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·Review·

Resting-state fMRI studies in epilepsy

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Abstract: Epilepsy is a disease characterized by abnormal spontaneous activity in the brain. Resting-state functional magnetic resonance imaging (RS-fMRI) is a powerful technique for exploring this activity. With good spatial and temporal resolution, RS-fMRI is a promising approach for accurate localization of the focus of seizure activity. Although simultaneous electroencephalogram-fMRI has been performed with patients in the resting state, most studies focused on activation. This mini-review focuses on RS-fMRI alone, including its computational methods and its application to epilepsy.

Keywords: resting-state fMRI; epilepsy; localization; network

1 Introduction

Epilepsy is a common brain disease characterized by recurrent and spontaneous seizures due to abnormal and excessive synchronization of neuronal activity. Surgical intervention for refractory epilepsy depends upon accurate localization of the epileptic focus, which is critical for resection and deep brain stimulation. Functional neuroimaging techniques are becoming increasingly important in the presurgical localization of epileptogenic foci.

The scalp electroencephalogram (EEG) remains the gold standard for the diagnosis of epilepsy. One of the shortcomings of EEG is its low spatial resolution, because scalp electrodes are insufficiently sensitive to deep patterns of activity. This greatly limits its role in epileptic focus localization[1,2]. Positron emission tomography (PET)[3] has been used to evaluate the local glucose metabolism and single-photon emission computed tomography (SPECT)[4] to assess the perfusion of epileptogenic foci, but they both use radioactivity and do not provide dynamic signal changes. Magnetoencephalography (MEG) has a temporal resolution similar to that of EEG. But one major limitation of MEG is its low sensitivity to deep brain activity. Although it has been used to detect neocortical spike discharges[5,6], accurate localization of the epileptic focus is still a problem.

Resting-state functional magnetic resonance imaging (RS-fMRI) has been widely used in patient studies since the first report by Biswal and colleagues[7], especially in epilepsy studies. Two main techniques of RS-fMRI are arterial spin labeling (ASL) and blood oxygen level-dependent (BOLD) signaling. ASL-fMRI is a noninvasive technique for the measurement of cerebral blood flow (CBF). One study found that in epilepsy the CBF in the ipsilateral mesial temporal lobe decreases[8]. However, ASL-fMRI is much less commonly used than BOLD-fMRI. One possible reason is the low ASL-fMRI signal-to-noise ratio. Another is that the time-course analysis of ASL data is challenging due to technical limitations, e.g., lower sampling rate (usually 4 s per CBF image) and potential contamination

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with the BOLD signal[9,10]. ASL-fMRI is not discussed in this mini-review and in the following, RS-fMRI refers to BOLD-fMRI. Biswal *et al.* found that the spontaneous low-frequency fluctuation (SLFF) (<0.08 Hz) of BOLD signals in the somatomotor system is highly synchronized during the resting state[7]. Subsequently, the RS-fMRI technique has been widely used to investigate synchronous brain activity in a variety of functional systems, such as the visual[11], auditory[12], emotional[11], attentional[13], language[14], reading[15] and memory systems[16], as well as the default mode network[17,18]. In addition, the SLFF of RS-fMRI signals has been widely used to explore the changes that occur in certain brain diseases such as depression[19], Alzheimer disease (AD)[20], attention deficit hyperactivity disorder (ADHD)[21], and epilepsy[22].

Combining the advantages afforded by the high temporal resolution of EEG and the high spatial resolution of fMRI, simultaneous EEG-fMRI recordings can help determine the brain regions in which a change in the BOLD signal is related to the epileptic discharge seen on the EEG. EEG-fMRI can greatly improve the accuracy of localization of epileptogenic foci[23]. In focal epilepsy, this technique has shown a good correspondence between the active region and the area where the epileptic discharge is generated[24,25]. In generalized epilepsy, the patients typically exhibit thalamic activation and widespread cortical deactivation, a pattern very similar to that seen in the "default" state of brain activity[25,26]. However, simultaneous EEG-fMRI is still challenging for the following reasons. First, an MRI-compatible EEG is required; second, the standard hemodynamic response function (HRF) is usually used to detect the BOLD responses to a stimulus to obtain the statistical map[23], despite the large variability of the spikes; third, scalp EEG is insensitive to spikes from deep epileptic foci[27]; and fourth, the electrode placement and recording procedures are complicated. The scalp electrodes must be delicately placed before scanning. The artifacts from head motion and heartbeats are much more complex than EEG recording from outside an MRI scanner. Among all the above techniques, RS-fMRI BOLD has the advantages of non-invasiveness, fairly high temporal and spatial resolution, and easy implementation. Among the functional brain diseases, epilepsy is probably the most typical disorder with abnormal spontaneous neuronal activity. Although simultaneous EEG-fMRI provides more information, RS-fMRI alone continues to be widely used in epilepsy studies. Below, we introduce a few computational methods commonly used in recent RS-fMRI studies and their application to epilepsy.

