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REVIEW

Recent Advances in Neuroimaging of Epilepsy

Adam M. Goodman[1] · **Jerzy P. Szaflarski**[1]

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Abstract
Human neuroimaging has had a major impact on the biological understanding of epilepsy and the relationship between pathophysiology, seizure management, and outcomes. This review highlights notable recent advancements in hardware, sequences, methods, analyses, and applications of human neuroimaging techniques utilized to assess epilepsy. These structural, functional, and metabolic assessments include magnetic resonance imaging (MRI), positron emission tomography (PET), and magnetoencephalography (MEG). Advancements that highlight non-invasive neuroimaging techniques used to study the whole brain are emphasized due to the advantages these provide in clinical and research applications. Thus, topics range across presurgical evaluations, understanding of epilepsy as a network disorder, and the interactions between epilepsy and comorbidities. New techniques and approaches are discussed which are expected to emerge into the mainstream within the next decade and impact our understanding of epilepsies. Further, an increasing breadth of investigations includes the interplay between epilepsy, mental health comorbidities, and aberrant brain networks. In the final section of this review, we focus on neuroimaging studies that assess bidirectional relationships between mental health comorbidities and epilepsy as a model for better understanding of the commonalities between both conditions.

Key Words: Neuroimaging · Epilepsy · Neurosurgery · Network disorder · Mental health

Introduction

Noninvasive neuroimaging tools have had a major impact on the understanding of the biological basis of human epilepsy and the relationship between pathology and the outcomes of interventions. Among the commonly utilized techniques are computerized tomography (CT), magnetic resonance imaging (MRI), electroencephalography (EEG), positron emission tomography (PET), spectroscopy (SPECT), and magnetoencephalography (MEG). Further advancements in human neuroimaging methods have afforded promising new insights into the biological basis of epilepsy and, importantly, our understanding of epilepsy as a network disorder. New techniques and approaches expected to emerge into the mainstream within the next decade will greatly influence our understanding of the biological basis of epilepsies and the mechanisms involved in symptom changes. In particular, investigations increasingly focus on epilepsy as a network disorder and in the context of comorbidities. For example, recent work has examined mental health comorbidities in epilepsies that are also related to aberrant brain function.

Network neuroimaging approaches have shown that focal epilepsies are characterized by distal and distributed disruptions in connectivity, function, and neurobiology [1, 2]. A similar recent shift in emphasis on brain network models is noted among psychopathologies [3, 4], including mood and anxiety disorders [5, 6] which share a high rate of comorbidity with epilepsies [7]. Together, novel neuroimaging approaches hold great potential for elucidating the bidirectional biological basis of mental health dysfunction and epilepsy [8]. In this review, noteworthy studies were included that we believe highlight promising new directions and important recent applications of novel imaging techniques on an editorial basis. In particular, we explore recent advances in whole-brain human neuroimaging approaches to understanding epilepsy as a distributed network disorder. This will encompass both new techniques to assess distributed network alterations, as well as tools that can be utilized to better assess the extent and intensity of neuroanatomical, functional, and physiological properties within discrete

✉ Adam M. Goodman
amgood@uab.edu

Jerzy P. Szaflarski
jszaflarski@uabmc.edu

[1] Department of Neurology, UAB Epilepsy Center, University of Alabama At Birmingham, 312 Civitan International Research Center, Birmingham, AL 35294, USA

nodes or regions of these networks. In the final section of this review, we focus on the effects of epilepsy on the networks associated with mood and anxiety disorders and vice versa as a way of linking both states.

Magnetic Resonance Imaging

Due to an ideal balance of relative abundance, spatial resolution, and non-invasive ability to assess a variety of tissue or biochemical properties, MRI has emerged as a broadly utilized tool in the study of epilepsy [9]. From a network neuroimaging perspective, MRI affords a relatively direct whole-brain approach that is not possible with non-invasive EEG, near-infrared spectroscopy (NIRS), or MEG [10]. Among the most common MR techniques (Table 1) to study changes in whole-brain networks linked to epilepsy phenotypes are assessments of anatomical structure (volumetric and morphometric MRI), white matter tissue properties (diffusion MRI), neuronal activation (functional MRI), and metabolite concentrations (MR spectroscopic imaging (MRSI)). However, more recent developments in magnetic field strength (high field 7 T MR imaging), acquisition and sequence optimization (multi-band echo planar imaging (EPI), MRI fingerprinting), physical mathematical modeling (neurite compartment modeling, MRSI thermometry), and sophisticated statistical analysis algorithms (graph theory, machine learning) have expanded the utility of MRI in assessing changes in human brain networks.

