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SPECIAL REPORT

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WONOEP appraisal: Network concept from an imaging perspective

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Abstract

Neuroimaging techniques applied to a variety of organisms—from zebrafish, to rodents to humans—can offer valuable insights into neuronal network properties and their dysfunction in epilepsy. A wide range of imaging methods used to monitor neuronal circuits and networks during evoked seizures in animal models and advances in functional magnetic resonance imaging (fMRI) applied to patients with epilepsy were discussed during the XIV Workshop on Neurobiology of Epilepsy (XIV WONOEP) organized in 2017 by the Neurobiology Commission of the International League Against Epilepsy (ILAE). We review the growing number of technological approaches developed, as well as the current state of knowledge gained from studies applying these advanced imaging approaches to epilepsy research.

KEYWORDS

calcium imaging, epileptic networks, fMRI, graph theory, neuroimaging

1 | INTRODUCTION

Epilepsy may be broadly defined by a state of enduring predisposition to seizures, which arise when the balance between excitation and inhibition is disrupted in the context of abnormal synchronization. Epileptogenesis can be examined at different "levels" of the nervous system: first at the level of the molecular building blocks including genes, proteins, ions and membranes,[1] then cells and circuits/synapses, and finally large-scale neuronal networks. Both due to the complexity of molecular disease mechanisms and the architecture of neuronal networks, application of systems biology approaches based on network neuroscience has found its entrance in epilepsy research. At its simplest, a network is a collection

of items (called nodes) that possess pairwise relationships (called edges). The brain as a whole can be considered a hierarchically organized network, partitioned into mutually interconnected units responsible for information processing spanning from local circuits to broad functional areas. A network perspective has a particular relevance in epilepsy, since structures within an epileptogenic network are thought to be involved in the generation and expression of seizures, and to the maintenance of the disorder.[2]

For this review, we focus on the network concept in epilepsy from an imaging perspective. Compelling evidence from preclinical models, experimental paradigms, and humans indicates that specific cortical and subcortical networks play a fundamental role in the genesis and expression of seizures. In the last two decades, converging evidence from neuroimaging literature has shown distributed anomalies in the neocortex and the white matter in epilepsy syndromes associated with structural abnormalities, challenging the conventional model of focal epilepsy (reviewed in Bernhardt et al[3]). The hypothesis that focal epilepsy may be more adequately described as a system-level disorder is now a bourgeoning research area fueled by advances in connectomics.[4] Recent technological advances in imaging of neuronal activity in animal models, and progress in structural and functional magnetic resonance imaging (MRI) in human studies have made it possible to examine regional networks involved in seizure onset and propagation, and to identify those displaying abnormal functional connectivity during interictal periods. In parallel, ongoing efforts aim at using neuroimaging to predict epileptogenesis as well as ictogenesis.[5] In this article, we provide an overview of high-end neuroimaging techniques used to study neuronal activity in vivo in animal models of seizures and epilepsy, and we show how these studies are improving our understanding of local and distributed networks in ictogenesis. Positron emission tomography (PET) studies have been thoroughly reviewed by van Vliet et al.[5] We also discuss the current state of knowledge gained by advancing MRI-imaging approaches to map whole-brain and epileptic networks in patients.

Key Points

- Epilepsy can be viewed as a system disorder with abnormal network interactions and connectivity at short and long range
- Advances in rodent in vivo imaging allow unprecedented insight into ictogenesis at multiple scales, from neuronal microcircuits to brain-wide networks
- In vivo human imaging combined with network neuroscience has shown a modulatory role of structural anomalies of the primary epileptogenic lesion on local- and large-scale networks

2 | ANIMAL STUDIES

Traditionally, electrophysiological recordings have been used to evaluate seizure activity in vivo, and benefit from high sampling rates. Imaging approaches can, however, offer substantial spatial advances over electrophysiology. Even when high-density surface arrays are employed, there can be difficulties in accurately localizing neuronal activity due to low spatial sampling and volume conduction.[6] Multielectrode extracellular probes can record simultaneously from hundreds of neurons,[7] but their readout is spatially restricted and limited to active neurons. Determining cell-type firing is difficult, particularly during a seizure when distortions of action potential waveform prevent spike sorting.[8] It has been known for many years that intrinsic optical imaging of hemodynamic signals can be used to monitor epileptiform activity and seizure propagation in vivo[9]; however, this approach has limitations. Renewed interest in high-resolution in vivo imaging was sparked only recently, due to the rapid and continuous advancement of fluorescent microscopy, development of novel fluorophores and, importantly, data analysis algorithms.

2.1 | Novel optical imaging methods to monitor neuronal activity

Recent advances in microscopy, coupled with the ability to express calcium- and voltage-sensitive indicators in subclasses of neurons in zebrafish and rodents, using either viral vectors or transgenic approaches, have resulted in the ability to image neuronal activity in exquisite detail. These methods have been used to determine the roles of different neuronal subclasses and local circuits during behavioral tasks in awake animals and have recently been applied to epilepsy research characterizing epileptic networks at multiple scales, from neuronal microcircuits to brain wide networks. These approaches rely on fluorescent reporters of neuronal activity. Bolus loading of traditional organic dyes capable of reporting changes in intracellular calcium or membrane voltage have proved very useful. However, cell specificity can be achieved using genetically encoded fluorescent reporters.[10] Genetically encoded indicators of calcium (GECI) or voltage (GEVI) have become the approach of choice, owing to the ever-increasing improvements in transgenic technologies,[11] viral vectors,[12] and fluorescent reporters, including those with red-shifted excitation and emission spectra, which allow deeper in vivo imaging and reduced phototoxicity.[13] Despite having superior temporal resolution, voltage-sensitive indicators have low signal-to-noise ratio

