INTRODUCTION

The human brain is a network of around 86 billion interconnected neurons. Epilepsy results from the pathologic dysfunction of neurons that manifests in a seizure due to dynamic activation or inhibition of electrophysiological generators. Frontal lobe epilepsy (FLE) is the second most common focal epilepsy after temporal lobe epilepsy and accounts for 20% to 30% of all focal epilepsy. John Hughlings Jackson commented that the frontal lobe is the brain’s “most complex and least organized center” and, yet even after significant progress in neuroscience, frontal lobes are still considered as an “uncharted province of the brain.” Around 25% of patients with medically refractory epilepsy have FLE, who need surgical intervention for any meaningful decrease in seizure burden. However, only one-third of patients with FLE achieve seizure freedom after surgical resection in comparison with around two-thirds of patients reporting seizure freedom from temporal lobe epilepsy. The objective of this paper is to review FLE as a network disease in contrast to the traditional idea of focal lesional disease.

EPILEPSY NETWORK

Brain function reflects a complex system with networks of several interacting elements. A complex system is defined as an entity with several interacting components whose aggregate activity is nonlinear, hierarchical, and has some capacity of self-organization under adaptive pressures. The International League Against Epilepsy Workshop on Neurobiology of Epilepsy in 2017 proposed a model for understanding epilepsy as a network disease due to pathologies affecting a complex system due to pathologies affecting a complex system (Fig. 1). To understand epilepsy as a network disease, we need to understand how pathologies manifest not only at levels of clinical scale but how they start at the level of genes and signaling pathways. Gene expression is required for protein production, which is needed for cell signaling, which facilitates transmission across a synapse, formation of microcircuits, and so on up to the level of whole-brain affects that lead to the emergence of seizures as a symptom. It is conceptually vital to understand that, within this framework, no level is biologically more important than any other because, in a complex system, all levels interact with each other to generate endpoint outcomes.
Historically, medical science research in epilepsy has focused on studying these elements at their local scale. With this method, many important discoveries have been made with genes directly related to epilepsy, role of membrane excitability, and synaptic transmission with seizure spread.8–10 However, therapeutic translation of these discoveries has been overall stagnant from the perspective of prevalence of intractable seizures. Even after discovery of many antiepileptic medications with novel targets, one-third of patients with epilepsy remain medically refractory. Thus, a network approach has been proposed to understand pathophysiology of epilepsy. The cellular level activity affects local circuits at the level of neurons and synapses and may be measured indirectly as local neuronal potentials. The next level is brain activity at macrolevel resulting in seizure and measured with modalities, such as electroencephalography (EEG) and single photon emission computerized tomography (SPECT) scans. The clinical outcome of these multilayer network activity is the final layer of the phenotypical expression of epilepsy and associated comorbidities.

### FRONTAL LOBE EPILEPTIC NETWORKS: GENES AND SIGNALING PATHWAYS

The most well-known FLE due to a known genetic mutation is autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), which is characterized by clusters of brief motor seizures, which occur mostly during non-REM sleep.11 Typically, the mutation is either in the α-4 subunit (CHRNA4) or β-2 subunit (CHRNB2) of the gene of neuronal nicotinic acetylcholine receptor (nAChR).12,13 The study with reconstituted neuronal nicotinic Ach receptors in *Xenopus laevis* oocytes showed that the mutation (α4S248F) leads to increased acetylcholine sensitivity of nAChRs, indicating a gain of function.14 The thalamocortical loop plays a significant role during sleep, and both thalamus and cortex receive cholinergic afferents and therefore are susceptible to the end effect of above mutations resulting in predominantly nocturnal seizures. It is proposed that mutations alter the activity of thalamocortical connections and favor the development of abnormal oscillations.14 Carbamazepine has been reported to act as a noncompetitive inhibitor at the α4β2 subunits of nAChRs, and α4S248F mutants are blocked at therapeutic concentrations.15 Genetic mutations in ADNFLE demonstrate how changes at the gene level result in specific dysfunction at the cellular level and expression of a specific clinical phenotype. The same gene is also affected by different mutations, and carriers of α4776ins3 and α4Ser252Leu mutations in the nAChR gene show higher risk of psychiatric disorders and mental retardation, respectively, which again shows how different mutations at the same gene might change the brain network in a specific way and result in specific phenotypical expression.16,17 A recent study has shown that novel missense mutations in the sodium-gate potassium channel gene (KCNT1) result in a severe form of ADNFLE, indicating that similar phenotypes can also result from different genetic mutations.18 In summary, different epilepsy phenotypes can result from mild variations in mutations at same gene and conversely similar phenotypes can result from genetic mutations at different locations, which highlights the importance of information at the gene level in understanding epilepsy as complex network disorder.

