Functional Networks in Epilepsy Presurgical Evaluation

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KEYWORDS

• Epilepsy surgery • MRI • Networks • Surgical planning

KEY POINTS

- Recent advancements in neuroimaging methodology have led to detailed in vivo characterization of structural and functional brain networks.
- Fueled by advances in network neuroscience, epilepsy increasingly is defined as a disorder of large-scale networks.
- Connectome-based biomarkers have the potential to improve surgical treatment of drug-refractory epilepsy.
- Future efforts should aim at integrating noninvasive multimodal techniques into a coherent, multidisciplinary approach.

CONTRIBUTION OF IMAGING TO PRESURGICAL EVALUATION OF DRUG-RESISTANT EPILEPSY

Epilepsy is one of the most prevalent neurologic disorders and affects up to 1% of the world's population.[1] Although usually remediable through anticonvulsive medication, up to 30% of all patients do not achieve freedom from seizures. Due to its devastating consequences on cognitive functioning,[2] socioeconomic status,[3,4] and risk of premature death,[5] drug-resistant epilepsy should be identified early[6] and treated accordingly.[7] The 2 most common drug-resistant epilepsy syndromes are temporal lobe epilepsy (TLE) due to mesiotemporal sclerosis[8] and extratemporal lobe epilepsy related to malformations of cortical development, in particular focal cortical dysplasia (FCD).[9,10] By offering sensitive and versatile tissue markers, magnetic resonance imaging (MRI) allows noninvasive detection of these structural epileptogenic lesions and has revolutionized the management of drug-refractory epilepsy, shifting the emphasis from purely electroclinical correlation to a multidisciplinary approach.[11] Surgical resection of epileptic lesions identified on MRI remains the treatment of choice for refractory epilepsy,[12] leading to freedom from seizures in a majority of cases.[10,13–15] Notably, both the presence of a lesion on MRI and its complete resection[16,17] are the most important predictors of a successful surgery. Despite careful selection, however, approximately 30% of patients undergoing surgery experience residual seizures.[18] Although the mechanisms leading to seizure relapse are not fully understood,[19] extensive literature has shown

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that the pathologic substrate may be less focal than traditionally presumed.[20–23] Structural abnormalities outside the presumed lesional area may contribute to poor postoperative seizure control,[24,25] possibly by maintaining a circuitry capable of propagating seizures.[26,27] Fueled by advances in network science, epilepsy increasingly is defined as a disorder of large-scale networks,[2,19,23,28] with the lesion defined by MRI being the central node.[29]

This targeted review summarizes current evidence on epilepsy as a network disorder. A special emphasis is on potential benefits of network analysis techniques for preoperative assessment and planning of the resection.

EPILEPSY AS A NETWORK DISORDER

At its simplest, a network is a collection of items (or nodes) that possess pairwise relationships (or edges). The brain as a whole is a hierarchically organized network, partitioned into mutually interconnected units responsible for information processing spanning from local circuits to broad functional areas. From a clinical standpoint, behavioral manifestations of seizures require the involvement of large-scale brain networks.[30,31] A network perspective has a particular relevance in epilepsy, because structures within an epileptogenic network are thought to be involved in the generation and expression of seizures, and to the maintenance of the disorder.[30] The same neuronal machinery involved in seizure propagation is active during normal, interictal brain function.[29] In this context, noninvasive neuroimaging techniques offer a unique opportunity to investigate networks in vivo at multiple levels.[32]

TLE is the most commonly studied syndrome from a network-level perspective. Advancements in neuroimaging have revealed extensive structural[23,33–35] and functional[2,23,36,37] alterations affecting temporolimbic circuits and several large-scale networks. Additionally, there is emerging evidence that widespread connectional reconfiguration occurs in epilepsy secondary to cortical malformations, particularly FCD.[28,38] Although a structural brain lesion is considered the core of the epileptogenic focus,[39] intralesional structural alterations may influence unfavorable seizure outcomes after surgery,[24,25] potentially by maintaining a circuitry capable of propagating seizures[26] not removed during surgery.[25] Furthermore, alterations in morphology[40,41] and structural connectivity[21,24] distant to the lesion may impair functional network organization,[42] with likely consequences to both seizure control[27] and cognitive outcomes.[43] In TLE, inferences made from these studies are that patients with excellent seizure outcomes mainly exhibit alterations limited to the resected or disconnected mesiotemporal lobe.[44,45] Although the contribution of aberrant connectivity to seizure control is increasingly recognized,[25] individualized predictive values on a single-patient level remain to be established, because most studies so far have focused on group analyses. Understanding the complex interplay between the epileptogenic zone/lesion and whole-brain connectivity is of special importance for clinical decision making in epilepsy surgery and should be the object of future in-depth, possibly prospective, analyses.