(SNR) and are not optimal for detecting neuronal inhibition or distinguishing between subthreshold depolarizations and action potentials in vivo.[14] In contrast, calcium indicators have a high SNR and a broad dynamic range[15] and are more commonly used in epilepsy research, despite their slower temporal properties. When a neuron fires an action potential, calcium enters the cells and GCaMP fluorescence transiently increases. Therefore, an increase in fluorescence can be used to identify neurons firing during a seizure. Modified and enhanced members of the GCaMP family of indicators (molecules created from the fusion of green fluorescent protein, calmodulin, and M13, a peptide sequence from myosin light chain kinase)[16] are usually expressed in specific classes of neurons using either viral-vector mediated approaches or through creation of transgenic organisms. Care should be taken to ensure that expression levels of indicators are optimized to avoid off-target effects.[17]

To understand how local and distributed networks are involved in epilepsy, different imaging approaches can be employed. To detect changes in intrinsic excitability, local imbalance in excitation and inhibition, and the initiation of seizures from a discrete focus, imaging of densely packed neuronal populations will be beneficial, ideally at single cell resolution and with indicators expressed in defined neuronal populations from the seizure-onset zone. However, the ictal focus does not operate in isolation and is connected to other areas of the brain via short- and long-range projections. Alternative mesoscopic imaging techniques are instead required to record propagation pathways and areas of the brain that are recruited for seizure "pace-making," or to detect interictal abnormalities between functionally connected but distant areas of the brain. Mesoscopic imaging refers to a spatial scale between microscopic and macroscopic. This approach does not permit single neuron imaging but is a powerful approach to determine areas of brain with enhanced neuronal firing rates. Neuronal activity can also be visualized in fixed tissue utilizing genetically modified mice that express fluorescent proteins under the control of early immediate genes, such as c-Fos and c-Jun. Although early immediate gene messenger RNA (mRNA) and protein expression have been used to map seizures, the transient nature of expression and low SNR limit their use. In recent years, genetically modified mice have been developed that express fluorescent proteins such as tdTomato or green fluorescent protein in neurons under the control of early immediate gene promoters. These promoters can be controlled temporally by drug-binding sites for tetracycline or tamoxifen.[18] Tissue-clarifying techniques further facilitate identification of neurons expressing fluorescent proteins. Brain tissue of various thickness can be clarified using active or passive clarification techniques,[19,20] and detailed three-dimensional (3D) images using confocal or two photon imaging can be obtained. In addition, these whole-brain microscopy approaches can also be used in coregistration with in vivo mesoscopic imaging modalities.[21]

The imaging approaches most commonly applied to epilepsy studies and discussed at the XIV Workshop on Neurobiology of Epilepsy (XIV WONOEP) meeting included two-photon, wide-field, and light sheet fluorescent microscopy; the use of miniscopes for chronic recordings in freely moving animals; and analysis of blood oxygen level–dependent (BOLD) signal during functional MRI (fMRI). A brief description highlighting the differences and particular advantages of each of these techniques is provided in Box S1. A detailed review of the growing number of microscopy techniques available for in vivo imaging of neuronal activity has been published recently.[22]

2.2 | Preclinical models of epilepsy

Because zebrafish and mice are genetically amenable, they have become powerful model organisms for analyzing genetic diseases. It is possible to derive transgenic lines that harbor the same mutations in genes found in human forms of genetic epilepsy. For instance, zebrafish and mouse models of Dravet syndrome have been developed.[23,24] These models could be used for detecting development of network abnormalities in genetic forms of epilepsy and may aid our understanding of the functional consequences of pathophysiological activity patterns from a cellular level to large-scale cortical networks. In models of acquired chronic epilepsy, there will be both proepileptic and compensatory changes of the network and neuronal firing patterns. A major complication that hampers imaging of spontaneous seizures is their low frequency. For this reason, the majority of neuroimaging studies have focused on acute pharmacologically or electrically induced seizures or have monitored interictal abnormalities in chronic epilepsy models.

2.3 | Insights obtained from in vivo imaging studies

2.3.1 | Calcium imaging of seizure activity from head-fixed rodents

Combining two-photon calcium imaging with a chronic model of temporal lobe epilepsy, Muldoon and colleagues[25] examined the microcircuits that participate in interictal spikes in awake animals. Epileptiform activity was recorded through electrophysiologic recordings in one hippocampus and via calcium imaging in the contralateral hippocampus. Although there was variability in the cellular dynamics of interictal spikes, γ-aminobutyric acid (GABA)ergic neurons are thought to be preferentially recruited during spontaneous interictal activity in the hippocampal CA1 region.[25] Notably, few studies have reported positive associations between interictal spiking, aberrant hippocampal interneuron firing, and cognitive impairment, suggesting a plausible link between GABAergic activation and cognition.[26]

Several studies have examined the role of inhibitory restraint[26] during seizure activity using a combination of two-photon calcium imaging and local field potential recordings. In response to chemoconvulsant-evoked seizures, neuronal populations within and across cortical layers are recruited in a reliable manner propagating with similar spatial directions. Temporal dynamics were, however, variable across seizures and relied on GABAergic input from the inhibitory surround.[27] Using a similar methodological approach, Liou and colleagues demonstrated that inhibition not only plays an important role in containing seizure invasion close to adjacent cortex, but also protects areas distant from the seizure focus. Acute focal breakdown of distant inhibition allows the development of a secondary focus, with seizures in this area triggered by input from the original focus.[28]

Dysfunctional astrocytes have been proposed to play an important role in epilepsy,[29] and the tools required to image their calcium signaling in vivo are available. Two recent studies employing either two-photon or wide-field florescent microscopy have determined that, although seizures induce a large calcium wave through the astrocytic syncytium, the latter occurs after seizure onset, is spatiotemporally uncoupled from faster neuronal activity, and terminates before neuronal activity.[30,31] These investigations suggest that the propagating glial calcium wave is not required for ictal initiation and propagation, as blockade of glial activity had no impact on seizure spatiotemporal dynamics.[30] These experiments were conducted in "healthy," nonepileptic brains, and seizures were induced using chemoconvulsants, therefore it cannot be excluded that astrocyte dysfunction in established epilepsy may occur, and that astrocytes may have a role in ictogenesis.