Volumetric and Morphometric Magnetic Resonance Imaging

T1-weighted MR imaging is known for its relatively increased sensitivity to assess soft-tissue properties in epileptogenic lesions [11, 12]. Hippocampal volume loss, signal changes, and loss of internal architecture are hallmarks of medial temporal lobe sclerosis associated with temporal lobe epilepsy (TLE) [13–15]. However, from a research perspective, evaluation of subtler abnormalities among volumetric structure offers additional insights into the networks affected in TLE. Traditional volumetric studies

Table 1 MRI-based methods and advanced techniques used in neuroimaging of epilepsy

Name (acronym)	References	Brief description	Advanced methods
Volumetric MRI	[11, 12]	T1-weighted MR imaging is known for its relatively increased sensitivity to assess soft-tissue properties in epileptogenic lesions	Morphometric dentation, morphometric analysis program (MAP)
Magnetic resonance fingerprinting (MRF)	[32]	Pseudorandomized multiparameter (e.g., T_1, T_2, B_0) data acquisition to assess multiple tissue properties using a single rapid sequence	MRF processing and visualization
Diffusion weighted MRI (DWI)	[205]	DWI relies on the Brownian motion of water molecules and relative permeability of lipids and other neuronal components to index the regional brain tissue properties and white matter microstructure and connectivity	Diffusion kurtosis, neurite orientation density and dispersion (NODDI), analysis along perivascular space (DTI-ALPS), graph theory
Functional MRI (fMRI)	[206]	Functional MRI (fMRI) assesses changes in deoxygenated hemoglobin as an indirect measure of regional brain activation and connectivity based on the energy requirements of adenosine tri-phosphate synthesis needed to maintain electrochemical homeostasis of neurons	Magnetic resonance encephalography EEG-fMRI, static and dynamic connectivity MREG, Effective Connectivity, Graph Theory
MR spectroscopy imaging (MRSI)	[126, 127]	^{1}H-magnetic resonance spectroscopic imaging (MRSI) is a well-established method for studying many major metabolites in the brain. Such as metabolites include inhibitory neurotransmitters gamma-aminobutyric acid (GABA) or glutamate and glutamine (combined peak known as GLX), as well as N-acetyl aspartate (NAA), choline (Cho), and creatinine (Cre) serving as an index of neuronal or cellular states and metabolic function	Volumetric MRSI, MRSI-thermometry (MRSI-t)

assess relative changes in regional volume using atlas-based segmentation methods. However, continued development of morphometric analysis techniques builds on these traditional methods by assessing changes in the arrangement of nuclei and subnuclei within a region to provide fine cortical pattern information not necessarily related to increases in volume [16]. Thus, although morphometry is an important part of volumetric studies, some morphometry studies extend beyond assessing regional volumetric changes to visualize and quantify changes in specific shape patterns and internal architecture of brain structures (e.g., dentation of the hippocampus). Visualization and quantification of fine cortical anomalies and changes in structural patterns of hippocampal nuclei and subnuclei has been made possible through optimization of T1- or T2- weighted imaging at 3 T (3 T) and 7 T MRI and/or introduction of new data collection schemes resulting in improved spatial resolution of the collected images [17]. Specifically, morphometric analysis of hippocampal dentations of the inferior surface has shown that greater dentation relates to better episodic memory performance in healthy controls [16]. Similar methods have recently been utilized to quantify smooth or mildly irregular hippocampi in TLE, suggesting that asymmetry in dentation may serve as a hallmark of TLE phenotypes [18]. Additionally, subsequent reconstruction of anatomical information acquired during T2-weighted imaging is susceptible to artificial smoothing during initial processing of the MRI data at 3 T [17]. However, the increased spatial resolution of 7 T imaging combined with automated segmentation methods can more accurately and precisely estimate internal architecture of the hippocampi [19].Thus, new understanding about the role of hippocampal subfields and dentation patterns in patient profiles and as predictors of surgical outcomes may be possible [20]. Further, 7 T MRI has demonstrated an increased detection of focal cortical dysplasia (FCD) that can improve surgical outcomes in patients who were previously deemed MRI-negative [21, 22]. New developments in automated detection of epileptogenic lesions may lead to improved surgical outcomes. For example, morphometric analysis program (MAP) is a practical and valuable tool to guide the search for subtle cortical abnormalities among T1-weighted imaging for otherwise MRI-negative patients [23, 24]. Substantial additional benefits of the MAP tool include robustness to lower field strengths (i.e., 1.5 T MRI), retrospective assessment on presurgical MRI data to compare resection overlap and long-term outcomes, and an automated objective assessment of lesion extents [25]. Clinically, MAP has been utilized for detection of focal cortical dysplasia [26] and in prospective presurgical evaluations of epileptogenic lesions with encouraging preliminary results [27]. Likewise, when combined with machine learning algorithms, T1-weighted structural imaging has broadened detection of subtle morphometric changes among MRI-negative patients [28, 29]. Future developments are anticipated in the utilization of 7 T MRI and the vast increases in spatial resolution that accompany high field MRI in humans. For example, a recent retrospective study on MAP lesion detection suggests a major benefit of high-field MRI in detecting subtle FCD lesions of otherwise MRI-negative treatment-resistant epilepsy patients [22]. Additionally, high spatial resolution in 7 T MRI may be used to non-invasively discriminate between myelin loss in temporal white matter and cortical dysplasia in TLE, previously only detectable in resected histopathological samples [30]. Limiting factors in the high field human MRI domain are increased specific absorption rate (SAR), relaxation times, susceptibility artifacts, and physiological sensory side effects (e.g., vestibular, gustatory) as well as lower clinical utilization, bore circumference, radiofrequency field homogeneity, and availability of 7 T MRIs among research institutions [31]. However, these limiting factors may be partially mitigated by further demonstration of benefits, increases in bore circumference, and broader availability.