METHODOLOGIES TO STUDY BRAIN NETWORKS

Ongoing methodological advancements in neuroimaging allow for noninvasive mapping of both structural and functional networks in vivo (**Fig. 1**). Structural networks[46] can be inferred from diffusion MRI tractography[47] or covariance of morphologic markers,[48] such as gray matter volume or cortical thickness[24] representing physical hard wiring. Although diffusion tensor imaging (DTI) analysis may be the method of choice to study white matter tracts, and their potential architectural disruptions, structural covariance analysis may be used to sensitively assess alterations in the trophic, morphologic coordination between gray matter regions.[2] Conversely, functional connectivity is estimated from statistical associations of neurophysiologic signals between brain regions,[49] with time series extracted from task-based or resting-state functional MRI (rs-fMRI)[32,50,51]; these examinations often are performed as part of the presurgical evaluation, mainly to determine the location of eloquent areas, such as hemispherical language dominance.[52] rs-fMRI offers several advantages over task-based paradigms, for example, reduced cognitive demand (lying still, eyes closed) and high reproducibility.[53] Graph theory, a framework for the mathematical representation and analysis of complex systems, has attracted considerable attention because it provides a powerful formalism to quantitatively describe the organizational patterns of brain networks. Its application to neuroimaging data[19,54,55] has revealed novel insights into normal brain function[54] and epilepsy.[21,28,56,57] In graph theory terms, a network is composed of nodes (brain regions), interconnected by edges (structural or functional connections).[58] Various criteria can be used to define nodes, for example, single voxels or, more often, anatomic parcellations.[19] By globally mapping pairwise connections