The spatiotemporal evolution of epileptiform activity in the awake cortex and its relationship with the underlying functional connectivity was recently investigated using wide-field imaging.[32] The functional connectivity within and across visual areas can be easily mapped, and the contribution of both local and long-range connections to the propagation of epileptiform discharges can be detected. This study demonstrates that both interictal spikes and seizures evoked in the primary visual cortex start as standing waves in the V1 focus and in homotopic locations in higher visual areas. Seizures then propagate as a traveling wave across adjacent cortex and jump to invade homotopic distal regions.[32]

2.3.2 | Calcium imaging of seizure activity from freely moving rodents

New miniaturized microscopes[33] combined with genetically encoded calcium indicators now allow recordings of activity from hundreds of neurons simultaneously in freely behaving animals. The use of miniaturized microscopes has several distinct advantages over electrophysiologic techniques. Most important, unlike electrophysiologic recordings where the same neuron can only be followed for 1 to 2 days, miniaturized microscope calcium imaging can follow the activity of the same sets of neurons for weeks (Figure 1). This allows investigators to determine how each neuron changes its firing patterns after learning or a disease-related insult. Second, the number of neurons investigated simultaneously is nearly an order of magnitude greater with calcium imaging, especially in mice that cannot carry a large number of electrode drives because of weight limitations. Finally, the use of imaging allows expression of GCaMP6 in specific cell types or specific projection neurons.[34] Although miniaturized microscopes from commercial sources are extremely costly, new open-source versions created by Daniel Aharoni in the Golshani, Silva and Khakh groups at UCLA (miniscope.org) are nearly 50 times less expensive and have allowed over 500 labs to quickly and easily build their own miniaturized microscopes. The Golshani group is using these microscopes to understand the mechanisms underlying poor spatial memory in temporal lobe epilepsy. By recording place-related activity in thousands of CA1 neurons over a week, results show dramatic reductions in the number, precision, and stability of place fields.[35]

2.3.3 | BOLD signals during fMRI

BOLD fMRI is widely used in human studies of focal and generalized epilepsy.[36,37] Investigations that employ fMRI in epilepsy animal models therefore have direct translational value. However, it is important to be cautious when interpreting BOLD fMRI because signals are only indirectly related to neuronal activity, sometimes resulting in paradoxical effects, particularly in subcortical structures or during epileptiform activity.[38] These concerns can be overcome through direct neuronal recordings to validate fMRI findings.[39] The combination of BOLD fMRI mapping followed by direct neuronal recordings has led to crucial new insights into network mechanisms in epilepsy. For example, impaired cortical function and consciousness in hippocampal seizures is associated with fMRI increases in subcortical regions including the lateral septum and anterior hypothalamus[40] (Figure 2). Follow-up direct electrical recordings confirmed increased neuronal firing in inhibitory regions such as the lateral septum, which can depress subcortical arousal leading to impaired consciousness in focal seizures.[40,41] Similar subcortical inhibitory mechanisms may play a role in depressed cardiorespiratory function and sudden unexpected death in epilepsy (SUDEP). The network understanding gained through fMRI has also guided potential therapeutic interventions for restoring consciousness during focal seizures through electrical or optogenetic stimulation of subcortical arousal systems.[42,43] BOLD fMRI with electrophysiologic verification and diffusion-tensor imaging (DTI) have also yielded crucial insights into mechanisms of seizure generation[38,44,45] as well as developmental epileptogenesis and epilepsy prevention.[46–49]

3 | CONTRIBUTION OF IN VIVO IMAGING TO UNDERSTAND THE NETWORK PROPERTIES OF EPILEPSY IN HUMANS

By offering several sensitive and versatile whole-brain tissue markers, MRI has improved our ability to noninvasively map epileptogenic lesions and has revolutionized the management of patients with pharmacoresistant epilepsy, shifting the field from prevailing electroclinical correlation to a multidisciplinary approach. Given the relevance for surgical target identification, initial neuroimaging studies focused on the detection of brain lesions; indeed, the resection of a lesion detected on MRI is currently the best predictor of postsurgical seizure freedom.[50,51] Over the past two decades, an increasing number of studies have also shown structural changes affecting distributed regions across the neocortex and the axonal bundles linking them, suggesting widespread abnormalities of brain organization. Although the majority of studies have so far focused on temporal lobe epilepsy, initial evidence of widespread structural and functional reconfigurations is also emerging for epilepsies secondary to cortical malformations.[52] Moreover, abnormalities outside the lesional boundaries have been shown to negatively impact seizure outcome after surgery, which is still suboptimal in up to 40% of patients despite rigorous selection.[53,54] These findings have prompted a major conceptual shift from the conventional interpretation of focal epilepsies and emphasize the importance of a network approach to adequately capture the neurobiology of this disorder. In this section, we discuss findings related to whole-brain network alterations and those associated with epileptic spikes.