Magnetic Resonance Fingerprinting

MR fingerprinting (MRF) is a new approach to MR data acquisition sequences and processing that could enable more comprehensive tissue diagnosis and development of imaging biomarkers in epilepsies. Specifically, MRF utilizes a single and time-efficient multicontrast acquisition sequence that measures unique combinations of signal responses (i.e., *fingerprints*) as a function of multiple tissue properties [32]. MRF holds great potential as a more sophisticated assessment of epileptogenic lesions, such as malformations that occur at the interface between gray and white matter tissues [33]. Initial findings have shown that MRF improves accuracy in detection of lesions within gray and white matter portions of medial temporal areas [34, 35]. However, future studies are needed to determine whether this enhanced detection will benefit pre-surgical evaluation and therapeutic interventions.

Diffusion Magnetic Resonance Imaging

Diffusion-weighted MRI (DWI) relies on the Brownian motion of water molecules and relative permeability of lipids and other neuronal components to index the regional brain tissue properties, particularly white matter microstructure and structural connectivity. The traditional approach has been to model movement of water molecules within and between cell membranes based on assumptions of a Gaussian-based tensor-fitting model (diffusion tensor imaging (DTI)). As a post-processing method, DTI takes advantage of diffusion properties of the tissue to show unrestricted (isotropic) or restricted (anisotropic) water movement that can be modeled

with a tensor resulting in eigenvectors (ε) and eigenvalues (λ) at every voxel. Next, eigenvalue measures based on the anisotropy of water movement yield a principle axis (λ1) and two secondary axes (λ2, λ3). These lambdas are utilized to then calculate axial diffusivity as an index of axonal integrity, radial diffusivity as an index of demyelination, and fractional anisotropy or mean diffusivity as an index of white matter health or integrity [36–38]. However, DTI is unable to discriminate between regions with isotropic movement due to an abundance of water with little to no cell membranes versus a large degree of axonal dispersion related to two or more crossing fibers [39]. Despite this limitation, DTI continues to provide new and valuable contributions to the understanding of epilepsy. In particular, a recent ENIGMA-Epilepsy (a large consortium dedicated to aggregating neuroimaging data) study utilized thousands of patient DTI scans to rank the most robust white matter microstructural differences, demonstrating syndrome-specific fractional anisotropy and mean diffusivity that may explain cognitive and psychiatric comorbidities or be used to guide treatment decisions [40]. Thus, while DTI has provided us with insights into the *white matter integrity*, traditional measures of diffusivity and anisotropy are limited by lack of biological specificity [41–43]. Another recent DTI study indicated that pre-operative tissue characteristics including fiber quantification could aid and provide better precision to predicting surgical outcomes of patients with TLE [44].

The abovementioned limitations in DTI have been mitigated by recently developed post-processing methods utilizing diffusion sequences with richer data acquisition, known as high angular resolution sequences (HARDI) multishell sequences. To address the limitation of crossing fibers and provide more accurate reconstructions of white mater fiber pathways throughout the brain, diffusion spectrum imaging (DSI) approach implements a multi-directional model instead of the bi-directional tensor model [45]. By combining DSI reconstruction with quantification of reconstructed white matter fibers, known as streamlines, increased neurodegenerative changes have been demonstrated recently in TLE patients [46]. Similar to DSI modeling that refines upon prior DTI-based approaches, diffusion kurtosis imaging (DKI) is another advanced diffusion post-processing technique that can better resolve crossing fibers in white matter. Based on the properties of water diffusion among cellular membranes, DKI utilizes a non-Gaussian tensor model to calculate mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK) that more accurately assesses the movement of these molecules among tissue [47]. MK, RK, and AK indices have extended the assessment of specific biomarkers within white matter for TLE [48, 49], post-traumatic epilepsy [50], and idiopathic generalized epilepsies (IGEs) [51]. While DSI and DKI improve resolution of crossing fibers, another approach known as neurite orientation dispersion and density imaging (NODDI) [52] has recently emerged to resolve both crossing fibers and biological specificity [53, 54]. NODDI works by assessing water movement among intra- and extracellular compartments to determine the orientation and density of neurites (i.e., to any process that emanates from the soma, such as axons and dendrites). The degree to which neurites are estimated to be dispersed, condensed, or absent is then used to make voxel-wise inferences about tissue properties throughout the brain. Specifically, resulting index maps are utilized as 1) orientation dispersion index (ODI) estimates of degrees of crossing fibers or dendritic branching; 2) neurite density index (NDI), also sometimes called intracellular volume fraction (ICVF), estimate of myelination; and 3) isometric volume fraction (V-ISO) estimates of extracellular free water [55]. Although the biological specificity of NDI and ODI for indexing myelin density and axonal dispersion has been validated histologically [54, 56], such validation of edema or neuroinflammation and V-ISO remains unclear due to the active physiological nature of inflammation and methods of the histological preserving techniques [57, 58]. Further, limitations for HARDI sequences related to physical principles include increased shell size and acquisition times [59]. Notwithstanding these limitations, recent applications of NODDI analysis to neuroimaging studies of epilepsy have shown that neurite density is diminished within otherwise MRI-negative epileptic temporal lobes [60] and in focal cortical dysplasia [61]. Thus, NODDI extends diffusion tensor and spectrum modeling approaches by providing greater specificity for changes compared to standard DTI. However, potential validation of V-ISO as a marker of neuroinflammation changes in epilepsy may serve as a valuable neuroimaging development in future studies.

