abnormal electrical activity

can be recorded at the scalp and cortical surface, which initiates as ripples and beta frequency oscillations, continues with increased synchronization, and finally terminates as an abrupt cessation of activity.[3],[4] It is widely accepted that the epileptogenic zone (EZ) in human partial epilepsy consists of one or more discrete focal sources but various studies in recent years have suggested that the ictal activity is thought to arise from the activity of dynamic epileptogenic cortical networks.[5] It has been shown that in focal epilepsies, these events begin in a spatially localized EZ, which further recruits connected areas in a cascade of spreading activity from the central focus outward through both normal and abnormal brain tissues, to different parts of the brain.[6] The "epileptogenic network" is defined as the area involved in generation and spread of epileptic activity.[7] The fundamental manner in which epileptogenic network is different from a "focus" is that the former is dynamic, does not follow linear dynamics, may be multiple and may change its character over a period of time proportionate to the duration of epilepsy [Table 1]. The presence of epileptogenic network is supported by certain clinical and mathematical modeling studies which show that longer the duration of epilepsy, the more complex becomes the network, thus supporting the concept of changing networks over a period of time.[7],[8],[9] When focal epilepsy does not respond to seizure medications, the EZ may be identified and surgically removed. Defining and localizing the EZ in human epilepsy is a major issue and warrants a thorough investigation along with the development of newer techniques for locating the EZ. Understanding the propagation and maintenance of the functional connectivity and network configurations in complex brain regions in epilepsy may open avenues for novel surgical interventions as well as for the accurate localization of the epileptic focus, thus resulting in a better surgical outcome.{Table 1}

In this review, some of the basic questions about the epileptogenic networks are being answered., Some of these questions include: What are the underlying mechanisms of these dynamic epileptogenic networks? How can these networks be analyzed using various investigative techniques? How can this network analysis be helpful in localizing the EZ with better accuracy? What are the advanced imaging investigative techniques? How are they better than the existing ones?

What are the Underlying Mechanisms of these Dynamic Epileptogenic Networks?

Epilepsy is a complex neurological disorder and the underlying mechanisms of epileptogenesis are still not clearly understood. Although multiple mechanisms have been proposed, no common theme applies to them. The most accepted hypothesis is the imbalance between the excitatory and inhibitory neurotransmission. Dysregulation of the mechanisms that inhibit excitatory synaptic transmission or promote excitation can lead to epileptogenesis.[2] Even though this hypothesis explains how this imbalance can initiate epileptiform activity, the dynamics of the changes in the network are not well-understood. The other recent hypothesis is based on neural network plasticity and postulates that seizure-induced alterations of brain plasticity including axonal sprouting, synaptic reorganization, neurogenesis, and gliosis contribute to the formation of abnormal neural networks.[10]

Imbalance between Excitatory and Inhibitory Neurotransmission

Numerous studies support the idea that seizure initiation and propagation is caused by an imbalance between the activity of inhibitory and excitatory neurons. Modulation of glutamatergic and GABAergic synaptic transmission has been reported in the zone of surgical resection in patients with epilepsy.[11] There are multiple mechanisms that cause a disruption of the processes that usually create a balance between the glutamatergic and GABAergic transmission. This causes the neurons to discharge excessive action potentials in an uninhibited manner.

Altered glutamatergic transmission

Excitatory synaptic transmission mediated by glutamate, which is released from pyramidal neurons, leads to depolarization and excitation of target neurons through ionotropic receptors, namely, the N-methyl-D-aspartic-acid (NMDA) receptor, a-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptor, and kainic acid receptor.[12],[13],[14] NMDA receptors, which are tetramers composed of GluN1, GluN2A-GluN2D, and GluN3A-GluN3B, have been extensively studied for their role in epilepsy.[15] Glutamate neurons synapse onto either glutamate neurons or onto GABAergic neurons. Thus, glutamate-induced seizure generation could be attributed to either an excessive glutamate receptor activity or an increased GABA release through depolarization of the GABAergic neurons.