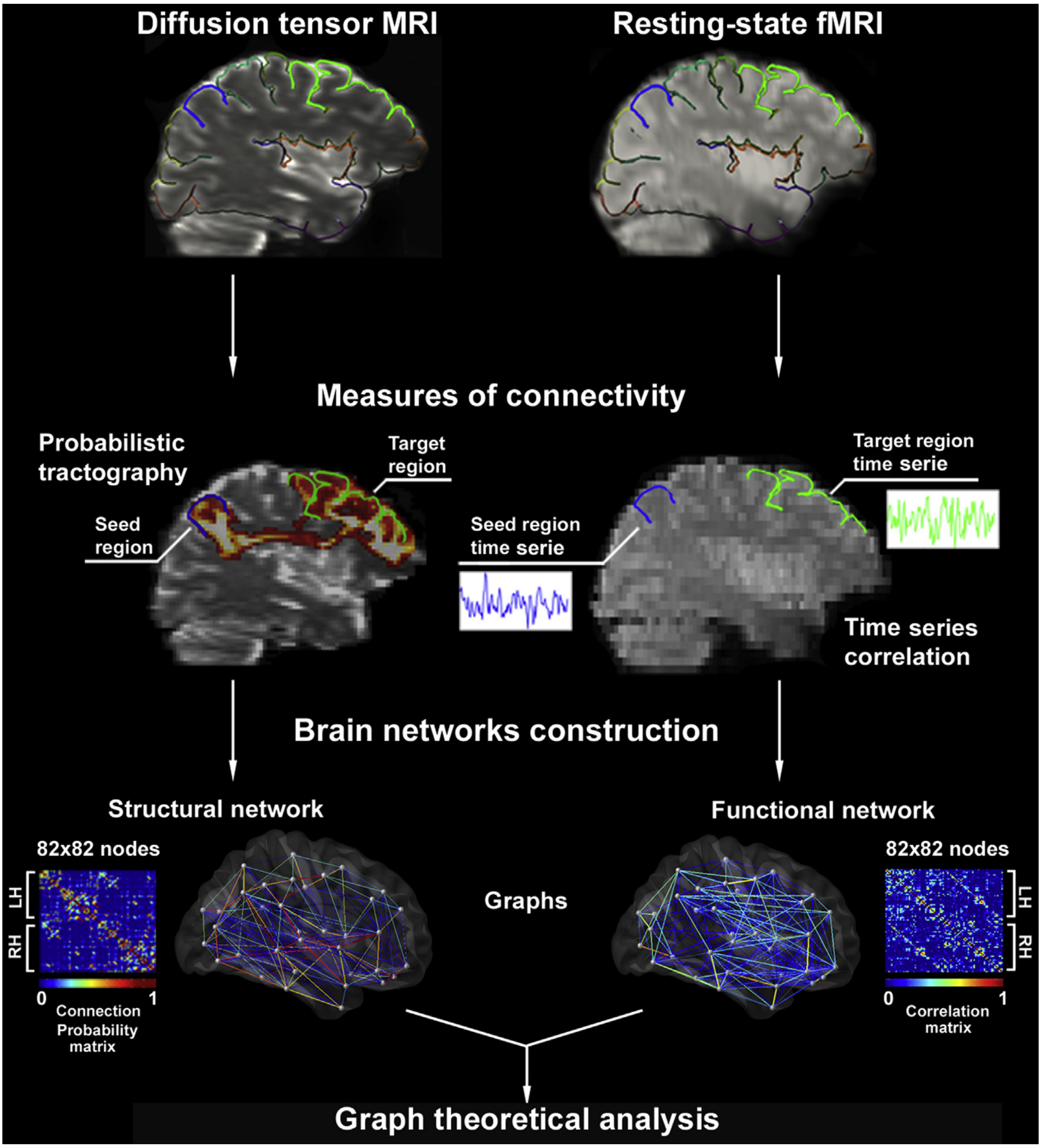

Fig. 1. Construction of structural and functional networks. (*Upper panels*) Parcellated surfaces mapped onto the native diffusion and rs-fMRI. Parcels are consistently located at equivalent position in each native space. Each parcel represents a seed. Its connectivity is estimated to all other parcels. (*Middle panels*) Exemplify DTI-probabilistic tractography and fMRI time series correlations between the superior frontal (*green*) and the postcentral (*blue*) parcels. (*Lower panels*) Connection probabilities and absolute value of partial correlation coefficients between all pairs of parcels are used to generate structural/functional association matrices. Matrices are the substrate for graph theory analyses of network properties. Visualization of graphs facilitates an intuitive understanding of their properties. Nodes (white dots) are placed in the center of gravity of each parcel. Edges (*lines linking nodes*) represent pairwise connections color-coded according to connectivity strength. LJ, left hemisphere; RH, right hemisphere.

between given numbers of nodes, a connectivity matrix can be constructed, that is, the connectome.[54] In TLE, studies using graph theory analysis have demonstrated increased path length, sometimes associated with increased local clustering,[56] reflecting overall network regularization[59] (**Fig. 2**); these changes can be interpreted as pathologic increased local and reduced global network efficiency.[21] Similarly to TLE, connectivity studies of extratemporal lobe epilepsy have revealed a

