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Review

Functional MRI-based connectivity analysis: A promising tool for the investigation of the pathophysiology and comorbidity of epilepsy

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ABSTRACT

Epilepsy has been recognized as a brain network disorder. Therefore, functional MRI (fMRI)-based connectivity is an ideal technique for exploring the complex effects of epilepsy on the brain. Functional connectivity studies have provided insights into the physiopathogenesis of the epileptic network underlying focal epilepsies, genetic generalized epilepsy, and specific epileptic syndromes. An increasing number of studies have focused on the deleterious effects of epilepsy on other brain networks to help to explain cognitive deficits and psychiatric symptoms. Anti-epileptic treatment studies have yielded information about the side effects and the restoration of functional abnormalities after using the drug. Researchers who have examined predictors of surgical outcomes have suggested that there might be identifiable pre-surgical patterns of functional connectivity that are associated with a greater likelihood of positive cognitive or seizure outcomes. However, knowledge regarding the role of fMRI connectivity remains limited in clinical settings. Further validation through invasive investigations and follow-up studies is required for its reliable application in the clinical management of individual patients.

1. Introduction

Epilepsy has been conceptualized recently as a disorder involving networks, rather than single sources of pathology in the human brain [1]. The notion of a brain network disorder makes functional connectivity an ideal technique in the study of the pathophysiologies of epilepsy and its comorbidities associated with psychiatric and cognitive complications [2]. Functional connectivity measures the statistical dependency between signals (*e.g.*, electromagnetic or haemodynamic signals) recorded in different brain regions. Functional magnetic resonance imaging (fMRI) detects blood oxygen level-dependent (BOLD) signal changes, which reflect metabolically active brain areas not only in relation to a specific physiological or pathological event but also in resting-state conditions (resting-state fMRI). We will review current fMRI studies that provide functional connectivity evidence of epileptogenic network or the psychiatric and cognitive complications. Given that the clinical applications of fMRI connectivity are still in the early stages, we will discuss the potential clinical value.

2. fMRI connectivity and pathophysiology

2.1. Focal epilepsies

Functional connectivity researchers increasingly have suggested that focal epilepsies are related to abnormal brain function within an epileptic network, rather than dysfunction in a single epileptogenic region.

2.1.1. Temporal lobe epilepsy

The majority of studies examining functional connectivity in focal epilepsies have focused on temporal lobe epilepsy (TLE), which is the most common focal epilepsy in adults. The most frequently used method to analyse functional connectivity to investigate epileptic networks in TLE has been the "seed-based approach". This approach involves the investigation of the relationships between a set of predefined, relevant brain regions (seeds) and the rest of the brain. Functional connectivity researchers have confirmed the involvement of widespread brain networks in TLE [3]. Regarding the different seizure semiology across TLE patients, impaired connectivity has been detected within mesiotemporal areas ipsilateral to the seizure focus, despite mixed descriptions of its change. Bettus et al. reported that decreased functional connectivity in the ipsilateral hemisphere co-occurs with increase in contralateral mesiotemporal networks [4,5]. However, Liao et al. found altered

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connectivity in TLE, involving increased connections within the mesial temporal lobe (MTL) but decreased connectivity to extra-temporal areas [6]. These mixed findings of altered functional connectivity within temporo-limbic circuits in TLE, which helps to explain varied seizure semiology. Moreover, functional connectivity could be a predictor of TLE lateralization. Left TLE seems to display more extensive connectivity alterations than right TLE, both in the epileptogenic hemisphere and in contralateral limbic areas [7]. Functional connectivity between some regions in the ventral lateral nucleus of the right thalamus and the hippocampus distinguishes left TLE patients from right TLE patients [8].

Tracy et al. found that TLE patients who display extratemporal interictal activity lack strong surround inhibition of brain activity in the contralateral hemisphere. Such inhibition may be adaptive by constraining epileptiform activity to the pathological temporal lobe [9]. This finding may explain the poor prognosis of TLE patients with bilateral interictal activity, as they might lack beneficial surround inhibition in the brain functional network [9]. Furthermore, functional connectivity may be a noninvasive tool for identifying seizure localization. For scalp-EEG monitoring in focal epilepsy patients, a particular distribution of electrical potentials recorded on the scalp can be explained by the activity of infinite different configurations of intracranial current sources. Consequently, reconstructing the current sources originating from the scalp EEG measurements is a well-known, ill-posed problem with no one solution. The development of simultaneous EEG and fMRI allows for the synchronic study of electrographic events and haemodynamic correlates to localize and track the evolution of activity, despite their operating at vastly different temporal resolutions. Recently, researchers reported that the overlap between hyperperfusion or subtraction ictal-SPECT coregistered to MRI and positive BOLD responses on EEG-fMRI [10]. In addition, the overlap between hypoperfusion and negative BOLD responses within the same network suggests good concordance between the irritative zone and the seizure onset zone [10]. Scholars have also proposed an independent component analysis of functional connectivity based on EEG-fMRI and a variety of classifiers that exclusively detects a single map related to interictal epileptic brain activity [11]. This method yields functional connectivity maps that correctly identify the epileptogenic zone in several EEG-negative cases while simultaneously maintaining high specificity (92%).