Altered GABAergic transmission

Dysfunction in GABAergic input that causes reduced inhibition of neurons may also contribute to epileptogenesis. Impaired inhibitory synaptic transmission causes neuronal hyperexcitability. GABAergic inhibition, under normal circumstances, regulates the spread of epileptic discharges[16],[17] and the intrinsic burst firing properties of neurons. In tissues resected in patients with temporal lobe epilepsy (TLE), the loss of interneuron density has been shown to cause reduced GABAergic synaptic transmission.[18]

Other neurotransmission modulators

There is evidence to suggest the role of α7 and α4 β2nAChRs (acetylcholine receptors) in nicotine-induced seizures.[19] Reduction in the nAChR function in the interneurons that synapse onto pyramidal neurons could contribute to the process of epileptogenesis.

Abnormal Neural Network Hypothesis

Epileptogenic neural network biology is well studied and understood in the case of mesial TLE (MTLE). Soltesz and Morgan have made a detailed computer model of the cellular structure of the dentate gyrus (DG), a brain structure involved in TLE. They incorporated the results of many published studies to examine the potential biological mechanisms which could allow for the formation of nonrandom circuitries that promote seizures.[20],[21] Pathological insults such as head trauma, ischemia, and repetitive seizures often lead to MTLE. This may be because the DG undergoes a dramatic structural rearrangement. These structural changes include loss of hilar interneurons and mossy cells, and the formation of recurrent collaterals between granule cells (GCs) via mossy-fiber (GC axon) sprouting.[21],[22] The recurrent excitatory GC network is a unique feature of the post-insult, epileptic DG. In the healthy DG, however, the GCs do not synapse with each other. It has been shown that the development of a few, but highly connected GC hubs is necessary for the (seizure-causing) network hyperexcitability found in epileptic brains. Even low levels of mossy fiber sprouting are sufficient to cause an increase in dentate excitability in response to lamellar perforant path activation. Furthermore, removal of mossy cells decreases GC excitability and impedes the propagation of network hyperexcitability, indicating that the surviving mossy cells amplify dentate excitability even without changes occurring in the intrinsic or synaptic properties of neurons.[23]

Excessive Neuronal Synchronization: "A Hallmark of Epilepsy"

Excessive neuronal synchronization could be associated with chemical and electrical synaptic, as well as ephaptic and nonspecific interactions between cells and within local networks at different time-scales. Most commonly, the generation of interictal epileptiform discharges in epilepsy is ascribed to the enhanced excitatory interactions within glutamatergic neuronal networks. During epileptogenesis, clusters of pathological neurons are interconnected leading to bursts of hyper-synchronous action potentials. Ligand-gated ion channels, electrical mechanisms, gap junctions, and ephaptic or field interactions contribute to a faster synchronization; whereas, G-protein coupled receptors, fluctuations in the extracellular concentration of ions (most notably K+), interactions between neurons and glia, and the dynamics of interaction between coupled hyper-excitable regions mediate slower synchronization.[24]

In summary, at a molecular level, the main factors modulating neuronal networks include the intrinsic properties of neuronal membrane, structural neural interconnectivity, and modulatory neurotransmitter systems. These factors can modulate the neuronal transmission as well as neural network connectivity leading to both the generation as well as the spread of excessive synchronization which forms the underlying mechanism of a seizure [Figure 1]. {Figure 1}

What are the Existing Investigative Techniques used for Localizing Epileptogenic Zone?

Many investigative techniques like electroencephalogram (EEG), video-EEG, magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT) are used in combination to obtain anatomical and functional information for the presurgical evaluation and localization of the EZ.

