Resting-state functional connectivity in epilepsy: growing relevance for clinical decision making

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Purpose of review
Seizures produce dysfunctional, maladaptive networks, making functional connectivity an ideal technique for identifying complex brain effects of epilepsy. We review the current status of resting-state functional connectivity (rsFC) research, highlighting its potential added value to epilepsy surgery programs.

Recent findings
RsFC research has demonstrated that the brain impact of seizures goes beyond the epileptogenic zone, changing connectivity patterns in widespread cortical regions. There is evidence for abnormal connectivity, but the degree to which these represent adaptive or maladaptive plasticity responses is unclear. Empirical associations with cognitive performance and psychiatric symptoms have helped understand deleterious impacts of seizures outside the epileptogenic zone. Studies in the prediction of outcome suggest that there are identifiable presurgical patterns of functional connectivity associated with a greater likelihood of positive cognitive or seizure outcomes.

Summary
The role of rsFC remains limited in most clinical settings, but shows great promise for identifying epileptic circuits and foci, predicting outcomes following surgery, and explaining cognitive deficits and psychiatric symptoms of epilepsy. RsFC has demonstrated that even focal epilepsies constitute a network and brain systems disorder. By providing a tool to both identify and characterize the brain network impact of epileptiform activity, rsFC can make a strong contribution to presurgical algorithms in epilepsy.

Keywords
clinical diagnostic, epileptogenic networks, resting-state functional connectivity, surgical outcome, temporal lobe epilepsy

INTRODUCTION

In recent years, resting-state functional connectivity (rsFC) methods have been increasingly used to reveal the integrity of brain cognitive networks [1,2]. Functional connectivity has also been shown to be of value in determining the impact of epilepsy on brain activity and identifying the abnormal brain networks associated with seizures [3–6]. Seizures produce dysfunctional, maladaptive networks by linking brain areas randomly through seizure propagation and secondary epileptogenesis, making functional connectivity an ideal technique for both identifying aberrant network organization and synchrony, and capturing such change over the course of the disease or in response to treatment. Although it is not surprising that patients with generalized epilepsy display functional connectivity abnormalities involving areas outside the presumptive ictal generator and irritative zone, it is also clear that even focal epilepsy can result in functional connectivity changes outside the epileptogenic region. Beyond cognition, there is evidence that rsFC may be able to identify epileptic circuits, pointing to where seizures are placing their most significant burden. Identifying abnormal networks, particularly those pointing to established or emerging epileptogenic foci, will be of value to surgical algorithms, as multiple foci or bilateral epileptiform activity are associated with poorer seizure outcomes [7].

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KEY POINTS

- RsFC provides clear evidence that even focal epilepsies constitute neuronal network disorders involving abnormal organization or synchrony.
- RsFC may be a particularly valuable and efficient technique for investigating cognitive networks in patients with significant cognitive impairment.
- RsFC remains an immature technology in terms of its use for clinical prediction in the setting of epilepsy surgery, yet rsFC does show great promise for identifying epileptic circuits and foci, and predicting cognitive and clinical outcomes following surgery or other treatments.

We will review resting-state functional magnetic resonance imaging (fMRI) studies that provide functional connectivity evidence of epileptogenic networks or help explain the cognitive and psychiatric comorbidities associated with the disease. We also review empirical work evaluating the ability of rsFC to predict cognitive or clinical outcomes following surgery. RsFC remains an immature technology in terms of its clinical use. We will address the progress made so far, and comment on the potential added clinical value of functional connectivity data to epilepsy surgery programs.

RESTING-STATE FUNCTIONAL CONNECTIVITY ABNORMALITIES REVEAL EPILEPTOGENIC NETWORKS

Although it is readily known that generalized tonic–clonic seizures [8] can disrupt neural connectivity and cause dysfunction outside the region of ictal activity, such remote effects can also emerge from focal epilepsies [6,9,10]. The most common functional connectivity method for investigating resting-state networks in focal epilepsies has been the seed-based approach. Thus far most commonly applied to temporal lobe epilepsy (TLE), these studies have characterized the spatial/organizational changes within networks, relative to healthy participants. This approach has succeeded in showing that the abnormalities produced by TLE pathology are not limited to the epileptogenic region, but extend to widespread areas of the brain. In large part, because of this research, TLE is now widely viewed as a systems disorder with broadly disrupted networks [11]. However, literature remains mixed in its description of connectivity changes. Liao *et al.* [6] demonstrated altered connectivity in TLE, involving increased connections within the mesial temporal lobe (MTL) but decreased connectivity to extratemporal areas. Other studies showed the opposite, decreased functional connectivity within the epileptogenic temporal lobe and increased contralateral temporal functional connectivity when compared with controls [5]. Some have suggested that such rsFC measures could be a biomarker of epileptogenic zone localization [12,13] and help explain varied seizure semiology [14].