3.1 | Network modeling using structural and functional MRI

Methodologic advances in noninvasive neuroimaging have led to mapping of structural and functional networks in vivo.

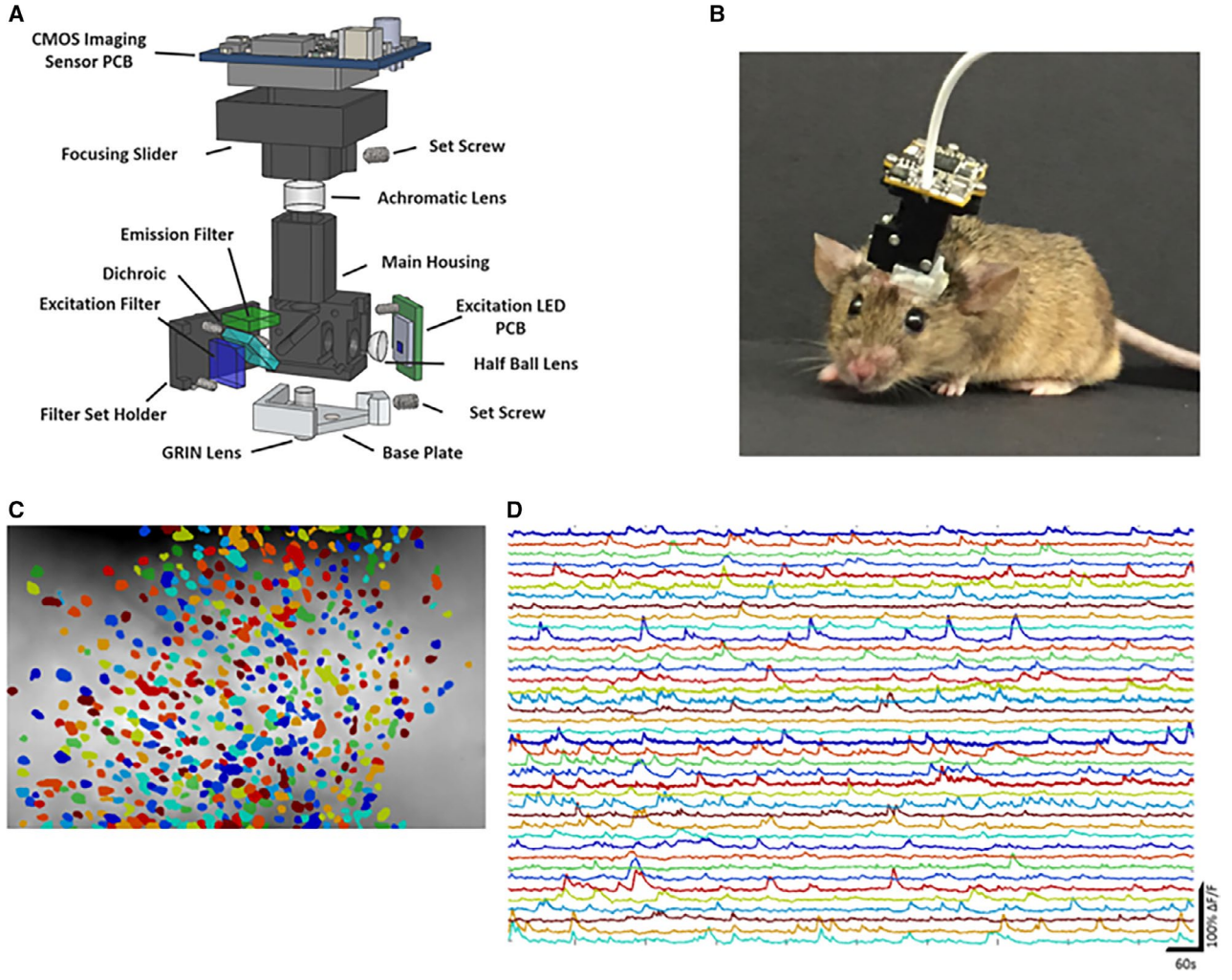

FIGURE 1 Calcium imaging of neuronal activity in freely moving mice. A, Schematic demonstrating all the components of the open-source miniaturized microscope. B, Photograph of mouse walking with a miniaturized microscope imaging the hippocampus. C, Schematic demonstrating a subset of the neurons imaged from hippocampal CA1 in freely behaving mice. D, Calcium traces from neurons demonstrated in C