Mutations in DEPDC5 have been known to cause autosomal dominant familial focal epilepsy with variable foci (FFEVF), now thought to be one of the common causes of familial focal epilepsy.19

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**Fig. 1.** Epilepsy network—hierarchical organization. EEG, electroencephalography; fMRI, functional magnetic resonance imaging; HFO, high-frequency oscillation. (From Scott RC, Menendez de la Prida L, Mahoney JM, et al. WONOEP APPRAISAL: The many facets of epilepsy networks. Epilepsia. 2018;59(8):1476; with permission.)
A significant proportion of these patients have FLE, which along with temporal lobe epilepsy accounts for over 70% of affected patients.\textsuperscript{19} DEPDC5 plays a role in controlling four full-length protein domains: “Disheveled, Egl-10, and Pleckstrin (DEP)” domain-containing protein,” which are involved in G protein signaling and membrane targeting.\textsuperscript{20} They mediate a broad range of cellular functions, notably including Wnt signaling, and affect neuronal circuit formation, neuronal polarity, axon guidance, and synaptic formation, and plasticity.\textsuperscript{21,22} Dysfunction of this pathway can produce epileptogenic networks at the neuronal circuit level, and, depending on lobar localization, results in unique phenotypical expression of focal epilepsy. DEPDC5 proteins also play an essential role in the mammalian target of rapamycin complex pathway along with other genes, including TSC, NPRL, all of which have been associated with specific lesions (tuberous sclerosis, cortical dysplasias) often found in patients with FLE.\textsuperscript{23–25}

FRONTAL LOBE EPILEPTIC NETWORKS: LOCAL CIRCUITS AND HIGH-FREQUENCY OSCILLATIONS

High-frequency oscillations (HFOs) are defined as spontaneous discharges in the frequency range between 80 and 500 Hz, consisting of at least 4 oscillations that clearly stand out from the background activity, and when measured intracranially they reflect the activity at the local neuronal circuit level.\textsuperscript{26} HFOs are subdivided into ripples ranging from 80 to 250 Hz and fast ripples greater than 250 Hz.\textsuperscript{27} The role of HFOs in epileptogenesis was first shown in rat models (intra-hippocampal kainic acid) with epilepsy. The microelectrode findings showed that the appearance of HFOs in the dentate gyrus ipsilateral to the injection was highly predictive of later development of spontaneous seizures in rat models and HFOs were absent in study animals that did not develop epilepsy.\textsuperscript{28} Interestingly, one of the first papers that described HFOs in 1992 was from a patient with known FLE.\textsuperscript{29} Since then, there have been no specific reports focusing on patients with FLE; however, a few studies have tried to investigate HFOs in different pathologies that may be applied to patients with FLE with those specific lesions. A study of 37 patients with diverse pathologies for focal epilepsy, showed that mesiotemporal lobe sclerosis, focal cortical dysplasia (FCD), and nodular heterotopia displayed higher HFO rates compared with polymicrogyria, tuberous sclerosis complex, or atrophy.\textsuperscript{30} Kerber and colleagues\textsuperscript{31} compared HFO rates in patients with FCD type I versus type II, and found that the rates of HFOs were significantly higher in patients with focal cortical dysplasia type II versus type I, correlating with their seizure burden. These studies show that how different pathologies affect local neuronal circuits and a distinct pattern identified by HFO analysis may provide us the data at a scale where noninvasive imaging may not identify lesions.