In examining right and left TLE group differences in functional connectivity, the epileptogenic MTL appears to impair heteromodal association regions in both hemispheres for both the groups [3,11,15]. Left TLE appears associated with more extensive network impairment than right TLE, also compared with healthy controls [3,16]. Morgan *et al.* [13] identified a specific region in the ventral lateral right thalamus, whose connectivity to the hippocampi separates left from right TLE patients. This suggests that rsFC across this network may be a potential indicator of TLE lateralization.

RsFC work [17] has shown that focal TLE, with no evidence of interictal activity outside the ictal temporal lobe, is associated with a strong inhibitory surround in the contralateral hemisphere (through anticorrelation, see Fig. 1). In contrast, TLE patients who display extratemporal interictal activity lack this surrounding activity. Thus, large regions of healthy cortex seem to respond even to focal seizures, providing adaptive inhibition, constraining epileptiform activity to the pathologic temporal lobe. This has clinical implications as loss of this anticorrelated signaling, in the setting of bilateral interictal electroencephalography activity, is a poor prognostic sign, indicating the loss of a beneficial inhibitory surround (see also [18]).

RsFC also shows promise for identifying the epileptogenic focus, noninvasively. Weaver *et al.* [18a] utilized a voxel-wise regional homogeneity measure to demonstrate that rsFC is significantly reduced in the area harboring the seizure focus (identified via electrocorticography, eCOG). In contrast, Stufflebeam *et al.* [19] described an rsFC increase in epileptogenic areas (identified by eCOG) (see Fig. 2). These studies had small samples and the data are discordant. Nonetheless, they make the point that rsFC may be a noninvasive source of corroborating data on seizure localization. Recent functional connectivity methods using a nonseed approach have reported a specific resting-state network in TLE involving the hippocampus and amygdala bilaterally, with this network absent in normal controls [20].

Age of seizure onset and illness duration are important factors potentially influencing brain connectivity, particularly as the disease process interacts with normal developmental changes. Evidence

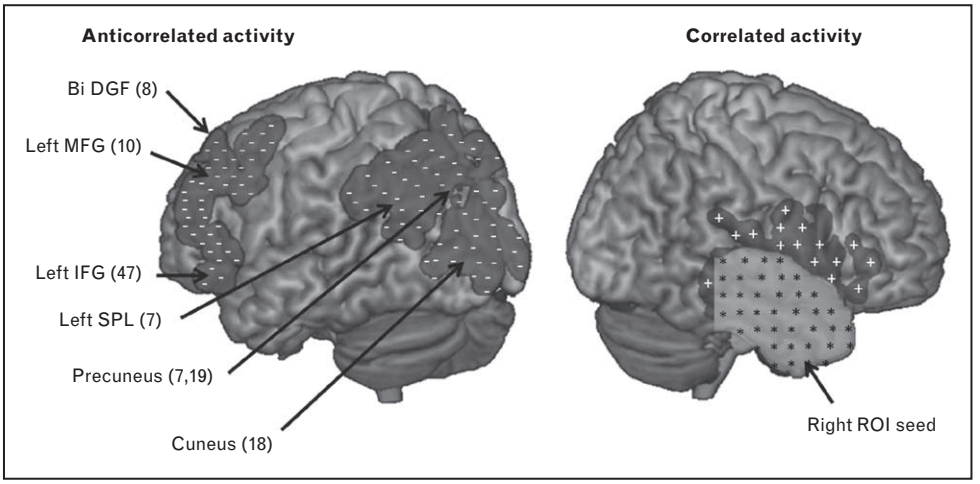

FIGURE 1. Positive (+) and negative (−) functional connectivity with the right temporal lobe region of interest (ROI) (*) in right unilateral temporal lobe epilepsy patients. DFG, medial part of superior frontal gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SPL, superior parietal lobule. Numbers in parentheses correspond to the Brodmann area. Adapted with permission from [17].