Techniques Based on Neurovascular and Neurometabolic Coupling

Traditional models of ictal propagation involve the concept of an initiation site and a progressive outward march of activation. The process of neurovascular coupling, whereby the brain supplies oxygenated blood to metabolically active neurons presumably results in a similar outward cascade of hyperemia.[25] Imaging techniques, like functional MRI (fMRI), SPECT, and near-infrared spectroscopy, can measure the thermodynamic changes on a wide variety of scales, from the movement of an individual blood cell or a single arteriole dilatation to the whole brain [Figure 2].[26]{Figure 2}

Techniques Based on Voltage Changes or Electric Currents

Methods are available to record voltage changes or electric currents on a wide variety of scales from single ion channel neuronal activity and intracellular recording to large-scale magnetoencephalography (MEG) and electrocorticography (ECoG). These tools have a limited capability to record from a large area of the cortex (several millimeters) with a high temporal (1 ms) and spatial (50 μ) resolution.[27] MEG has been particularly very promising in the localization of the EZ in concordance with other imaging techniques [Figure 2].

The invasive ECoG is the current gold standard for the localization of the cortical regions responsible for the initiation and propagation of the ictal activity.[28] There are limitations in the use of spike analysis through ECoG recordings. The interictal spikes of the irritative zone (IZ), a source of epileptogenic spikes, may or may not be containing the EZ. The analysis can be further confusing as some of the anesthetic agents such as halothane, nitrous oxide, and propofol can suppress the spikes, whereas other agents such as enflurane and etomidate can activate them. Such misleading recordings can be one of the factors responsible for the failure of guided surgery in patients where the suspected focus has been resected.[29] Thus, there is a need to develop new investigational techniques to understand the underlying mechanisms of synchronization and for characterizing the brain networks in the normal or in the epileptic brain to better characterize and localize the epileptic focus.

How are these Epileptogenic Networks Analyzed using Existing Investigative Techniques?

To understand the seizure spread and cortical dynamics, synchronization measures are applied to the voltage activity of the brain. A modular description of brain networks can be obtained from the brain activities recorded with various neuroimaging techniques. Several studies have analyzed the network connectivity in patients with epilepsy using functional data obtained from the ECoG,[7],[28] EEG,[30],[31] MEG[31],[32] and fMRI[33] measurements.

Tools used for Analyzing Network Connectivity

Multivariate autoregressive modeling

On the basis of the concept of Granger causality,[34] derived from the multichannel EEG signals, multivariate autoregressive (MVAR) directed connectivity measures have been developed which make it possible to evaluate the direction of the information flow between structures. This is also termed as effective connectivity.[35] These tools

have proven to be instrumental in studying the flow of seizure activity in patients with focal epilepsies.[36]

Partial directed coherence

Partial directed coherence (PDC), that has been used to evaluate connectivity patterns introduced by Baccalá and Sameshima,[37],[38] is based on the multi-variate autoregressive (MVAR) coefficients transformed into the frequency domain. PDC can distinguish direct and indirect causality flows in the estimated connectivity pattern. However, even when this approach is used, it is not possible to fully understand the complexity of brain as a network.

Graph theory

Graph theory[5] provides a powerful mathematical framework for characterizing the topological properties and in extracting quantitative indices. These frameworks are capable of capturing changes in the connectivity pattern and analyze the structure and evolution of complex networks in a quantitative manner.[37]

Computer modeling

Soltesz et al., have demonstrated a computer model of the DG to reconnect the aberrant and recurrent GC network in four biologically plausible ways to determine how nonrandom connectivity promotes hyperexcitability. They have used a published, large-scale model of the rat DG, complete with ~50,000 detailed single-cell models of various cell types, each constructed based on anatomical, cellular, and electrophysiological data derived from the literature.[39]

Major Findings of the Epileptogenic Network Analysis Studies

Using the computer model, Soltesz and Morgan have proposed the appearance of hub neurons in the DG, which effectively turns brain structure into a "small-world network." Stimulation of these hubs shows seizure-like activity but the randomly connected network without hubs does not. Thus, they suggested that the prevention of mossy cell death may not be the most promising strategy to prevent epileptogenesis. Instead, treatments intended to prevent epilepsy after brain trauma should focus on the prevention of mossy fiber sprouting and the development of hub neurons.[20]