2.1.2. Frontal lobe epilepsy

Frontal lobe epilepsy (FLE) is the second most common form of focal epilepsy [1]. Motor symptoms occur during the ictal period in FLE patients [12]. Patients exhibit deficits in motor control, coordination, and planning during the interictal period [12]. Woodward et al. found that patients with FLE who experienced a recent seizure relied more on the sensorimotor cortex of the contralateral hemisphere during finger-tapping and coordination tasks compared to those with lower seizure frequency, as evidenced by fMRI [13]. In addition, researchers have reported that patients with FLE exhibit decreased connectivity within the motor network in association with number of lifetime seizures [14]. These studies had small sample sizes and divergent data. Nonetheless, they described the functional cortical motor organization in FLE patients. In fMRI study, during a memory task, 32 patients with drug-resistant FLE showed recruitment of wider areas, particularly in the contralateral frontal lobe, which suggested that interhemispheric functional reorganization is effective in maintaining the memory function in FLE patients [15].

2.2. Genetic generalized epilepsies

Genetic generalized epilepsies (GGE), including absence seizures (AS), myoclonic seizures (MS), and generalized tonic–clonicseizures (GTCS), account for approximately 20% of epilepsy diagnoses [1]. Thalamocortical dysfunction is considered to be the major mechanism of GGE. *In vitro* and *in vivo* animal studies of thalamocortical circuitry have clearly established the underlying cellular mechanisms of spike-and-wave discharge [16]. However, it is obvious that clinical concomitants that are necessary for establishing whether a neuronal firing pattern in a slice can be identified as epileptic cannot be studied in slices. Therefore, a more definitive answer regarding the generalized epileptic neuronal firing patterns awaited verification in a validated genetic model *in vivo* or in patients. The fMRI functional connectivity method enabled the translation of animal models of seizure generation to humans, provided a map of the neural networks needed for seizure generation, and demonstrated ictal and interictal disturbances in normal physiological networks.

2.2.1. Absence epilepsy

EEG-fMRI has become the dominant means of studying the functional pathophysiology of generalized spike and wave discharges in absence epilepsy. Carney et al. described the “core” network that is crucial for the generation of spike-and-wave discharges (GSWD) in AS [17]. This network includes the thalamus, default mode network (DMN) and striatum, predominantly the caudate nuclei. The DMN is involved in internalized cognitive activity, such as random thought and the free association of ideas and memories [18]. Blumenfeld proposed a network inhibition hypothesis in which they associated the inhibition of sub-cortical activating systems with awareness loss during seizures through disruptions in their interactions with the DMN [19]. The evidence of early change in the BOLD signal in the DMN suggests that either activity in the DMN initiates the GSWD in AS or the DMN must be in a certain state to permit or facilitate the occurrence of epileptiform events [20]. The observation that AS often occurs during times of fatigue or rest, when the DMN is engaged, supports this notion. Furthermore, decreases in resting-state functional connectivity have been demonstrated in the DMN in patients with childhood absence epilepsy (CAE) compared to controls, even during resting interictal durations without interictal epileptic discharges [21]. In addition to the DMN, the thalamus has a central role in models of AS generation, given its role as a relay station for information transfer in the brain due to a strong reciprocal connection to the cortex. In EEG-fMRI studies [17,20], a robust positive thalamic BOLD response has been consistently associated with AS and the GSWD. Frontal lobe cortex abnormality is also a consistent finding in EEG-fMRI studies [22]. Killory et al. used an attention task to describe a frontal lobe network and assessed its functional connectivity to other brain regions. They found that children with CAE had impaired frontal lobe functional connectivity within the attention network compared to controls, providing the anatomical and functional bases for impaired interictal attention [23]. An abnormal increase in resting-state functional connectivity was identified in the orbitofrontal cortex in CAE, which implied an altered resting-state network in the frontal lobe cortex [24].