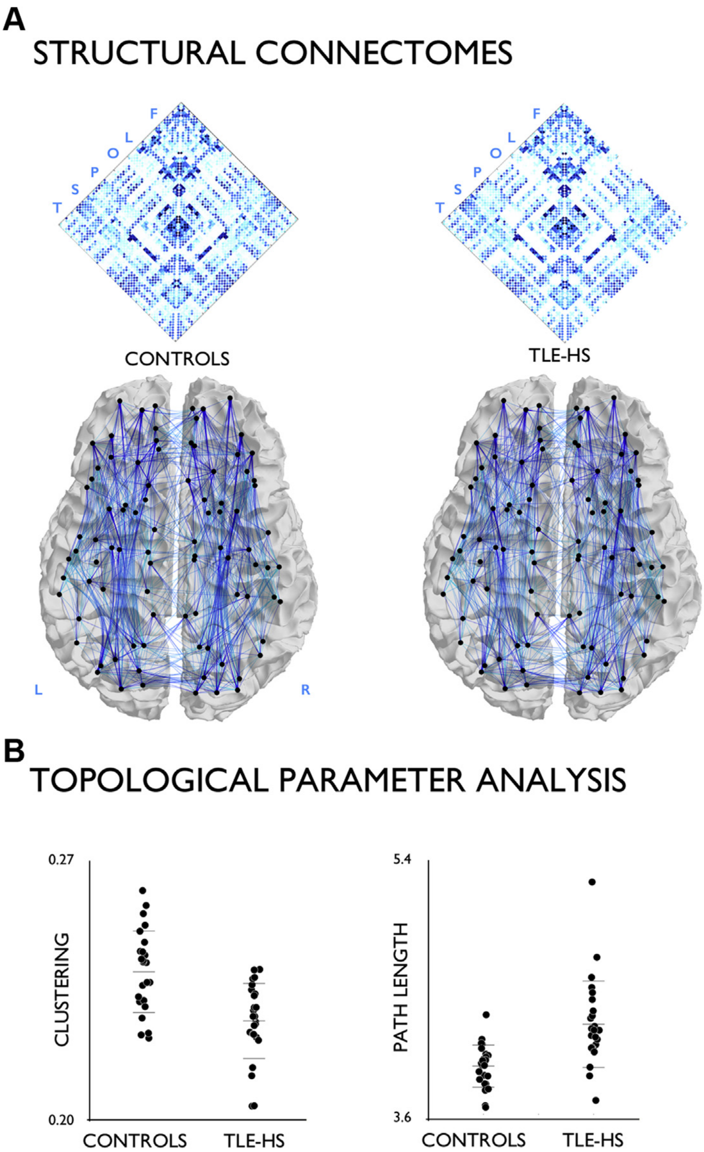

Fig. 2. Diffusion-based connectome analysis in TLE. (*A*) Whole-brain structural connectomes in healthy controls and in TLE patients with histologically confirmed hippocampal sclerosis (TLE-HS). Connectomes were generated using systematic diffusion tractography between all regions, parcellated according to the automated anatomic labeling. Letters in the matrix refer to regional groupings of the nodes (F, frontal; L, limbic; O, occipital; P, parietal; S, subcortical; and T, temporal). (*B*) Graph theory topological parameters of clustering coefficient and path length highlight marked alterations in patients compared with controls. L and R in controls refer to left and right hemispheres, respectively.

more regularized network topology.[38,60] Specifically, late-stage malformations, such as polymicrogyria and type I FCD, may selectively disrupt the formation of large-scale corticocortical networks and thus lead to a more profound impact on whole-brain organization than early-stage disturbances of predominantly radial migration patterns observed in cortical dysplasia type II, which likely affect a relatively confined cortical territory[38] (**Fig. 3**).

NETWORK ANALYSIS IN PRESURGICAL EVALUATION

Because the objective of epilepsy surgery is to remove the epileptogenic brain area, it is of crucial importance to identify hemispheric lateralization and localization of cognitive functions in its proximity.[61] To this purpose, task-based fMRI is of fundamental importance for noninvasive mapping of eloquent areas.[62–67] Language fMRI has revealed atypical dominance[68] and altered language network organization[69,70] in TLE with a left-sided focus. Additionally, current practice guidelines recommend considering fMRI to predict postoperative language outcome after anterior temporal resection.[71] Memory fMRI has revealed activation of a distributed, bilateral network, including temporal, parietal, and frontal lobes.[72,73] Greater left hippocampal activation for word encoding was found to correlate with better verbal memory in patients with left TLE, whereas