FRONTAL LOBE EPILEPTIC NETWORKS: WHOLE-BRAIN LEVEL

The clinical focus to define the epileptogenic zone during presurgical testing usually involves many modalities, such as MRI, fMRI (functional MRI), scalp EEG, intracranial EEGs, PET, MEG (magnetoencephalography), and SPECT. These modalities provide data regarding the probable epileptogenic zone at the lobar and whole-brain levels. In comparison with temporal lobe epilepsy, there is a paucity of studies focusing on investigating networks in FLE, likely due to significant causal heterogeneity. A few studies, however, have used fMRI, diffusion tensor imaging, intracranial EEG, and MEG data to identify frontal epilepsy networks.

A resting-state functional magnetic resonance imaging (rs-fMRI) study was done in FLE by Woodward and colleagues\textsuperscript{32} to evaluate motor network disruption. Thirteen FLE patients and 9 control subjects were included and functional connectivity was calculated between the sensorimotor cortex contralateral to the seizure focus and then compared with controls. Patients with FLE exhibit decreased connectivity within the motor network, in correlation with the number of lifetime seizures, thus demonstrating a potential relationship between seizure activity and changes in motor network organization. Another functional connectivity study of 23 patients with FLE compared scalp EEG and fMRI signals with 63 healthy control subjects.\textsuperscript{33} Compared with control subjects, patients with FLE showed significantly increased connections in the epileptogenic region (ER), but the connections between the ER and remote regions actually decreased. The abnormally high connectivity might reflect a predominant attribute of the epileptic network, which may facilitate propagation of epileptic activity among regions in the network.

A study by Englot and colleagues\textsuperscript{34} used MEG recording in focal epilepsy patients who underwent surgical resection and included a proportion of patients with FLE. Global functional connectivity maps and regional functional connectivity maps in the region of resection were created. Compared with healthy controls, epilepsy patients had...
decreased resting-state functional connectivity in widespread regions, including perisylvian, posterior temporoparietal, and orbitofrontal cortices. Mean global connectivity decreases were higher in patients with longer duration of epilepsy and higher frequency of consciousness-impairing seizures. Furthermore, patients with increased regional connectivity within the resection site were more likely to achieve postoperative seizure freedom than those with decreased regional connectivity.

Lagarde and colleagues\(^{35}\) investigated functional connectivity alterations measured with interictal spikes during intracranial EEG as a marker of cortical epileptic network organization in association with postsurgical outcomes. These investigators studied a large cohort of 59 patients with focal epilepsy and known malformation of cortical development explored by stereotactic EEG (SEEG), 20 of whom had apparent lesions in the frontal lobe. They defined 3 zones by SEEG ictal activity: the epileptogenic zone, the propagation zone, and the noninvolved zone. The findings showed higher within-zone functional connectivity for the epileptogenic zone and propagation zone, and lower for noninvolved zones. Comparison of these functional connectivity measures with postsurgical outcomes demonstrated that patients with higher functional connectivity of the noninvolved zone (within-noninvolved zone, between noninvolved zone, and propagation zone) had poorer outcomes, which the authors hypothesized was due to a more diffuse disease/epileptic network.

Corticocortical evoked potentials (CCEPs) have also been studied with intracranial EEG to define functional networks in epilepsy patients. The studies focusing on frontal lobe networks have shown dense connections within the frontal lobe, and to the temporal and parietal lobes. Garell and colleagues\(^{36}\) showed that a single bipolar electrical pulse to perisylvian temporal auditory cortex resulted in polyphasic evoked potentials clustered in ventrolateral prefrontal cortex, with the highest activation occurring in pars triangularis of the inferior frontal gyrus (IFG). Another study by Greenlee and colleagues\(^{37}\) showed dense cortico-cortical potentials spread within the IFG with independent stimulation of IFG subgyri, the pars orbitalis, pars triangularis, and pars opercularis. Similar studies with CCEP have shown activation of the frontal lobe with stimulation of parietal cortex and robust connectivity between the frontal lobe and an anterior insular network.\(^{38,39}\) CCEPs have been proposed as a measure of effective functional connectivity between brain regions that may help identify epileptogenic networks. A study by Hong and colleagues\(^{40}\) focused on whole-brain morphometry and compared MRI-based cortical thickness and folding complexity between 2 FLE cohorts with histologically verified FCD and healthy matched controls. Pattern learning algorithms showed that relative to controls, FCD type I displayed multilobar cortical thinning, which was significant in the ipsilateral frontal cortices, whereas patients with type II FCD showed thickening in temporal and postcentral cortices. Also, cortical folding with increased complexity was noted in prefrontal cortices in type I but was decreased in type II. These findings suggest widespread cortical involvement beyond the identifiable lesions on regular MRI. In summary, the above studies suggest that the network connectivity pattern may help to delineate the epileptogenic zone and also help to prognosticate the outcome of epilepsy surgeries.