of altered functional organization varying with age of seizure onset has been demonstrated through rsFC [4,21,22]. A recent study by Morgan *et al.* [21] showed that there is an initial disruption of cross-hemispheric networks and an increase in static functional connectivity in the ipsilateral temporal network accompanying the onset of TLE seizures. As seizures progress over years, functional connectivity declines within both a static ipsilateral network and a dynamic midline (e.g., cingulate) network; however, these networks appear to be independent of each other. This implies a gradual breakdown of ictal onset and early propagation networks involving the ipsilateral hippocampus and temporal lobe as these become more synchronous with the regions (or networks) responsible for secondary seizure generalization. Such data are concordant with the notion that longer illness duration is associated with stronger functional connectivity abnormalities. There are some data showing that earlier age of onset may be associated with compensatory mechanisms in networks, with type of pathology also playing a mediating role [23]. There is important work to be done to understand the degree to which these factors interact with normal developmental processes of neuroplasticity to heighten the negative effect, or confer protection, from the impact of seizures.

RESTING-STATE FUNCTIONAL CONNECTIVITY REVEALS NEUROCOGNITIVE ABNORMALITIES

RsFC provides a very different lens to view the well known cognitive dysfunction associated with epilepsy. FMRI studies have demonstrated the deleterious impact of seizures on the spatial distribution of task-driven activation [24–26]. RsFC has shown that there are altered network organization patterns of relevance to cognition, with the bulk of the data involving TLE. Although the exact behavioral and cognitive implications of rsFC are debated, it is clear that abnormalities in rsFC are observed in a variety of neurologic diseases such as Alzheimer's [27,28]. [The neurobiologic basis of functional connectivity remains unclear (e.g., what does a negative correlation represent?), as does the relation between functional connectivity and brain structure. Significant processing and statistical analysis issues exist (e.g., proper thresholding of the data). Hence, there remain problems in making behavioral or cognitive interpretations when abnormalities in network organization and synchrony are observed. At its core, FC data can only be said to reflect the synchrony (positive or negative) of two or more brain regions.] Nonetheless, our current knowledge about the consequences of abnormal network organization and synchrony on overall cognition remains very limited.

RsFC provides a means of characterizing functional impairments associated not just with the epileptogenic region but with the broader cortices affected by seizure spread or epileptogenesis (e.g., the so-called extratemporal deficits of TLE) [9,29]. Resting-state studies have described functional connectivity abnormalities in several cognitive networks in epilepsy such as the well known default-mode network (DMN) [30,31], and its subdivisions [32], in addition to attentional [33], language [34,35], and visuospatial working memory [36] networks putting at risk a wide range of neurocognitive and affective functions.