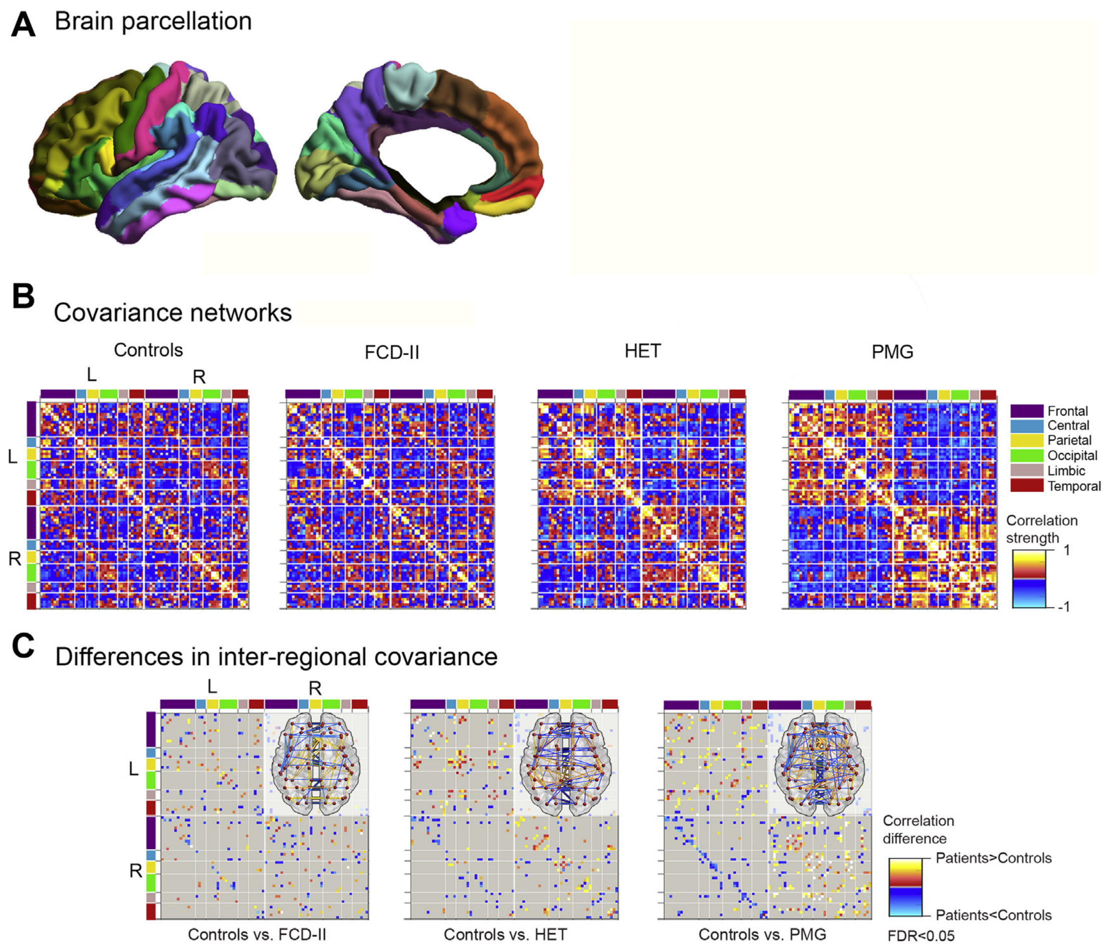

Fig. 3. Structural covariance analysis in malformations of cortical development. (*A*) Brain parcellation into 39 cortical regions per hemisphere according to automated anatomic labeling. (*B*) Covariance networks based on cortical thickness correlations in healthy controls, and patients with FCD type II (FCD-II), heterotopia (HET), and polymicrogyria (PMG). For display purposes, parcels are color-coded according to brain regions listed beside the matrices. The color bar indicates the correlation strength. (*C*) Significant group differences in inter-regional correlations corrected for multiple comparisons at FDR less than 0.05. Increase/decrease in patients relative to controls are shown in red/blue in the matrices and corresponding network graphs. L, left hemisphere; R, right hemisphere.

greater right hippocampal activation for face encoding correlated with preserved visual memory in right TLE.[36,74] Verbal memory fMRI was further used to assess lateralization of memory and associated language functions.[64,75] In short, fMRI contributes high-value clinical information to preoperative planning.[50]

CONNECTIVITY-INFORMED SEIZURE FOCUS LOCALIZATION

Successful surgery is heavily reliant on accurate lateralization of the seizure focus, which is strongly associated with a structural brain lesion. In TLE, several rs-fMRI and DTI studies have investigated the potential of connectome parameters to lateralize the seizure focus. By combining graph theory network measures with machine learning, the focus could be predicted with superior accuracy compared with visual expert MRI assessment.[76] Additionally, rs-fMRI of thalamo-hippocampal connectivity patterns successfully separated left from right TLE, with specific disturbances seen in patients who did not become seizure-free after surgery.[77] These findings are corroborated by the study of Barron and coworkers,[78] which identified thalamic functional connectivity as a strong marker of hemispheric seizure laterality in TLE. Although functional metrics may have potential to assist the lateralization of the seizure focus, their yield compared with hippocampal volumetry[79,80] or more advanced surface shape models[81,82] remains to be determined. Besides the importance of the structural lesion, as determined by MRI, a precise delineation of the epileptogenic zone during surgery is key to successful surgery. In a previous rs-fMRI connectivity study of intractable epilepsy, the seizure-onset zone defined by electrocorticography showed overlap with intrinsic local connectivity alterations[83]; most lesions, however, were seen on routine structural MRI and all patients underwent large resections, undermining the specificity of the connectivity metrics for noninvasive diagnostics. More recently, however, normalization of rs-fMRI–derived connectivity patterns associated with seizure freedom has been observed in a pediatric cohort after network-targeted surgical interventions; predictions reached sensitivity of 96% and specificity of 93%.[84,85]