**EPILEPSY NETWORK: PHENOTYPICAL EXPRESSION—SEIZURES SEMIOLOGY**

Neocortical epilepsy affecting the frontal lobe results in highly variable semiology due to dense and complex corticocortical and cortical-subcortical white matter connections that facilitate rapid propagation of seizure activity within and between cerebral hemispheres.\(^{41}\) At times, seizure onset may occur in noneloquent areas of the frontal lobe, which may remain clinically silent, and propagation of to a remote region may give rise to a seizure pattern implicating the brain region to which activity has propagated, leading to incorrect localization of seizure onset.\(^{41}\) Understanding semiology, however, serves an essential step in presurgical evaluation, as seizures with similar semiology involve neuronal activity in the same specific brain networks.\(^{42}\) Semiological involvement can give us highly reliable information regarding involvement of specific areas within the frontal lobe. Bonini and colleagues\(^{43}\) studied 54 patients with FLE who underwent SEEG recording during presurgical evaluation. Four distinct patterns of semiology were noted that correlated with anatomic seizure localization on SEEG. The first group with elementary motor signs had seizures involving precentral and premotor areas. The second group with a combination of elementary motor signs and nonintegrated gestural motor behavior had seizures involving premotor and prefrontal regions. The third group integrated gestural motor behavior with distal stereotypies involved anterior lateral and medial prefrontal regions. The fourth group, demonstrating fearful behavior, had seizures involving ventromedial prefrontal cortex with or without anterior
temporal structures. The matrix analysis of these semiological features showed a clear trend from rolandic cortex to frontal pole. The most integrated behavior was produced by seizure activity arising from rostral prefrontal regions, becoming progressively less integrated with posterior prefrontal regions, whereas exclusive elementary motor signs, with no gestural components, were noted in posterior motor regions. A similar anatomic gradient was noted in the study done by Gibbs and colleagues among patients with sleep-related hypermotor epilepsy. Gestural behaviors with high emotional were noted in seizures originating from frontopolar and orbitofrontal cortex contents (16/19 patients, 84%), whereas elementary motor signs were seen in seizures starting in the vicinity of precentral sulcus (16/19 patients, 76%).44 Seizures originating from intermediary regions exhibited integrated hyperkinetic behavior (eg, kicking, rocking) and nonintegrated hyperkinetic movements in a scattered pattern but showed similar anteroposterior tendency. Thus, the semiology of frontal lobe seizures can be used to identify frontal lobe regions involved seizure onset and propagation networks in an anatomic pattern.

SUMMARY

Understanding epilepsy as a network disease, in the context of a complex system, is a relatively new approach in the United States and has opened new doors to targeting these networks at both horizontal level and vertical hierarchical levels. Studies of genetic mutations in ADNFLE have shown the importance of genes in the phenotypic expression of FLE networks. Pathophysiology at the local neuronal circuit level studied by HFO analysis may hint toward the underlying causes in patients with FLE even when standard imaging does not identify structural lesions. Connectivity studies with fMRI, MEG, and electrophysiological markers in intracranial EEG, along with detailed semiological evaluation, can guide us in investigating the epilepsy network at the lobar and whole-brain level. Approaching FLE as a network provides a perspective for understanding the disease in a comprehensive way.

DISCLOSURE

The author has nothing to disclose.

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