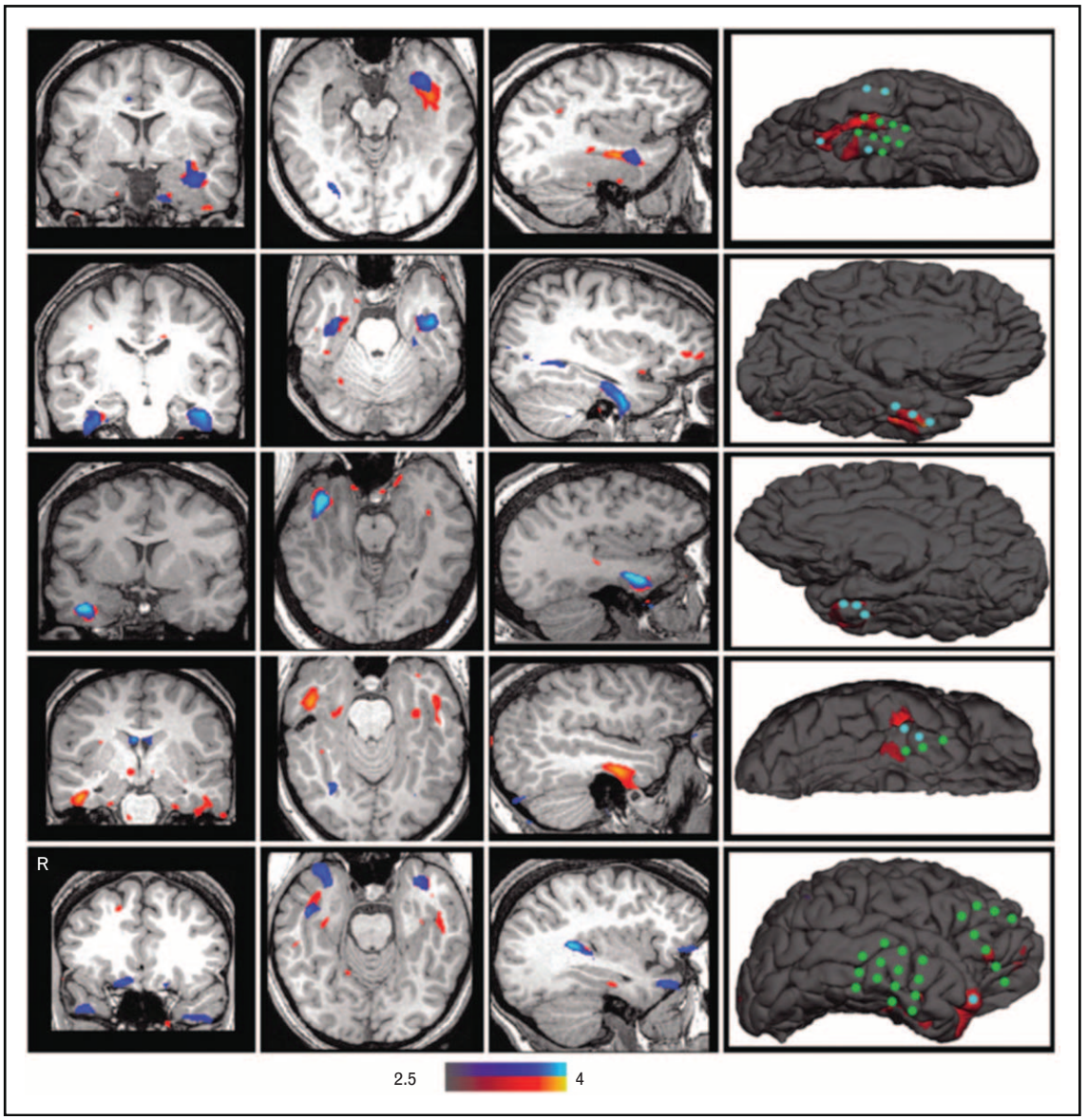

FIGURE 2. Epileptic foci localized based on degree of functional connectivity. Each row shows the functional abnormality scores of one patient. Remote (blue) and local (red) functional connectivity differences revealing abnormal cortex are displayed, both representing *Z*-scores compared with a normative sample of 300 healthy individuals. The first three columns illustrate the functional abnormality in three orthogonal views. In the fourth column, the functional abnormality scores (remote and local combined) were rendered on the surface and compared with intraEEG findings. The blue circles in the map indicate the intraEEG electrodes corresponding to seizure onset. The green circles indicate the electrodes corresponding to frequent interictal discharges. Adapted with permission from Stufflebeam *et al.* [19]. EEG, electroencephalography.

Importantly, changes in network organization and functional connectivity appear related to actual cognitive performance. Wagner *et al.* [37] showed that stronger functional connectivity between the hippocampus and neocortical regions was associated with better performance in TLE during a verbal memory task. Other work also demonstrates that functional connectivity impairments between the MTL and extratemporal regions in the DMN are related to episodic memory performance [3], with the response in right TLE more adaptive and compensatory. This suggests that cognitive reorganization varies for right and left TLE, and implies hemispheric dominance that may be an important factor mediating compensation.