2.2.2. Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy (JME) is characterized by myoclonic jerks, generalized tonic–clonic seizures, and, less frequently, AS. Thalamocortical dysfunction is considered to be the major mechanism of JME as well as for other IGE syndromes. However, the development of functional connectivity techniques has allowed the identification of subtle functional abnormalities, providing a means to elucidate the underlying mechanisms of JME and the relative contribution of focal *versus* generalized dysfunction. In one recent study involving a working memory paradigm [25], the authors also described increased functional connectivity

between the motor system and areas of higher cognitive functions within the frontal and the parietal lobes. Precipitation of myoclonic jerks during cognitive tasks is a known clinical feature in some JME patients [12]. Therefore, the increased functional connectivity was interpreted as a possible mechanism for seizures that are triggered by cognitive effort [26]. The abnormal motor cortex co-activation during a working memory task may represent the functional correlate of this mechanism. Valproic acid (VPA), the JME treatment of choice, has a beneficial effect. Abnormal left motor cortex co-activation is correlated negatively with an increasing daily VPA dose, implying a normalization of function and possibly reflecting the positive effect of VPA on controlling myoclonic jerks [25].

2.3. Specific epileptic syndromes

Functional connectivity based on EEG-fMRI also sheds light on mechanisms underlying specific epileptic syndromes, which are age-dependent and in which epileptic discharges are abundant and less localized. The idiopathic focal epilepsies of childhood comprise a broad spectrum of phenotypes, ranging from rolandic epilepsy (RE) to more severe seizure disorders, such as atypical benign partial epilepsy (ABPE), continuous spikes and waves during slow sleep (CSWS), and Landau–Kleffner syndrome (LKS) [27]. The EEG-fMRI results underscore the notion that idiopathic focal epilepsies of childhood form a continuum of different overlapping phenotypes, whereas RE is characterized by focal BOLD signal changes in the area of the spike field [28]. Patients with ABPE [29] and CSWS [30] showed focal BOLD signal changes in both the area of the spike field and distant cortical and subcortical areas. Patients with RE did not show thalamus involvement in the EEG-fMRI study [28]. Thalamus involvement has been observed in patients with both CSWS [30] and ABPE [29]. It seems likely that the thalamus plays an important role in the spectrum of idiopathic focal epilepsies of childhood. Avanzini et al. proposed the term “system epilepsy” to support the hypothesis that idiopathic focal epilepsies of childhood are characterized by varying degrees of dysfunction within the somatosensory network [31]. Consequently, it can be suggested that more structures of the somatosensory network and the thalamus become involved with increasing severity of idiopathic focal childhood epilepsies.

Several studies on Lennox–Gastaut syndrome have shown functional alteration involvement of the brainstem, thalamus, and basal ganglia during paroxysmal fast activity and slow spike-and-wave discharges, which underlies the importance of cortical–subcortical networks in this syndrome [32]. A study involving 13 patients with myoclonic astatic epilepsy showed that GSWDs are related not only to a thalamocortical network that is commonly found in GGE but also to brain areas associated with motor function [33]. This finding suggests that the involvement of these structures may predispose patients to the typical myoclonic jerks observed in this syndrome [33].

A study of 4 patients with eyelid myoclonia with absences (EMA) showed no GSWD-related thalamic activation. The authors found that the distribution of activation associated with ictal epileptic discharges was wider and the distribution of deactivation was closer to anterior frontal lobe, parietal area, and cingulate gyrus compared with the BOLD change linked with interictal epileptic discharges. These results imply that the combination of different patterns of activation with a consistent pattern of deactivations (“default” pattern) in patients with EMA may predict different states of consciousness in response to ictal and interictal epileptic discharges [34].

All these findings indicate that each specific syndrome has a particular resting-state physiological functional network underlying the discharges and specific semiology.