Based on the EEG data analysis, Varotto et al., in 2012 have reported in Type II focal cortical dysplasia (FCD), a significantly different connectivity pattern develops that distinguishes the EZ from other cortical regions during the ictal as well as inter- and pre-ictal events.[36] They proposed that (1) the lesional nodes, as the hubs of the epileptic network originating and sustaining seizure, play a leading role in the generation and propagation of ictal EEG activity; (2) post cortical regions outside the region of dysplasia are involved in the ictal activity as "secondary" generators of synchronous activity and starts after the "hub" activation; and, (3) complete resection of the lesion (which is the primary hub) is essential for the successful surgical treatment of drug-resistant epilepsy in patients with type II FCD.

Using ECoG data and graph theory based analysis, van Dellen et al., reported that there is both a decrease in connectivity of functional networks in the temporal lobe as well as increased randomness of networks in patients with TLE who have a long history of epilepsy.[8] The functional neural networks of these patients with TLE also become more random under the influence of the ongoing seizures on the structure of the network irrespective of the presence of a structural lesion. This fact suggests that a surgical intervention might be more effective if performed earlier on in the course of TLE.

These networks, therefore, offer novel therapeutic targets. Disruption or inhibition of these hubs have the potential to either prevent or abolish seizure activity without the need for removal of the entire network. Disruptions of such networks have already been reported to exist in a range of neurologic disorders.[20]

What are the Advanced Imaging Techniques? How are they Better in Localizing Epileptogenic Zone/Networks than the Existing Techniques?

More intensive investigational tools are necessary to assess the plasticity of network characteristics. These include advanced signal processing techniques that are aimed at studying the cortical dynamics. They attempt to understand synchronization within the brain networks in order to improve the presurgical evaluation of patients with epilepsy. Various combinations of optical imaging technologies, with the ability to conduct a detailed neuronal circuit characterization, have emerged as powerful investigative tools [Figure 2].

Optical intrinsic spectroscopy and auto-fluorescence imaging

In optical intrinsic spectroscopy (OIS) and auto-fluorescence imaging (AFI), endogenous fluoro- and chromophores are imaged at the cortical surface before surgery. These techniques have the unique capacity to visualize the heterogeneous seizure focus with better spatiotemporal resolution.[26],[40],[41],[42] OIS relies on neurovascular coupling and AFI signals follow changes in metabolism caused by neuronal activity. Schwartz and their group, have shown that AFI could be used in mapping changes observed in mitochondrial metabolism during seizure discharges by measuring transformations in the redox state of mitochondrial flavoproteins.[42] Furthermore, few studies have shown that vascular measurements in OIS may reflect the activity of both inhibitory and excitatory neurons. This warrants further investigations in the use of OIS to study the interaction between inhibitory and excitatory neurons in seizure initiation and propagation.[43]

Intrinsic optical signal and voltage sensitive dye imaging

Using simultaneous intrinsic optical signal (IOS) and voltage sensitive dye (VSD) imaging of cerebral blood volume (CBV) and membrane potential changes, Schwartz and his group have demonstrated that seizures consist of multiple dynamic multidirectional waves of membrane potential change. They have a variable onset at different sites and propogate through a widespread network.[42] On a spatiotemporal scale, a pattern was observed: At seizure onset, the VSD waves extend beyond the IOS signal; during evolution of the seizure, the IOS signal only exists briefly at the site of the maximal spread of the VSD signal; and, at termination, the IOS signal extends spatially and temporally beyond the VSD waves. Hence, they concluded that vascular reactivity evolves in a separate but parallel fashion to membrane potential changes, resulting in a mechanism of neurovascular coupling and uncoupling, which is as dynamic as the seizure itself. The limitation of this method is that the illumination (600–650 nm) and the fluorescence wavelength (>665 nm) of VSD imaging is overlapped by the popular visible wavelength used in IOS that reflects blood oxygenation (610–700 nm), permitting only blood volume to be recorded concurrently with the VSD data. They suggested that near infrared spectroscopy using a longer wavelength can also record oximetry and blood volume changes. However, it is technically difficult for the near infrared spectroscopy data to be recorded concurrently with the VSD imaging. Likewise, VSD imaging primarily records subthreshold synaptic activity in the neuropil but carries little information on the glial activity or the suprathreshold action potentials in neurons. The latter two recordings could actually hold important information regarding the neurovascular coupling.