McCormick *et al.* [38▪] showed that a close dialog between both MTLs and the posterior components of the DMN is required to express episodic memory abilities (see Fig. 3). Functional connectivity studies of the language deficits known to be present in TLE have emerged (for review of language deficits see [39,40]). Pravata *et al.* [35] showed that for both left

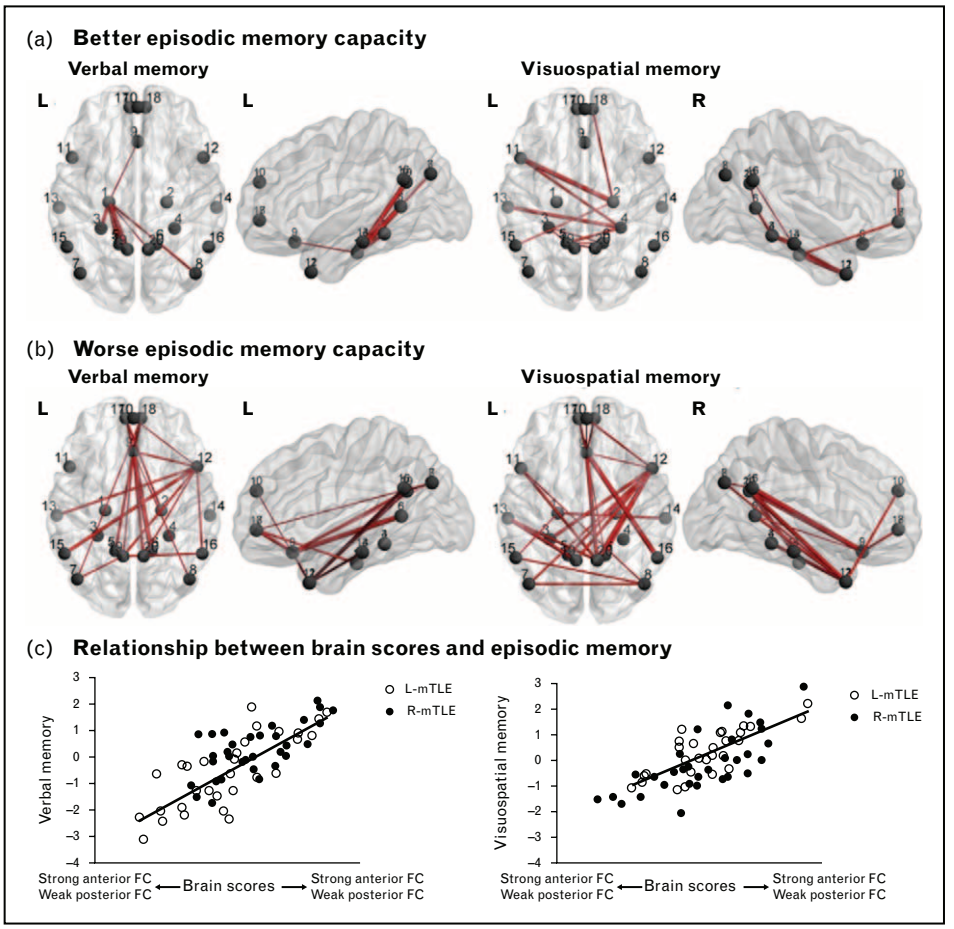

FIGURE 3. Functional connectivity alterations of the default-mode network indicate episodic memory capacity in mesial temporal lobe epilepsy (TLE). (a) Networks that are associated with better episodic memory capacity and (b) Networks that are associated with worse episodic memory capacity in patients with left TLE and right TLE. Significant connections are displayed in red. The line thickness indicates the bootstrap ratio value. (c) Relation between brain scores (i.e., how well a participant expresses the above networks) and individual episodic memory capacity. For example, patients with higher brain scores have stronger connectivity within the network associated with better verbal memory and weaker connectivity within the pattern associated with worse verbal memory. Adapted with permission from McCormick *et al.* [38▪].

and right hemisphere epilepsy, functional connectivity was significantly reduced within the left (dominant) and between the two hemispheres. Other language functional connectivity work has demonstrated the power of rsFC to predict language laterality (e.g., strong versus weak left hemisphere laterality) in TLE patients [41], indicating that rsFC data may potentially be used on its own to verify the strength of hemispheric dominance.

What is particularly interesting about functional connectivity-based methods is that they can demonstrate group differences in network activity even when the groups do not differ in cognitive performance [23,42]. For instance, right and left TLE groups show distinct patterns of hippocampal functional connectivity during visuospatial working memory although recall accuracy is the same in each group [23]. Accordingly, functional connectivity may be a means of identifying abnormal or unique brain networks implementing a task [43], information that cannot be discerned at the level of behavior through such techniques as neuropsychological testing.