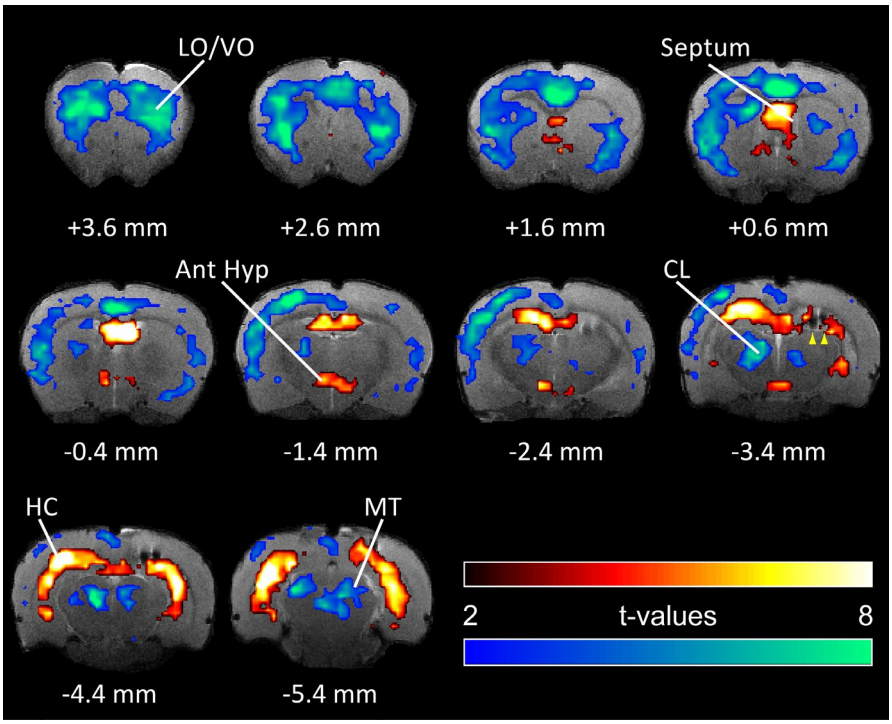

FIGURE 2 Blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI) changes during focal limbic seizures in a rat model. T-map of ictal changes during focal seizures induced by brief 2 s hippocampal stimulation (10 animals, 34 seizures, mean seizure duration ± standard error of the mean [SEM] 70.72 ± 4.01 s). Widespread cortical decreases are accompanied by mixed subcortical increases and decreases. Increases are in known areas of seizure propagation such as the hippocampus (HC) and lateral septum as well as in sleep-promoting regions such as the anterior hypothalamus (Ant Hyp). Decreases are seen in the cortex, most prominently in lateral and ventral orbital frontal cortex (LO/VO) and in medial regions including the cingulate and retrosplenial cortex. Decreases are also seen in arousal promoting regions such as the thalamic intralaminar nuclei including centrolateral nucleus (CL), as well as in the midbrain tegmentum (MT). Arrowheads at anteroposterior (AP) −3.4 mm signify hippocampal electrode artifact. Warm colors represent fMRI increases, and cool colors decreases. Reproduced with permission from reference[41]

Although structural networks can be inferred from diffusion MRI tractography and interregional covariance patterns of structural measures such as cortical thickness, functional connectivity is generally computed based on statistical dependencies of neurophysiological time-series, measured through fMRI techniques. In addition, network science offers increasingly sophisticated analytical methods to parametrize topology and organizational properties of large-scale networks (reviewed in Caciagli et al[55]).

3.2 | Network studies in drug-resistant epilepsy—insights from temporal lobe epilepsy

Temporal lobe epilepsy is associated with widespread abnormalities affecting temporolimbic circuits as well as several large-scale networks. Morphometric correlation analyses revealed decreased structural coordination between mesiotemporal regions and numerous neocortical areas.[56] Covariance of atrophy between the thalamus, mesiotemporal lobe, and multiple frontal and temporal cortices points to a prominent involvement of this subcortical region in the pathologic network.[57] Considering the underlying white matter, severe abnormalities in multiple diffusion markers point to a reconfiguration of the architecture of several temporolimbic tracts, with changes displaying a progressive reversal as a function of the anatomic distance from the epileptogenic focus.[58] Diffusion derangements also encompass specific connections arising from the thalamus, such as ipsilateral anterior thalamic radiation, and tracts linking ipsilateral thalamus with the precentral gyrus.[59] Diffusion changes display a progressive reversal as a function of the anatomic distance from the epileptogenic focus.[58]

3.3 | Graph theory—a formal framework to model network topology

Conventional analysis approaches, mainly based on between-group comparisons, can capture disease-related regional and connectional alterations. However, they are not tailored to address topologic aspects of whole-brain interactions. Graph theory, a framework for the mathematical representation and analysis of complex systems, has attracted considerable attention, as it provides a powerful formalism to quantitatively describe the organizational patterns of brain networks. The

global topology of healthy brain networks is characteristic of a small-world, an architecture that enables functional specialization and integration at relatively low wiring costs. Small-world networks are defined by tightly interconnected nodes, which are themselves linked to other nodes through few interconnector links. Modularity, that is, network decomposability into smaller communities, offers adaptability and robustness to changing environmental conditions. Modularity is undermined by disease processes.[60] In addition to the characterization of global and modular properties of large-scale networks, graph-theoretical techniques allow the localization of core regions, so-called hubs, through centrality-based metrics.[61] Hub regions are more densely interconnected than would be expected from a rich-club subnetwork. Of interest, the latter encompasses mostly long-range connections, indicating its role as a backbone for cross-module connectivity[62] and functional diversity.[63]

In temporal lobe epilepsy, nearly all studies have focused on patients with a unilateral seizure focus. Graph-theoretical studies based on structural MRI have shown profound rearrangements within mesiotemporal lobe subnetworks,[54,64,65] with a shift toward a more regularized topology[64] (Figure 3A). Analyses of functional data also showed deranged limbic nodal topology[66] and changes suggestive of compensatory reorganization of the contralateral networks.[66] The severity of topologic anomalies within and outside the temporal lobe positively scale with the degree of hippocampal sclerosis, indicating a major role of the epileptogenic lesion in the remodeling of whole-brain networks.[64,67,68] Regularization of whole-brain network topology as well as pronounced shifts in the distribution of hubs and modularity were collectively reported across modalities, including structural MRI, diffusion MRI, and electroencephalography (EEG)–derived networks.[69] Graph-theoretical studies also indicated reduced