Intrinsic optical signal, voltage sensitive dye, and calcium imaging

Recently, this group has described a reliable method using a combination of calcium imaging with voltage-sensitive dye and intrinsic signal imaging that can simultaneously record neuronal, glial, and hemodynamic changes with the same spatiotemporal resolution over a large area of cortex. This combination is, therefore, very useful to study the spatial and temporal features of network neurovascular coupling with precision.[27] In vivo calcium imaging provides simultaneous information on the fast neuronal events (such as action potentials and subthreshold synaptic activity) as well as slower events that occur in the glia and the surrounding neuropil. It is now well known that changes in Ca2+ affect long-term physiological changes in neurons by activating numerous enzyme systems or by triggering specific signal transduction pathways.[44] Calcium imaging is emerging as a powerful tool in the imaging of cortical dynamics including that of neuronal input and output activity and of glial and metabolic signaling.[45],[46] Wide-field, single-photon calcium imaging has also been widely used to measure the neuronal activity.[46],[47] Calcium signals can be simultaneously recorded with intrinsic optical imaging allowing the measurement of cerebral blood volume changes.[48] Bulk-loading methods that involve multiple injections can be used for single-cell as well as wide-field imaging studies. However, multiple injections result in homogeneous loading and may also cause cortical injury. Schwartz and his group used convection-enhanced delivery to create smooth, continuous loading of a large area of the cortical surface through a solitary injection site. They demonstrated the efficacy of the technique using the confocal microscopic imaging of single cells and the physiological responses to single-trial events

of spontaneous activity, somatosensory-evoked potentials, and epileptic form events.

All these functional imaging techniques can be used to study the dynamic neural network changes that will not only help in the better localization of the EZ but will also advance our knowledge of the underlying mechanisms of epileptogenesis.

Conclusions

The EZ is not focal but is rather heterogeneous. The ictal activity could arise from the abnormal epileptogenic cortical networks. Imbalance between the excitatory and inhibitory synaptic transmission and the network reorganization can result in alterations in the synchronization, leading to both the generation as well as the spread of seizures between different regions of the brain [Figure 2]. Therefore, understanding the processes of synchronization in the neuronal networks may aid in defining the EZ and in developing diagnostic/prognostic biomarkers of epilepsy. Although network connectivity studies in epilepsy based on the ECoG, EEG, MEG, and fMRI measurements provide useful information for the identification of zones of ictal onset and improve our understanding of ictogenesis, they do not evaluate dynamic changes in connectivity patterns within the EZ and between the EZ and other cortical regions. Various combinations of the advanced imaging techniques such as OIS, AFI, VSD, and most importantly, calcium imaging with better spatiotemporal resolution over a large area of cortex, are better suited for understanding the wide-scale dynamic networks in epilepsy and will also be instrumental in localizing the EZs with better accuracy in the future [Figure 2]. We propose that the advanced imaging techniques have the potential to serve as an effective tool in the functional mapping of epileptogenic networks by identifying the synchronization patterns within the brain. A more comprehensive analysis of the dynamic states of neuronal networks based on a combination of basic neurophysiology based imaging, and computer and mathematical modeling will not only enhance our understanding of the complexity of epileptogenesis (as explained by "networks" in comparison to a "zone" concept [the latter being a more traditional concept]), but will also have a significant impact upon the medical treatment of the patients with PRE.

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Conflicts of interest

The authors have no conflicts of interest.

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