The glymphatic system, a central nervous system (CNS) analog to the lymphatic system, has recently received increased interest because of its potential role in brain health and disease. There is evidence that the glymphatic system provides extracellular drainage of waste within cerebrospinal fluid (CSF) and that disruption of this system may be linked to neuroinflammation and function disruption [62, 63]. Non-invasive techniques have been developed and implemented to study the glymphatic system [64]. For example, DTI-derived indices of ventricular diffusion velocity along the perpendicular planes of the projection and association fiber white matter pathways, known as the DTI-based analysis along the perivascular space (DTI-ALPS), may serve as an estimate of the glymphatic system functioning [65–67]. Glymphatic system activity is impaired with advanced age in disorders such as Parkison's disease (PD) and AD [68, 69]. DTI-ALPS may provide new understanding of age-related neuroinflammatory changes in epilepsy, yet no study to date has assessed the potential unique relationship between glymphatic system activity and aging in epilepsy. However, there

has been limited evidence of the validity of the DTI-ALPS method and future investigations may lend additional evidence in support of its utility.

Functional Magnetic Resonance Imaging

Functional MRI (fMRI) assesses changes in regional blood-oxygenation to determine neural function and connectivity related to information processing. Data acquired from fMRI are used to make inferences about regions or networks involved in active processing during responses to a stimulus or behaviors (task-based fMRI) or passive information processing networks during rest, in which no exogenous stimuli are presented (resting-state fMRI). The main impetus for utilizing fMRI in epilepsy has traditionally been replacing the intracarotid amobarbital procedure (IAP) used to determine hemispheric lateralization of language and verbal memory to aid surgical decisions [70]. Although traditional fMRI approaches to replace IAP perform similar in predicting post-surgical outcomes [71], recent studies have shown promise for the future utility of fMRI. For example, increased predictive validity may arise from progress in visual and verbal task-development, replication across imaging centers and platforms, evaluation of the resection of the implicated in the task brain tissue, and task-based connectivity studies [72]. Outside of pre- and post-surgical evaluations, the use of fMRI in the study of epilepsy has also contributed greatly to the understanding of focal and distributed disruptions in neural function and information processing related to seizure control, comorbidities, and other patient outcomes. Task-based fMRI epilepsy studies have shown network disruptions during psychosocial stress [1, 73], emotion recognition [74, 75], memory encoding and retrieval [76–78], working memory [79–81], language [82–85], and cognitive control tasks [86]. In one of these investigations, altered language task-related thalamic network functional connectivity is proposed as an imaging biomarker of active secondary generalization [84]. By comparing changes in cognitive performance during cognitive task paradigms, fMRI studies may also be utilized to evaluate how specific anti-seizure medications such as levetiracetam [87], topiramate [88–90], or cannabidiol [91, 92] affect the neural substrates of cognition in epilepsy. Thus, in addition to the growing popularity of fMRI studies in replacing IAP for surgical evaluations, this approach is also increasingly used for assessing neural basis of comorbidities and treatment outcomes. Assessment of such neural correlates may point to a common neurobiological etiology or a consequence of the seizures themselves.

While fMRI provides improvements over IAP for spatial localizations of function, the temporal resolution of fMRI does not compare to the high temporal resolution of electrophysiological assessments (EEG and MEG). By combining fMRI and EEG, studies can capitalize on the spatial benefits of fMRI and the temporal benefits of EEG. Specifically, MRI compatible EEG systems are used simultaneously with fMRI (EEG-fMRI) to provide a more granular time course assessment of event-related potentials within a specified region than would be possible with fMRI or EEG alone [93]. Recent advancements in EEG-fMRI post-processing have overcome technical challenges such as strong physiological and gradient artifacts [94]. Accordingly, improvements in assessing the concordance between EEG event-related potentials and fMRI regional brain activation will provide new insights on neurological diseases and treatment approaches [95]. Among neuroimaging studies of epilepsy, EEG-fMRI has been utilized for a variety of both clinical and research applications. For example, EEG-fMRI can be used to improve localization and surgical outcomes in MRI negative patients with focal cortical dysplasia [96] and TLE [97]. As an example, resection of the localized with EEG-fMRI putative epileptogenic region has been shown to be superior to not removing this area which was associated with poor outcome [98]. In another study, 10 out of 59 EEG-fMRI assessments provided critical information allowing progress toward resective epilepsy surgery with all 10 patients afforded good seizure outcomes at 1 year [99]. EEG-fMRI has also been extensively utilized to assess widespread and transient disruptions in language, memory, or executive function networks of IGE in order to improve decision making regarding the therapy of patients [100]. Thus, by combining EEG and fMRI imaging modalities to synthesize the advantages of each, new applications and developments in EEG-fMRI techniques offer yet another approach to uncover latent aberrant brain function that can inform treatment and better understand comorbidities in patients with epilepsy.