2 Computational methods used in the application of RS-fMRI to epilepsy

2.1 Temporal clustering analysis (TCA) TCA was proposed by Liu *et al.* to detect the peak response of the fMRI signal after eating[28]. This method was used to search for the maximal response in a combination of signal intensity and spatial extent[28]. Later, Morgan *et al.* used TCA to localize the epileptic focus in nine patients, among whom six temporal lobe epilepsy (TLE) patients had confirmed localization indicated by successful seizure control after resection[29]. A modified version of TCA, 2D-TCA, was proposed by Morgan *et al.* to improve the sensitivity and reduce the impact of physiological noise in detecting an epilepsy focus[30,31]. A more recent study suggested that, although simulated data showed a potential advantage of 2D-TCA over EEG-fMRI in detecting activity restricted to deep brain structures, patient data did not show such results[32]. Another concern is that it still lacks specificity for epileptic activity[32] and therefore more studies are warranted.

2.2 Regional homogeneity (ReHo) The ReHo method reflects the temporal synchronization of the BOLD signal from neighboring voxels[33]. ReHo is calculated by measuring the Kendall coefficient of concordance of the time courses of neighboring voxels (e.g., 27 neighboring voxels) in a voxel-wise manner[33]. This method has been used to study spontaneous brain activity in various diseases, such as major depressive disorder[34], Parkinson disease[35], Alzheimer disease[36], ADHD[21] and autism spectrum disorders[37,38]. The ReHo method has also been used to study epilepsy. Mankinen *et al.* found increased ReHo in the medial temporal lobe in medial TLE (mTLE) patients[39]. Besides, increased ReHo has also been detected in the thalamus in patients with generalized tonic-clonic seizures (GTCS)[40], which is consistent with the results of EEG-fMRI activation studies[23,26]. Evidence from these two studies suggests that the ReHo method can detect abnormally increased local synchronization and hence may be helpful for the localization of the epileptic source. Moreover, Zhong *et al.* found decreased ReHo in the default mode network in GTCS[40], indicating a suspension of self-referential activity due to the increased activity in the epileptic network. This decreased ReHo is in line with the "deactivation" reported in the default mode network in EEG-fMRI studies[23].

2.3 Amplitude of low-frequency fluctuation (ALFF) ALFF measures the magnitude of the spontaneous BOLD activity of each voxel[41]. ALFF can differentiate eyes-open from eyes-closed in the resting state in the visual cortex and sensory motor cortex[42] as well as in the default mode network[43]. Also, ALFF can predict the activation of a cognitive task in the resting state[44]. ALFF has been used to study brain disorders, e.g. ADHD[41], post-traumatic stress disorder[45], Alzheimer disease[36,46] and schizophrenia[47,48]. However, there is only one report of ALFF application to epilepsy[49]. In that study, Zhang and colleagues recruited 24 left and 26 right mTLE patients[49]. They found increased ALFF in the ipsilateral medial temporal lobe. In a smaller sample with simultaneous EEG-fMRI recording, they found that the number of epileptic spikes was positively correlated with ALFF in the medial temporal lobe. They concluded that the increased ALFF may be an index of the epileptic focus[49]. In addition, they found a decreased ALFF in the default mode network[49], which is consistent with the results of "deactivation" in the default mode network in EEG-fMRI studies[23] as well as the decreased ReHo in the default mode network in GTCS patients[40]. One limitation of the ALFF method is that it focuses on the low-frequency (usually <0.1 Hz) BOLD signal, but the frequencies of epileptic discharges are complex. Therefore, the frequency relationship between the spontaneous BOLD signal and EEG signal needs to be investigated.

2.4 Functional connectivity based on linear correlation The most common method for the measurement of functional connectivity is extracting the time course of the BOLD signal from a seed region of interest (ROI) and calculating the temporal correlation between the extracted time course, usually termed the seed time-course, and that of each voxel in the brain image[7], or between the seed time-course and the time-course of a predefined region.

Bettus *et al.*[50] studied 26 controls and 11 mTLE patients. From each hemisphere they chose five ROIs involved in the mTLE epileptogenic network: Brodmann area 38, the amygdala, entorhinal cortex (EC), anterior hippocampus (AntHip), and posterior hippocampus (PostHip). They measured the correlation coefficient for each pair of time-courses extracted from the five ROIs. Compared with the controls, decreased functional connectivity was found for the ipsilateral AntHip-PostHip in the mTLE patients, while increased functional connectivity was found for the contralateral AntHip-PostHip. This suggests a compensatory mechanism in which the functional connectivity of the contralateral link is increased[50].

Pereira *et al.*[51] studied nine healthy subjects, nine patients with right mTLE, and nine with left mTLE. They selected two ROIs (left and right hippocampi), and found more abnormal connections in the hemisphere ipsilateral to the seizure focus than contralateral in both patient groups compared to the control subjects. This effect was even more remarkable for the left than right mTLE group.