RsFC also provides a rich source of information on connections that may represent forms of functional compensation in the face of neurologic injury or disease. In fact, compensation is one of the key frameworks used by researchers to interpret functional connectivity results, but only a few studies have examined correlations with cognitive performance, a needed ingredient in order to claim compensation [3,5,38▪,44▪]. Several studies in TLE have presented evidence to suggest the presence of functional compensatory mechanisms in the contralateral/nonictal hemisphere [3,5]. For instance, Bettus *et al.* [5] demonstrated a positive relation between the functional connectivity of the nonepileptogenic

hippocampus and a working memory measure in left TLE, indicating the healthy hemisphere may be playing a compensatory role to support cognition (for other potential compensatory findings in memory, see [3,36]).

RsFC may be a particularly efficient technique for investigating cognitive networks in patients with significant cognitive impairment as rsFC does not depend on task engagement and is unaffected by confounds such as varying performance levels. Tie *et al.* [45] makes this point by showing that language-related activations can be derived from an individual's rsFC map by comparing it to a normative rsFC template.

FUNCTIONAL CONNECTIVITY ABNORMALITIES AND PSYCHIATRIC SYMPTOMS

RsFC has also been used to study psychiatric disorder. Up to 20–55% of TLE patients suffer from depression [46–48]. Indeed, studies have strongly supported the notion that depression in TLE is caused by pathological epileptic activity [49]. Given the major role of the amygdala in the processing of fear and related emotions [50,51], this structure has been used to explain comorbid emotional conditions (see review of [52]). The amygdala has been described as hyperactive in left TLE patients with mood disturbance [53,54]. RsFC studies have provided evidence of connectivity abnormalities with the amygdala contralateral to the epileptogenic zone [5,55–57]. Chen *et al.* [58] described decreased functional connectivity within a prefrontal-limbic system in TLE patients who were depressed, but increased functional connectivity within the limbic system and angular gyrus, indicating that interactions among networks may be crucial to the appearance of depressive symptoms. Kemmotsu *et al.* [56,59] demonstrated that hippocampal–anterior prefrontal functional connectivity was a stronger contributor to depressive symptoms in left compared with right TLE, and right amygdala functional connectivity correlated with depressive symptoms in both the groups (a positive correlation in the left and negative in the right TLE).

These results highlighted how TLE alters functional connectivity emerging from the limbic system, and suggest that right versus left hemisphere pathology may have a different impact on emotion-related networks and symptoms, perhaps related to the greater role the right hemisphere plays in emotion dysregulation [60]. The field awaits a more complete functional connectivity network analysis of emotion and psychiatric processing in epilepsy, TLE in particular.

PRESURGERY FUNCTIONAL CONNECTIVITY: ADDED VALUE AS A PREDICTOR OF COGNITIVE AND SEIZURE OUTCOMES

Although the prediction of cognitive or seizure outcomes is a major clinical goal, there is, to date, a limited number of studies testing the predictive power of presurgery rsFC. Regarding neurocognitive outcome, McCormick *et al.* [44▪] provided the first evidence that presurgery rsFC can predict episodic