EEG-fMRI has been applied to generalized epilepsies as well. These studies have initially focused on investigating the fMRI correlates of generalized spike and wave discharges (GSWDs; e.g., [101–103]), response to medications [104], and thalamic correlates of GSWDs [105, 106]. For example, this method has previously shown that GSWDs during EEG are related to thalamic fMRI connectivity, implicating thalamocortical interactions as an important mechanism in IGEs [106, 107]. More recently, this line of questioning has been extended to better understand pre-ictal fMRI connectivity leading up to GSWD simultaneously recorded by EEG. Specifically, higher degrees of fMRI connectivity among prefrontal and motor regions in IGEs immediately preceded ictal activity, suggesting that hypersynchrony initiated from motor regions engages a prefrontal-motor network that may be a key causative factor in initiating a GSWDs [108]. Likewise, EEG-fMRI has suggested response to valproic acid may be predicted prospectively by thalamofrontal connectivity, which serves as a distinct GSWDs generator in treatment-resistant IGEs [104]. Alternatively, resting-state connectivity within the default mode network differentiates between IGEs already identified with and without

treatment-resistance undergoing valproic acid regimens [109]. EEG-fMRI has also been applied to the investigation of the biological basis of symptomatic generalized epilepsies including the Lennox-Gastaut syndrome as well. For example, one study documented clear thalamic and brain stem fMRI correlates to the epileptiform discharges [110] while others investigated the generalized paroxysmal fast activity and its temporal course indicating initiation in the prefrontal cortex with later propagation to the brain stem and finally to the thalamus [111, 112].

Improvements in scanner hardware and optimization of sequences for data acquisition have led to increased temporal and spatial resolution for assessed neural functioning during task-based and resting-state fMRI studies. While beneficial to both types of fMRI studies, increases in temporal resolution via multiband echo sequences are particularly beneficial for resting-state connectivity analysis [113]. Standard correlation analysis in resting state fMRI provides assessment of the strength of functional connections from one region to another (functional connectivity). From a multi-modal perspective, combinations of structural (i.e., white matter, DTI) and functional connectivity have also demonstrated the ability to use network connectivity as a clinical tool for prediction of resective or ablative epilepsy surgery outcome [114]. Recent applications of resting-state functional connectivity suggest patients with different seizure types present unique patterns of decreased thalamocortical functional connectivity [115]. However, the latest analytical approaches have further divided and assessed static and dynamic functional connectivity during resting-state fMRI. Dynamic connectivity assesses the brain's ability to flexibly shift between networks, while static connectivity assesses the invariant robustness of network connectivity over time [116]. Static and dynamic functional connectivity offer a more nuanced view of alterations in network connectivity in epilepsy that may help better explain seizure propagation and seizure-related disruptions. For example, static functional connectivity across the ipsilateral network diminishes in TLE over time, while dynamic functional connectivity measures show the functional independence of this ipsilateral network [117]. These findings suggest that the ipsilateral temporal lobe becomes more synchronous with the secondary generalization of the seizures and may facilitate the spread of seizures across the brain. Thus, applications of new analysis approaches that assess co-activated brain regions during resting-state fMRI has provided new models to better understand whole brain epilepsy networks.

Another class of recent advanced analysis techniques to study functional connectivity assesses directional influence, or effective connectivity (i.e., Granger causality), between brain regions [118–120]. In studies of epilepsy, these techniques have been utilized to assess which brain regions within a network are exerting influence on other brain regions that lead to distributed dysfunction within that network [103, 121, 122]. Accordingly, a better understanding of directional influence between regions within brain networks may aid localizing the source of network dysfunction linked to epilepsies and inform potential targets for stimulation intervention studies and treatments. Another novel method of rapid fMRI acquisition in addition to multiband echo sequences that also capitalizes on optimization of temporal resolution is magnetic resonance encephalography (MREG) [123]. Because the temporal resolution is dramatically decreased (i.e., ~ 100 ms TR for whole-brain images), MREG is capable of measuring very rapid physiological activity in the brain, such as glymphatic function related to cardiac pulsations [124]. Thus, MREG can potentially be combined with DTI-ALPS to derive better understanding of glymphatic dysfunction in epilepsy [64]. In addition, recent work has utilized MREG to demonstrate aberrant increases in cerebral pulsation rates for epilepsy patients and drug-naïve seizure patients compared to healthy controls [125]. Accordingly, improvements in scanner sequences and hardware that have increased spatial and temporal precision for fMRI sequences hold a broad spectrum of potential for assessing whole-brain functional changes associated with epilepsy.

Magnetic Resonance Spectroscopy Imaging

^{1}H-magnetic resonance spectroscopic imaging (MRSI) is a well-established method for studying many major metabolites in the brain. Such metabolites include inhibitory neurotransmitters gamma-aminobutyric acid (GABA) or glutamate and glutamine (combined peak known as GLX), as well as N-acetyl aspartate (NAA), choline (Cho), and creatinine (Cre) serving as an index of neuronal or cellular states and metabolic function [126, 127]. Recently, the use of high field 7 T MRI has made individual metabolite assessment of glutamate (excitatory neurotransmitter) from its precursor glutamine possible, and has suggested a role of this glutamate hyperexcitability in post-stroke epileptogenesis [128]. These metabolites have traditionally been assessed in epilepsy within a single region of the brain (e.g., medial temporal or medial frontal regions) using a relatively large single-voxel, known as single-voxel MRSI. However, recent developments allow for volumetric whole-brain MRSI assessment of these metabolites [129, 130] while maintaining consistency to single-voxel approaches [131]. Applications of whole-brain MRSI to characterize distributed metabolite changes throughout the brain in epilepsy, rather than a specific region. For example, recent work examining MRSI in patients with epilepsy demonstrated widespread decreases in NAA throughout the brain including areas outside of the ictal onset zone indicating neuronal dysfunction in the absence of other signs of tissue atrophy [132, 133].