NETWORK PARAMETERS AS POTENTIAL PREDICTORS OF SEIZURE OUTCOME

With the recent introduction of minimally invasive techniques, such as MRI-guided laser thermal therapy,[86] targeting epileptogenic nodes guided by connectome analysis becomes a plausible approach,[87] allowing for hyperselective interventions in eloquent brain areas.[87,88] Besides the identification of the surgical target,[42] network parameters also may be of use for seizure outcome predictions. So far, connectome-derived markers have been used mainly in TLE.[27] Combining DTI-derived structural connectivity parameters with deep learning, a recent study accurately predicted seizure recurrence, whereas clinical parameters were accurate only in less than 50% of patients.[89] Moreover, postoperative reorganization of mesial prefrontal and temporoparietal connections was seen, more pronounced in seizure-free patients.[90,91] Functional connectivity also has been used as a predictor of seizure outcome. By analyzing connectivity patterns derived from rs-fMRI of temporolimbic and default mode networks, a recent study was able to predict early seizure recurrence with high accuracy[92]; another showed value of interhemispheric asymmetries to differentiate patients with favorable from those with suboptimal outcome.[93]

NETWORK PARAMETERS AS POTENTIAL PREDICTORS OF COGNITIVE OUTCOME

Besides leading to a cessation of seizures,[14] a successful surgical intervention is expected to improve quality of life.[94] Almost every surgery within the dominant hemisphere may expose patients to a risk of cognitive decline.[95] Therefore, information on potential postoperative cognitive sequelae is crucial for adequate patient counseling. Connectivity markers derived from fMRI and DTI increasingly are utilized to identify hemispheric language dominance TLE.[37,96,97] In parallel, network-level phenotyping[42] has aided in cognitive performance profiling and prediction of postoperative deficits.[98] Also, fMRI may help to estimate postoperative verbal memory performance,[64] naming decline[37,99] and overall language outcome after anterior temporal lobectomy.[100] By combining rs- and task-based fMRI with networks parameters derived from DTI, a recent study was able to predict verbal fluency outcomes after anterior temporal lobectomy,[101] while regional graph theory parameters were harnessed to predict postoperative performance across several cognitive domains.[102]

CHALLENGES AND FUTURE PERSPECTIVES

A close overlap between structural and functional domains has been demonstrated in healthy individuals[103] and in epilepsy.[104] Additionally, there is emerging evidence for multilevel interactions between local function, structural pathology, and whole-brain connectivity.[28,39] In TLE, decreased functional connectivity of the ipsilateral hippocampus with the default mode network, a pivotal hub,[105] has been shown,[106,107] the severity of which is modulated by mesiotemporal pathology.[108,109] Recently, a distinctive effect of structural pathology on functional networks also was identified in FCD-related epilepsy[28,38]; that is, locally disconnected lesions seem to exert less influence on whole-brain connectivity, whereas highly connected lesions strongly modulate network topology at large.[28] Moreover, the position of a lesion seems to be of importance, because those within connector hubs cause most widespread disruptions of whole-brain networks.[110] Although this apparent structure-function discrepancy likely represents nodal influence,[28] it also is conceivable that epileptogenicity may functionally isolate portions of a lesion or disrupt large-scale brain connectivity.[111] Altogether, these findings highlight the importance of the structural lesion as the main node within the epileptogenic network[39] and prompt its complete removal.[112] This concept may be relevant particularly for patients in whom the structural lesion MRI is not readily apparent.[11] They often undergo invasive electroencephalogram recordings guided by clinical hypotheses only and limited by low spatial resolution and sensitivity.[113]

Connectome-based biomarkers have the potential to improve surgical treatment of drug-refractory epilepsy significantly.[42] Future efforts should aim at integrating in a coherent multidisciplinary approach noninvasive, whole-brain electrophysiologic techniques[114] with advanced structural and fMRI.[115,116] Ultimately, these modalities may improve minimally invasive neuroablative methods[117] and refine current MRI-based predictors.[42] For this strategy to succeed, however, reliability assessment prior to integration into clinical routine is needed. Additionally, standardization of acquisition protocols and harmonization of analysis techniques will be vital to ensure adequate data quality and reproducibility.[118] Results from the Enhancing Neuroimaging Genetics through Meta-Analysis epilepsy initiative have demonstrated that large-scale, multicentric data pooling and coordinated analysis strategies are feasible.[119] The success of establishing network parameters as a biomarker in clinical routine is largely dependent on such coordinated efforts. Moreover, analysis pipelines should be easy to use and integrate with an existing environment to facilitate clinical decision making.

DISCLOSURE

The authors have nothing to disclose.

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