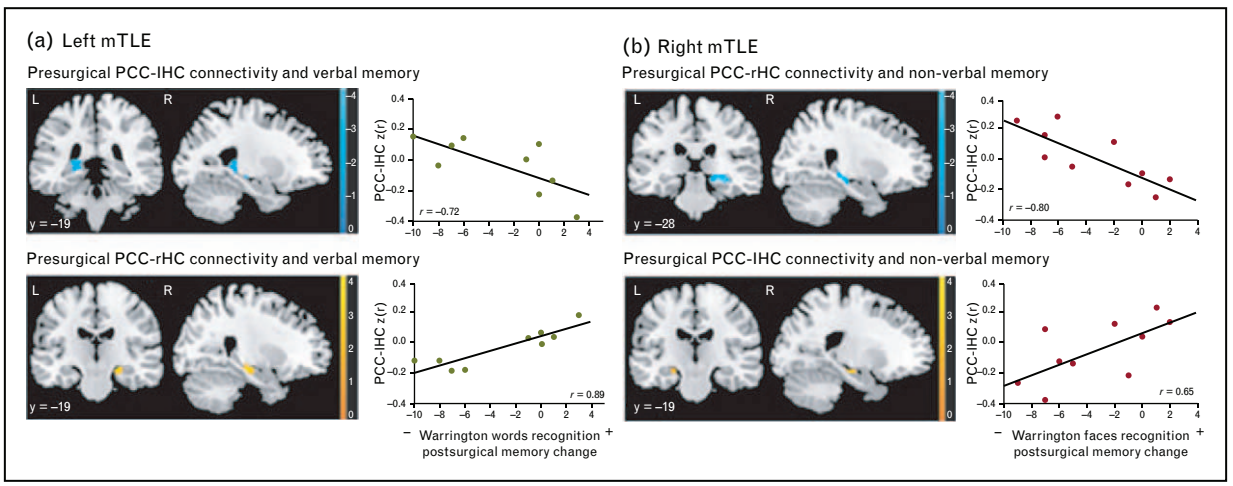

FIGURE 4. Prediction of postsurgical memory change. The upper row displays negative correlations between posterior cingulum (PCC) connectivity to the epileptogenic hippocampus and postsurgical memory change for left (a) and right (b) mesial temporal lobe epilepsy (mTLE) patients. The lower row displays positive correlations between PCC connectivity to the contralateral hippocampus and postsurgical memory change for left (a) and right (b) mTLE patients. Adapted with permission from McCormick *et al.* [44▪].

memory outcome in TLE patients after anterior temporal lobectomy. They found that stronger functional connectivity between the epileptogenic hippocampus and posterior cingulum was associated with greater postsurgical memory decline, whereas stronger functional connectivity between the contralateral hippocampus and posterior cingulum was associated with less memory decline (see Fig. 4). In contrast, to date, the prediction of language changes postsurgery by rsFC appears less optimistic. Pravata *et al.* [61] did not find any correlation between functional connectivity within a language network and postsurgery verbal intelligence quotient change. However, this study was low powered ($n = 5$) and relationships to more specific language functions (e.g., semantic fluency and object naming) were not investigated. Negishi *et al.* [62] were among the first to explore seizure outcome prediction after resective surgery. They utilized both rsFC and surface electroencephalography. Seizure recurrence was associated with a less lateralized functional connectivity pattern than seizure freedom, suggesting that high laterality (i.e., stronger functional connectivity in the ictal hemisphere) predicted better outcome. More recently, Xu *et al.* [63] found that compared with poor outcomes, a successful surgical outcome in TLE was associated with larger interhemispheric homotopic functional connectivity differences. Unfortunately, based solely on rsFC, the number of studies investigating the prediction of seizure outcome following anterior temporal lobectomy remains small. Thus, the above results need to be taken with caution.

CONCLUSION

RsFC analyses have clearly demonstrated that even focal epilepsies are a brain network and system disorder. Characterizing the nature of disease network alterations will be necessary before we can effectively explain the multiple cognitive and behavioral effects of seizures, and make headway toward the prediction of cognitive and seizure outcomes following surgery (or other treatments). RsFC provides clear evidence for abnormal connectivity, but the degree to which these represent adaptive or maladaptive plasticity responses is unclear. Empirical associations between rsFC and cognitive performance or psychiatric symptoms have helped us understand the deleterious impact of seizures outside the epileptogenic zone. There are numerous indications that compensatory responses involve recruitment of the nonictal hemisphere. Initial studies in the prediction of outcome suggest that there are identifiable presurgical patterns of functional connectivity associated with a greater likelihood of positive cognitive or seizure outcomes. Important theoretical and empirical links need to be drawn between fMRI-based functional connectivity and functional connectivity data emerging from other methodologies such as eCOG, so as to understand neural synchrony and organization at the multiple temporal and spatial time scales at which brain networks truly operate. The findings reviewed here provide grounds for optimism that rsFC can become an important biomarker for assessing the brain network changes set in motion by seizures. The goal is to test rsFC for all its potential added value to existing clinical algorithms for surgery and other epilepsy treatments.

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Conflicts of interest

There are no conflicts of interest.

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