Another promising analysis advancement in the field of MRSI is the use of relative shifts in metabolite peaks to infer changes in temperature throughout the brain. Specifically, voxel-level brain temperature can be calculated using the chemical shift difference between peaks for creatine and water [134, 135]. This method, known as MRSI thermometry (MRSI-t), may provide additional assessments of focal and generalized changes in neuroinflammatory biomarkers involved associated with seizure generation and maintenance in epilepsies. Specifically, neuroinflammation has recently emerged as an important phenomenon that may be related to neuronal hyperexcitability in epilepsy [64, 136]. In general, the neuroinflammatory cascade serves as an adaptive response to repair local damage when glia activates in response to an insult, such as infection or injury [137]. However, in epilepsy, this cascade functions in the absence of tissue damage or infection and remains perpetually active which disrupts the blood–brain barrier and lowers the seizure threshold by increasing hyperexcitability throughout the brain [138, 139]. Measuring neuroinflammation of epilepsy patients *in vivo* currently relies on positron emission tomography (PET) imaging (see below), yet MRSI-t offers a noninvasive and efficient alternative to measure temperature and metabolic concentrations throughout the brain that is not limited by radioactive injections.

Positron Emission Tomography

Despite being an early precursor to MRI and being limited by invasive radioactive injections, important advancements have also recently occurred for PET imaging. Historically, ^{18}Fluoro-2-deoxyglucose (^{18}F-FDG) PET imaging of brain glucose metabolism has been a well-established and widely available technique used to localize epileptogenic foci [140]. More recently, the use of PET for the quantification of translocator protein (TSPO) density serves as another method to assess glial activation and neuroinflammation in the brain. Unlike MRSI-t, PET-TSPO has been validated as an index of glial activation over the past 25 years [141]. With the recent implications of neuroinflammation in epilepsy, PET-TSPO has become a valuable tool in understanding the role of glial activation and hyperexcitability in epilepsy. For example, recent work using PET-TSPO has demonstrated increased binding of TSPO in ipsilateral and contralateral to seizure foci temporal lobes in patients with TLE [142, 143]. PET-TSPO has also shown that although increasing dramatically following a seizure, detectable levels of TSPO during seizure-freedom may aid in surgical evaluations as well as understanding effects of seizures and epilepsy on inflammation throughout the brain [144]. Specifically, TSPO is thought to be overexpressed as part of the neuroinflammatory process [145]. Initial TSPO-PET studies using [^{11}C]PK11195 aimed to image activated microglia; however, poor signal-to-noise ratio led to conflicting results across studies [146, 147]. The next-generation radioligand [^{11}C]PBR28 exhibits a higher specific binding but is limited by a requirement of genetic stratification, which excludes a substantial portion of patients with epilepsy from testing [148, 149]. [^{11}C]DPA-713, however, possesses greater specificity than [^{11}C]PK11195 and [^{11}C]PBR28 for discriminating between healthy and abnormal tissue. Further, [^{11}C]DPA-713 has a much larger total volume of distribution and is less sensitive than [^{11}C]PBR28 to the TSPO-binding polymorphism, thus increasing the proportion of patients with epilepsy that can be assessed [64].

Magnetoencephalography

MEG assesses changes in magnetic fields (i.e., dipoles) that arise from the bioelectrical signatures generated by excitatory and inhibitory postsynaptic potentials with greater precision than EEG and greater temporal resolution than fMRI [150]. EEG benefits from broader clinical utilization and research applications in studies of epilepsy due to the relative ease of implementation and greater abundance compared to MEG, which must be housed in extensive magnetic shielding. However, MEG serves as a superior electrophysiological imaging technique that extends measurement of postsynaptic potentials and provides a broader and more spatially precise assessment of the entire brain [151]. Thus, where it is available, MEG serves an important clinical tool in pre-surgical evaluations of epilepsy by detecting the unique magnetic signatures of epileptiform spikes, which aids in accurately localizing epileptogenic zones [152, 153]. In a recent study, performing MEG provided clinically useful and new information in 34% of patients undergoing presurgical testing [154]. However, the strength of the dipole signal is inversely proportional to the distance from the detector, orientation to the skull, and interferences from multiple electrical sources of epileptiform discharges in the brain [155]. Accordingly, use of invasive multimodal techniques (e.g., ECoG and sEEG) in combination with MEG is sometimes warranted for localization of epileptogenic zones. For example, MEG increases the chance of localizing an epileptic area with sEEG, while sEEG guided resection is more likely to succeed in seizure reduction when guided by positive MEG source localization [156]. Thus, MEG adds valuable precision to the presurgical evaluation by guiding placement of electrodes to improve surgical outcomes.

MEG has also recently emerged as a valuable tool in high temporal resolution whole-brain neuroimaging approaches to aberrant network function in epilepsy. For example, a recent MEG assessment of aberrant network connectivity extends the approach of fMRI network analysis by providing

evidence of altered signal frequencies in TLE, including increases of delta and theta connectivity within resting-state networks [157]. Likewise, MEG findings utilizing a short temporal resolution have demonstrated increased connectivity of oscillations between brain regions in focal cortical, subcortical, and cerebellar regions during absence seizures and interictal periods [158, 159]. Thus, MEG extends current and prior fMRI approaches to assess aberrant network function in epilepsy with combined high degree of temporal and spatial resolution. This high degree of spatiotemporal resolution provides both spatial specificity and frequency information, which may be critical to epilepsy network models.