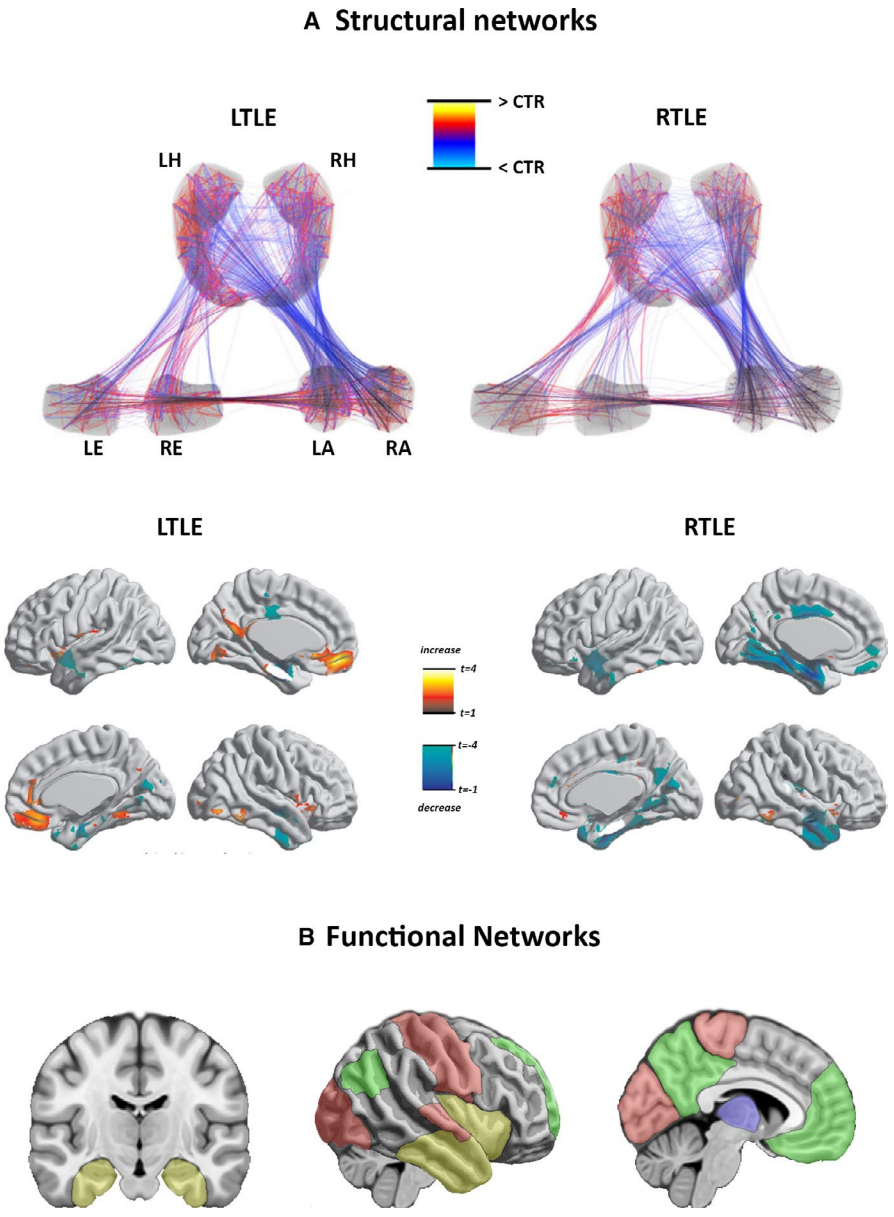

FIGURE 3 Network abnormalities in temporal lobe epilepsy. A, The upper panel of section shows differences in structural covariance of mesiotemporal subnetworks between patients with a left (LTLE) and right temporal lobe epilepsy (RTLE) and controls (CTR), pointing to striking reconfigurations of mesiotemporal connectivity (adapted with permission from reference.[64]). The lower panel displays abnormalities of structural connectivity of the ipsilateral entorhinal cortex in LTLE and RTLE compared with healthy controls, suggesting a reorganization of temporolimbic and default mode networks ([DMNs] adapted from Bernhardt et al[56] with permission). B, Maps show corticosubcortical regions exhibiting aberrant functional connectivity in TLE, mostly belonging to temporolimbic, default-mode, sensory-motor, and thalamocortical networks (adapted from Caciagli et al[55] under the terms of Creative Commons Attribution License: CC BY). Abbreviations: LA/RA, left/right amygdala; LE/RE, left/right entorhinal cortex; LH/RH, left/right hippocampus

coupling between structural and functional networks, which may be partially modulated by disease duration.[70]

With respect to functional connectivity measures, resting-state fMRI (rs-fMRI) studies found impaired connectivity of mesiotemporal structures, mostly involving links between anterior and posterior hippocampus, and between anterior hippocampus and entorhinal cortex, ipsilaterally.[71] Reduced functional connectivity was additionally detected between ipsi- and contralateral hippocampus, insula, and between ipsilateral mesiotemporal structures and bilateral lateral temporal neocortices.[66,72] Altered functional integration has been found between mesiotemporal and subcortical structures, including the thalamus,[73–77] and may coexist with enhanced connectivity in contralateral mesiotemporal networks.[71] At a whole-brain level, bilaterally impaired functional connectivity has been detected consistently for areas pertaining to the default mode network (DMN), which is traditionally composed of mesiotemporal lobes, mesial prefrontal, lateral, and midline parietal areas.[67,73,76] Connectional derangements in temporal lobe epilepsy have also been documented for sensory-motor, attentional, episodic memory, working memory, and language networks, supporting the pervasive nature of the disease, affecting multiple systems (Figure 3B).