3. fMRI connectivity and neurocognitive and psychiatric comorbidities

fMRI connectivity analysis can be utilized to investigate the interaction between the epileptic network and neurocognitive networks underlying neuropsychiatric comorbidities in patients with epilepsy. The majority of fMRI researchers have focused on the effect of TLE on resting-state networks. This effect has important implications for understanding why TLE often is accompanied by higher-order brain function impairments that are dependent on the coordinated activity of multiple brain regions. As many as 20%–55% of TLE patients suffer from depression [35]. Alterations in the fronto-limbic network in a group of TLE patients with depressive symptoms were observed in a functional connectivity study [36]. In another study, the authors demonstrated that hippocampal–anterior prefrontal functional connectivity contributed strongly to depressive symptoms in a left TLE group compared to a right TLE group and that right amygdala functional connectivity was correlated with depressive symptoms in both groups [37]. These results suggest that right hemisphere pathology may have a different impact on emotion-related networks and symptoms than left hemisphere pathology, possibly related to the greater role that the right hemisphere plays in emotion dysregulation. In TLE, epileptic activity affects normal left hemisphere language organization [38]. In language-paradigm fMRI studies [39,40], researchers investigated the language network reorganization in patients with left TLE, revealing a shift towards the right hemisphere. In a combined language task and rest-state fMRI study [41], it was found that reduced connectivity in left TLE may reflect a disturbance of the language network during resting state and may be related to subtle language difficulties in patients. Memory decline is a major concern for people with epilepsy and their families, with TLE being a major risk factor [42]. Voets et al. described a loss of functional connectivity between bilateral mesial temporal lobes, occipital and left orbitofrontal regions involved in memory processing in patients with left TLE [43]. In another functional connectivity study combined with task-based and resting-state fMRI [44], it was found that altered signalling during task performance and aberrant resting fMRI connectivity within anterior and posterior hippocampal-cortical networks associated with memory decline distinguished memory-intact patients from memory-impaired patients. In a resting-state fMRI study investigating short-term and long-term memory in TLE, researchers reported that thalamo-temporal functional connectivity reflected long-term memory performance and predicted short-term memory performance [45]. Furthermore, several authors have explained the compensatory functional connectivity in the contralateral hemisphere for memory performance in TLE [4,7]. Doucet et al. found that the functional connectivity between left nonpathological medial temporal lobe and medial frontal cortex correlated with non-verbal memory in right TLE patients, suggesting potential adaptive changes preserve this memory function [7]. In patients with JME, neuropsychological researchers have reported subtle frontal dysfunction characterized by social immaturity, impulsivity, and impatience [12]. The reduced functional connectivity within the prefrontal cortex found in patients with JME may be the basis for impaired frontal lobe functioning [46].

Functional connectivity studies based on EEG-fMRI were conducted to determine the influence of interictal epileptic activity on determined functional networks. The effect of interictal discharges on neurocognitive development in children with drug-resistant focal epilepsies has been studied using fMRI in combination with MEG (acquired separately) [47]. Results demonstrated that greater vulnerability to interictal discharges is associated with less resting-state functional connectivity and

poorer neurocognitive outcomes. Xiao et al. investigated the transient effects of interictal centrotemporal spikes on functional brain networks that are responsible for behaviour, language, and cognition in rolandic epilepsy [48]. They stated that abnormal network connectivity may contribute to long-term learning risk, despite good seizure control. EEG-fMRI studies also revealed extensive decreases in intrinsic functional connectivity related to attention and higher cognitive processes during the GSWD in patients with AS [49,50].

4. fMRI connectivity and its potential value in clinical decision making

fMRI connectivity studies also allow for the prediction of treatment or surgery outcomes. Several task-fMRI studies revealed that topiramate reduced task-related actions in the language network, suggesting that topiramate impairs cognitive processing during language function [51,52]. A retrospective study on TLE patients treated with or without levetiracetam indicated that the alteration in working memory networks was restored by levetiracetam treatment, highlighting the effect of the antiepileptic drug on functional connectivity [53]. In an examination of seizure outcome prediction after resective surgery, Negishi et al. utilized fMRI connectivity and scalp-EEG and suggested that seizure recurrence was associated with a less lateralized functional connectivity pattern than seizure freedom, showing that high laterality predicts better outcomes [54]. In a recent study, these authors combined functional connectivity and intracranial EEG to predict the seizure onset zone more effectively, which may improve surgery outcomes [55].

Despite the 80% success rate of anterior temporal lobe resection (ATLR), memory decrements are the main neurocognitive complication in TLE patients after surgery [56]. In a longitudinal fMRI study in TLE patients after ATLR, researchers 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 [57]. Sidhu et al. showed that fMRI activations in both the frontal and the temporal lobes are involved in successful verbal memory formation, suggesting that activations outside the temporal lobe could predict verbal memory decline after surgery [58]. A subsequent longitudinal study of the same group of patients suggested that postoperative changes occur in the memory-encoding network in TLE patients [59]. Further, compensatory contralateral posterior hippocampal reorganization initially occurred as many as 3 months after surgery, but the efficient reorganization begins 12 months after surgery [59]. This finding indicates that the contralateral hippocampus contributes to memory recovery one year after surgery. In an investigation of language outcomes after resective surgery, Bonelli et al. showed that preoperative left middle frontal activation for verbal fluency predicted naming decline in left TLE after ATLR and ipsilateral recruitment involving the posterior hippocampal remnant is important for maintaining language [60].

5. Conclusion

Functional MRI connectivity studies have provided invaluable insights into the multifocal aspect of the neuronal network underlying epilepsy. The procedure shows great promise for identifying epileptic circuits and foci; explaining the cognitive deficits and psychiatric symptoms of epilepsy; and predicting memory deficits after surgery. Despite the progress to date, the utility of functional connectivity remains limited in most clinical settings. The application of functional connectivity for diagnostic or prognostic purposes requires further validation *via* invasive studies and adequate follow-up investigations before it can be applied reliably to the clinical management of individual patients.

Conflict of interest statement

None of the authors have any conflicts of interests to disclose.

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