Advancements in Group-Level Analysis: Graph Theory and Machine Learning

Regardless of the neuroimaging modality, advancements of the group-level analysis methods have contributed to new understanding of how distributed networks throughout the brain are affected in epilepsy. Two relatively recent developments, graph theory analyses and machine learning, have provided particularly compelling new evidence and potential for better understanding of epilepsy as a network disorder.

Graph Theory

Graph theory metrics have increased our understanding of how brain networks are disrupted in epilepsy. To simplify several of the high-level mathematical concepts that comprise fundamental metrics of graph theory [160], such as centrality, small-worldness, and global efficiency, consider airport travel as a relatable model of transmission within a network. In order for passengers to travel from origin to destination, connecting flights between airports in this network must be made. Centrality, in this example, is an index of how many travel connections rely on a given airport of the network. Because there are a higher number of total flights made in or out of the Atlanta Hartsfield (ATL) airport, GA than the John F. Kennedy (JFK) airport, NY, the importance (or centrality) for the network is higher for ATL than for JFK. Thus, both of these airports form part of a network, yet they have different centralities or importance for the cohesiveness of this network. Alternatively, other graph theory metrics are a function of the entire network itself, such as small-world connectivity. For this example, imagine that instead of comparing airports to nodes of a network, we are comparing two different airlines (i.e., networks). Small-worldness, in this analogy, is scaled as a function of whether some airports connect mostly with smaller sub-networks that contain few connections to outside airports (high small-worldness), or whether connections are equally distributed across all airports (low small-worldness). Because Airline A has many flights with a terminal destination in the southeast that will connect through ATL (i.e., a module of hubs), while many flights with a terminal destination in the northeast will connect through JFK (i.e., another module of hubs), the modularity, or small-worldness, would be higher for Airline A. However, if Airline B offers many direct-flights to final destinations without connecting flights, the small-worldness for Airline B would be relatively low (and likely with very high in travel costs). Another example is global efficiency, which assesses the shortness of path length and connections within a network. Airline A most frequently offers tickets that will require the passenger to make two connecting flights with a total flight time of 11 h, while Airline B most frequently offers tickets with a direct-flight and a total flight time of only 2 h. Airline A, in this example, would be less efficient than Airline B based on the total number of flights and duration of the air travel. Application of graph theory metrics, as exemplified above, has brought a new approach to characterizing and assessing complex neural networks.

By applying graph theory analysis to characterize neural networks in epilepsy, resting-state connectivity and white matter tractography analyses have been used separately and sometimes combined [2]. Recent findings have shown changes in ipsilateral node centrality associated with TLE [161, 162]. Likewise, decreases in global efficiency and small-worldness are associated with both generalized [163] and focal [164, 165] epilepsies. Furthermore, centrality, small-worldness, and global efficiency measures have also shown early promise in the utility to predict surgical outcomes in anterior temporal lobectomy [166–168]. Accordingly, innovative applications of graph theory assessments to neuroimaging analyses provide a valuable extension to prior assessments and a more sophisticated characterization of whole-brain neural networks that will broaden our understanding of epilepsy as a network disorder.

Machine Learning Classifiers

Machine learning, as applied to neuroimaging, is a class of artificial intelligence methods that attempt to train computer-generated algorithms to cluster or classify sets of neuroimaging data [169]. Of particular interest to clinical diagnoses and research applications in epilepsy, machine learning classifiers hold significant potential for utilizing neuroimaging data to identify biomarkers of neurological and psychiatric disease states [170]. Within new emerging studies of epilepsy networks, machine learning techniques play an important role in identifying aberrant brain networks across the gamut of imaging modalities and can serve to aid in predicting surgical outcomes and future diagnostic and seizure treatment approaches [171]. For example, unsupervised

machine learning, which in contrast to supervised machine learning that includes a clinical diagnosis to train models, bypasses the notion of an a priori categorization and instead allows a data driven model to cluster datasets based on like and unlike components [172]. Unsupervised machine learning classifiers hold the potential for identifying distributed components of epileptic disorders forming patterns that were not previously understood, such as predictors of surgical outcomes [173], variability in dysplasia subtypes [29], and improvements in lesion detection via morphometric MRI post-processing (MAP) of MRI-negative patients [23, 174]. From a clinical and research perspective, increased widespread utilization and familiarity with machine learning techniques applied to whole-brain neuroimaging assessments will provide vital new understanding of epilepsy as a network disorder.

Imaging Mental Health Comorbidities in Epilepsies

In this review, we have so far highlighted some of the promising recent developments and advancements in human neuroimaging. In this section, we will discuss important future directions for these neuroimaging studies with two points of emphasis. First, from a neurotherapeutic perspective, assessment of the neurobiological basis of the bidirectional relationship between epilepsy and mental health comorbidities (i.e., mood, anxiety) can provide a better understanding of the functional network alterations associated with epilepsy and involved in seizure precipitates. Second, although temporal lobe epilepsy is at the forefront of human epilepsy research and should continue to be studied extensively, idiopathic generalized epilepsies (IGEs) and extra-temporal neocortical epilepsies (e.g., frontal lobe epilepsies) are under-investigated but can serve as valuable models for understanding both epilepsy and psychiatric conditions. Despite the synchrony and episodic nature of both mental health disorders and epilepsy [175], there is a paucity of studies that focus on their corresponding fluctuations [176].