Although neuroimaging-derived structural and functional abnormalities show considerable overlap in temporal lobe epilepsy, relatively few studies have directly addressed cross-domain relationships. Decreased network integration of the hippocampus could be partially explained by estimates of its gray matter density.[76] Recent data suggest that the magnitude of hippocampal structural damage may relate to the extent of its functional disconnection from the DMN.[68] Moreover, disrupted functional connectivity between mesiotemporal structures and neocortical targets was associated with altered diffusion parameters of the interconnecting white matter tracts.[76] In a recent study, abnormal function of midline and lateral default mode areas were shown to be mediated by microstructural abnormalities of the temporolimbic superficial white matter.[78] In addition to the effects of structural damage and possibly seizure activity itself, emerging data show evidence for effects of antiseizure drugs on cognitive networks.[79,80] Prospective studies in patients with new-onset epilepsy may help disentangle medication-related effects from those related to seizures.

3.4 | Combined analysis of EEG and functional MRI to analyze epileptic networks

EEG-functional MRI (EEG-fMRI) is a noninvasive tool that combines electrical and hemodynamic information. The regions of hemodynamic changes are presumed to be involved in the abnormal neuronal activity at the time of epileptic discharges.[37,81–83] Regardless of the etiology and type of epilepsy syndrome, interictal scalp EEG-fMRI analyses in patients with focal epilepsy often reveal distributed patterns of BOLD activation, usually with the maximum in the presumed epileptogenic zone,[37] and secondary clusters in remote ipsi- and contralateral cortices, as well as subcortical regions, interpreted as epileptic networks[84–86]; conversely, deactivation tends to occur in the DMN.

In temporal lobe epilepsy, EEG-fMRI studies have indicated that activations correlated with temporal lobe interictal discharges encompass a widespread ipsilateral network, most frequently extending to an ensemble of limbic and subcortical structures[84] (Figure 4). The widespread nature of epileptogenic networks implies increased functional connectivity between the epileptogenic region and remote brain areas, possibly with patient-specific connectional profiles.[87] Functional abnormalities have even been shown in regions unaffected by epileptic discharges,[88] suggestive of a widespread pathologic process that alters whole-brain intrinsic functional network architecture. Despite its limitation to only patients with subclinical seizures or seizures with very little movements, a few studies described the epileptic network associated with ictal activity during EEG-fMRI.[89,90] Overall, results suggest that seizure onset is limited to a single region, while seizure propagation involves a complex network.

In a study combining EEG-fMRI and EEG source imaging to better understand the neuronal dynamics of the BOLD response, the maximum BOLD response (either activation or deactivation) was shown to correspond to interictal epileptiform discharge (IED) onset, whereas secondary BOLD clusters were related to propagation.[91] In another study of patients in whom both EEG-fMRI and intracranial EEG recordings were available, synchronized intracerebral IED activity was found between regions showing a significant BOLD response, demonstrating the existence of an actual neuronally based interictal epileptic network, and suggesting a role for EEG-fMRI as a noninvasive tool for mapping this network.[92]

4 | CURRENT CHALLENGES AND FUTURE OPPORTUNITIES

Networks can be mapped noninvasively at multiple levels, spanning from local and interregional connectivity to whole-brain topologic attributes, thus providing a window into the complex patterns of disease effects.

In preclinical models, imaging technologies are rapidly evolving. It is now possible to image functionally connected areas of the brain, and their dynamic changes and perturbations. Refinements in application of these techniques permit repetitive, noninvasive measurements that can track changes in connectivity during the disease course.[93] In the near future real-time whole-brain imaging technologies at single cell resolution in awake rodents may be feasible. Such technology will impact greatly on our ability to understand cellular and