More recently, Negishi *et al.* measured the laterality of functional connectivity[52]. The seed regions for functional connectivity analysis were obtained from EEG-fMRI "activation" areas before surgical resection. They compared the predictive effects of the laterality of functional connectivity between two groups of epilepsy patients, an epilepsy-recurrence group after surgery and an epilepsy-free group after surgery. They found that the seizure-recurrence group had less lateralized functional connectivity than the seizure-free group. This predictive effect of presurgical resting-state functional connectivity analysis has potential clinical use.

In addition to the abnormal network of epileptic foci described above, RS-fMRI studies have also found decreased functional connectivity in the attentional[53], perceptual[54], and default mode networks[55,56], as well as subcortical regions[57,58]. These results indicate that abnormal synchronization is widespread in mTLE patients.

Although the algorithm and the physiological meaning of linear correlation functional connectivity are straightforward, several issues need to be addressed. First, the definition of the seed ROI should be based on a strong hypothesis. Virtually every brain area or even each voxel could be taken as a seed ROI, so thousands of papers could be generated from a single dataset. Second, it would be better to know beforehand how exactly a covariate impacts on the result, not only on the interim functional connectivity result within a group, but also on the final results of between-group differences. Most linear correlation functional connectivity studies have used covariates, e.g., time-courses of global mean signal, white matter, cerebrospinal fluid (CSF), and head motion parameters, on a presumption that these variants have confounding effects. However, few studies have revealed exactly how these confounding factors impact on the final results. Further, the time-course of white matter or CSF varies a lot in different brain regions. Researchers should be cautious when selecting the white matter or CSF as covariates. Third, an abnormal functional connectivity means abnormal correlation between brain areas. It is unknown which brain area has contributed to this abnormal synchronization. Future studies could combine functional connectivity analysis with methods for depicting local activity (e.g., ReHo or ALFF) to study epilepsy from the aspects of both functional integration and functional segregation. Fourth, while most current functional connectivity studies take the time-course as a whole session, moment-by-moment dynamic changes in resting-state functional connectivity[59] provide a new approach to the network dynamics during different phases of seizures[60]. Fifth, linear correlation-based graph theory has been used to depict the complex network and has shown an altered small-world property in epilepsy[61,62]. More studies are needed to determine its clinical importance.

2.5 Granger causality analysis (GCA) While linear correlation analysis measures the functional interaction between two distinct brain regions, it does not provide information on causality. In contrast, GCA is proposed to be able to specifically measure the causal influence between time-courses. If the past of time-course X can predict the present time-course Y, X has a Granger causal effect on Y[63]. David *et al.*[64] applied GCA to a rat model of absence epilepsy with the epileptic locus in the somatosensory cortex. They obtained both intracerebral electrophysiological data and BOLD fMRI data. Their GCA results showed that the epileptic locus in the somatosensory cortex had a causal influence on the striatum and thalamus in terms of both the electrophysiological and BOLD-fMRI signals, suggesting the value of applying RS-fMRI with GCA to epilepsy studies[64]. One concern for fMRI GCA studies is the slow sampling rate (e.g., 2 or 3 s)[65]. A recent study used fast scanning with a repetition time of 500 ms and measured the GCA laterality between left and right hippocampi in mTLE patients[66]. It was found that, while normal controls showed a right-over-left causal influence (i.e., the influence of right on left was greater than that of left on right), patients with right mTLE showed an inverse laterality pattern[66]. This result was contrary to the authors' hypothesis that "the ipsilateral hippocampus would influence the contralateral hippocampus"[66]. The authors speculated that "this may be a reflection of the extent of neuronal damage of the ipsilateral hippocampus, with the contralateral hippocampus acquiring dominance"[66]. Although the interpretation of this study is tentative, the high sampling rate seems more meaningful. Using time-resolved analysis, some fMRI studies have reported that the time-delay may be quite short, e.g., ~0.9 s between the supplementary motor area and primary motor area[67]. Therefore, faster sampling (e.g., 0.2 s) would be a great improvement for future GCA studies.

3 Summary

Having both fairly high spatial and temporal resolution, RS-fMRI is a promising technique for the localization of the seizure focus and epileptic network. TCA, which measures the temporal maximum of spontaneous brain activity, ReHo, which measures local synchronization, and ALFF, which measures the amplitude of fluctuation, have been used to detect local activity and have the potential to reveal an epileptic focus. However, currently no studies have made a comparison among them. In addition, the electrophysiological mechanisms of these BOLD measurements are yet to be clarified. Although this review focuses on RS-fMRI, simultaneous recording of EEG and fMRI enhances the individual advantages of each technique. It should be noted that some comprehensive analytical RS-fMRI methods are not reviewed here, e.g., independent component analysis[68-70], graph theory[61,62], and dynamic causal modeling[64]. Applications of these methods to epilepsy need close collaboration among multi-disciplinary investigators, especially when multiple techniques (e.g., structural MRI, diffusion MRI, EEG, as well as fMRI) are required.

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