Mental Health Comorbidities

The bidirectional relationship between mental health comorbidities and epilepsy constitutes a major health concern. Of the 70 million people with epilepsy worldwide [177], nearly 50% will develop mental health comorbidities and people with psychiatric disorders are more likely to develop epilepsy [7, 178]. Given that mood and anxiety disorders carry nearly a 30% lifetime prevalence rate [179], the need for better understanding of the neurobiological mechanisms that underlie the bidirectional relationship between mental health comorbidities and epilepsies extends far beyond the treatment of epilepsy alone. In fact, investigating the interplay between mental health comorbidities and epilepsies will provide guidance on how mental health symptom improvement impacts response to epilepsy treatment, and vice versa. Further, understanding the link between mental health symptoms and seizure control may shape the clinical management and future treatment studies of both entities.

The relationship between epilepsy and mental health comorbidities may arise from disruptions in the prefrontal cortex-hippocampal-amygdala (PFC-HC-AMY) network that produces symptoms of depression and anxiety due to a large degree of overlapping changes within these regions and their connectivity [8, 180]. In general, patients with poorly controlled epilepsy can predict subsequent seizure occurrence immediately after acute stress experience [181–183]. Behavioral stress management techniques like progressive muscle relaxation, biofeedback, and cognitive-behavioral therapy have been proposed as adjunct to seizure medications [184, 185] with their efficacy depending on whether they reduce perceived stress [186, 187]. Thus, an important area of future research is better understanding of this bidirectional relationship between mood, stress, and epilepsy. TLEs have a high rate of comorbid depression and anxiety [188] and are associated with disruption within the PFC-HC-AMY circuit underlying emotion processes [1, 73, 74, 183, 189]. Furthermore, psychiatric comorbidities and cognitive dysfunction in TLE are associated with volumetric AMY increases [190] and hippocampal sclerosis [191], which is common among TLEs but not necessarily mental health comorbidities. Consequently, abnormalities in neural transmission originating within HC-AMY regions induce broadly distributed network disruption, including PFC connectivity [176]. Extending the focus beyond discrete HC and AMY abnormalities underlying mental health comorbidities and epilepsy to fronto-limbic network dysfunction is consistent with recent shifts in emphasis from regional to network models among mental health comorbidities [3, 192]. Thus, a better understanding of disruptions in specific neural networks related to epilepsies and impaired inhibition of emotion responses will serve as a valuable model for better understanding of epilepsy as a network disorder.

Mental Health Comorbidities in Generalized Epilepsies

The vast majority of prior literature on the relationship between mental health comorbidities and epilepsies has assessed a locus of deficit arising from a specific epileptic focus (i.e., TLEs). Furthermore, TLEs typically have a relatively poor prognosis for treatment response [193]. Thus, TLEs may have limited potential as a model for assessing neurobiology linked to mental health comorbidities given a poor treatment response among HC-AMY

structural abnormalities and mental health symptom severity. IGEs constitute ~20% of all epilepsy diagnoses and include patients with absence, myoclonic, and generalized tonic–clonic seizures [194]. As IGEs are non-focal, seizure onset occurs over a large cortical and subcortical network that includes a thalamic hub, rather than a specific node, with rapid spread via a network of cortical and subcortical regions [195]. Thus, IGEs are classified by widespread cortical spike-and-wave discharges and seizures without a definite focal origin [105, 196]. Consequently, comorbid mental health pathophysiology in IGEs extends beyond the scope of disruptions in function and connectivity that arise from a specific epileptic focus [197, 198]. Mental health comorbidities are estimated to occur in up to 50% of adult patients with IGEs. Yet, IGEs have a relatively good prognosis and high remission rate with treatment (64–82%) [193]. IGEs are associated with decreased functional connectivity within medial PFC and limbic regions [109, 199–201], which correlates with increased seizure frequency [199]. Interestingly, dMRI studies have shown degradation within the uncinate fasciculus (PFC-AMY) and fornix (HC-hypothalamus) white matter pathways in patients with IGEs [202]. Further, IGEs are associated with broad disruptions in frontal lobe function and connectivity that may specifically affect emotion processes and inhibitory control that generalize broadly to depressive and anxiety mental health comorbidities [203, 204]. Despite the vast potential for utilizing IGEs as a model to understand changes in neural networks related to mental health comorbidity status, underlying links between IGEs and mental health comorbidities have received modest attention compared to vastly more commonly studied TLEs. Future research investigating disruptions of specific neural networks related to fluctuations in mental health states in IGE will serve as a valuable model for better understanding epilepsy as a network disorder.

Conclusion

Recent advancements in neuroimaging methods, including MRI, PET, MEG, and techniques discussed in this review such as graph theory and machine learning have opened new potential for better understanding of epilepsy as a network disorder. The techniques and methods reviewed are of particular importance for network models of epilepsy given they provide a variety of functional and structural measurements at a whole-brain global level. Utilizing these advanced techniques to assess mental health comorbidities in IGEs will drive forward the understanding of epilepsy as a network disorder. IGEs are an ideal model to assess particular changes in emotion processing and brain network connectivity that correspond to changes in comorbid mental health symptoms given that they have relatively high comorbidity and remission rates, and network pathophysiology that does not arise from a specific epileptic focus.

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