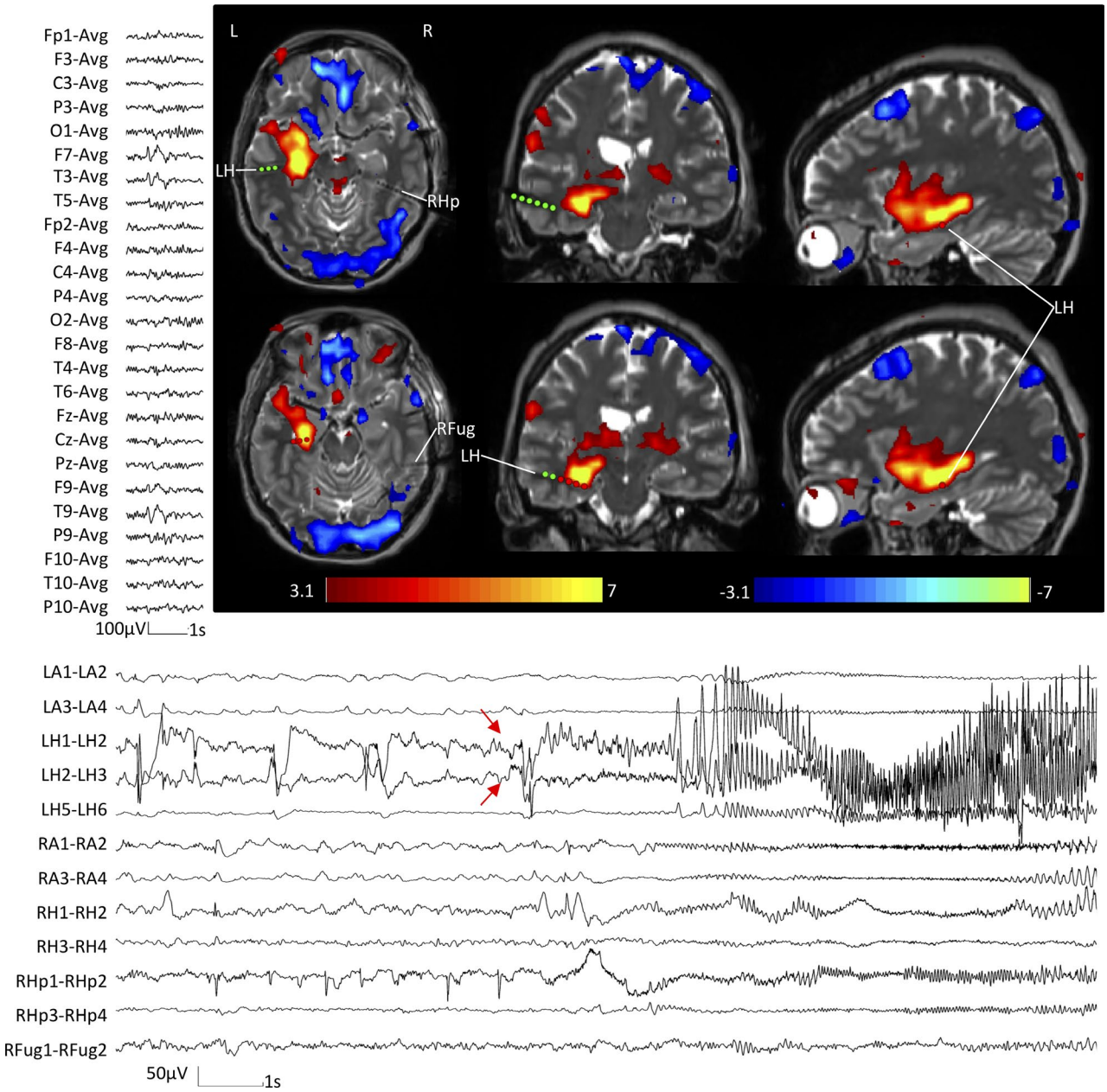

FIGURE 4 Electroencephalography–functional magnetic resonance imaging (EEG-fMRI) findings in temporal lobe epilepsy. In this example, EEG-fMRI hemodynamic responses (top right) correlated with epileptic discharge over the left temporal region on scalp EEG (top left). The hemodynamic response involved a widespread network, with the maximum in the epileptogenic zone (in this case the left hippocampus). The patient underwent a stereo-EEG study, which confirmed the left hippocampus as the main generator of the seizures (bottom). Red arrows indicate the EEG onset of the seizure

circuit mechanisms that result in the development of an epileptic network. For technical reasons, calcium-based imaging has focused mainly on recording activity in superficial layers of the cortex. A clear advance will be to adapt these techniques to target deeper brain structures such as the hippocampus and thalamus. However, the biggest preclinical challenge will be to image spontaneous seizures in disease-relevant models. Spontaneous seizures can be relatively infrequent, just 1-4 a week in some models. A main advance for the future will be to develop technology that allows continuous imaging of brain activity in freely moving rodents prone to spontaneous seizures. Although miniscope calcium imaging[33] goes some way toward addressing this, development of less-invasive technologies will be beneficial. The future may see a switch from a preference of calcium-sensitive probes to voltage-sensitive indicators. Constitutive high expression of calcium indicators can perturb neuronal calcium homeostasis due to alterations in basal calcium buffering within cells.[17] Voltage-sensitive indicators would circumvent this concern. Improvements in SNR ratios coupled with faster response

times for genetically encoded voltage-sensitive indicators may find these probes becoming the preferred choice.

In human epilepsy, imaging studies have unveiled complex patterns of reorganization of structural and functional networks in various syndromes. The majority have remained observational, largely neglecting the modulatory role of the primary epileptogenic structural lesion and mechanisms leading to network reshaping. It is important to note that emerging studies suggest that derangements of lesional morphology and architecture may account for aberrant intrinsic functional connectivity.[94,95] Cross-domain interactions have also been only rarely assessed. Methodological advances such as network control theory allow addressing structure-function links mechanistically, specifically predicting how the brain moves between functional states drawn from white matter network organization. This framework thus lends a novel perspective to examine structurally governed macroscale dysfunction observed in epilepsy.[94] Combination of connectome models together with imaging of structure and function is likely to further our understanding of the associated cognitive and comorbid psychiatric dysfunction prevalent in many epilepsy syndromes.

A pivotal property of the human connectome is to support efficient communication and integration of information. Methods from network science are thus expanding in new directions, going beyond description of topology toward addressing dynamics, a concept building on the notion that physiologic activity of neural systems is constrained by the patterns of connections.[96] To date, brain communication models have been derived mainly from diffusion-weighted MRI data estimating white matter tracts; most metrics have been designed to quantify information flow along the shortest paths, a mode of communication relying exclusively on a small fraction of high-strength connections. Communicability of complex networks may, however, be a broader measure, capturing information flow along all possible paths between any two nodes. Network communication dynamics might be of fundamental importance for understanding plasticity and resilience to disease-related damage, and communicability metrics may indeed be more sensitive to organizational changes than standard connectivity measures. Another line of research in generative models currently operating on intracranial EEG and connectomes derived from diffusion-weighted MRI to study patterns of seizure spread.[97] However, due to the limited and partial sampling of intracranial EEG, it is imperative to validate these models with noninvasive, whole-brain electrophysiologic techniques and integrating them with advanced structural and fMRI. A coherent multidisciplinary approach will help determine whether a connectome-based mapping of the epileptogenic network is clinically relevant, particularly in relation to surgery. It may also help define the role of novel antiseizure approaches still in their infancy, such as gene therapy,[98] optogenetics[99] or chemogenetics.[100]

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DISCLOSURE

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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