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Review

A review on epileptic foci localization using resting-state functional magnetic resonance imaging

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Abstract: Epilepsy is a brain syndrome caused by synchronous abnormal discharge of brain neurons. As an effective treatment for epilepsy, successful surgical resection requires accurate localization of epileptic foci to avoid iatrogenic disability. Previous studies have demonstrated the potential of resting-state functional magnetic resonance imaging (rs-fMRI) technique to localize epileptic foci though clinical applications of rs-fMRI are still at an early stage of development. fMRI data analysis approaches seek pre-defined regressors modeling contributions to the voxel time series, including the BOLD response following neuronal activation. In present study, localization strategies of epileptic foci in rs-fMRI technology were classified and summarized. To begin with, data-driven approaches attempting to determine the intrinsic structure of the data were discussed in detail. Then, as novel fMRI data analysis methods, deconvolution algorithms such as total activation (TA) and blind deconvolution were discussed, which were applied to explore the underlying activity-inducing signal of the BOLD signal. Lastly, effective connectivity approaches such as autocorrelation function method and Pearson correlation coefficient have also been proposed to identify the brain regions driving the generation of seizures within the epileptic network. In the future, fMRI technology can be used as a supplement of intraoperative subdural electrode method or combined with traditional epileptic focus localization technologies, which is one of the most attractive aspect in clinic. It may also play an important role in providing diagnostic information for epilepsy patients.

Keywords: epilepsy; fMRI; localization of foci; data-driven approach; brain functional network connectivity

1. Introduction

Approximately 30% of epileptic patients are drug-refractory epileptics. Repeated seizures can cause cognitive function damages and abnormal behavior. Fortunately, surgery is an effective treatment method helpful to these patients [1]. Clinical studies confirmed that surgical treatment is a promising technique that can improve patients' cognitive function, behavioral ability, and quality of life. A successful outcome after resection for epilepsy depends on accurate localization of the epileptogenic zone. However, owing to lack of accurate localization of epileptic foci, clinical practice is often difficult to implement. Therefore, finding an appropriate method to locate the epileptogenic area accurately is the key to solve this problem. Morphological examinations such as CT and structural MRI can only detect symptomatic epileptic foci caused by obvious morphological abnormalities, such as tumors, infections, etc. For epilepsy without significant morphological abnormalities, functional and electrophysiological tests have important significance. Electroencephalography (EEG) is a commonly used method to monitor epileptic foci, but it does not have enough spatial resolution for resection. Besides being cumbersome, it is also difficult for scalp EEG to accurately detect epileptic foci in deep brain or interictal epileptiform discharges. Intracranial EEG examination has higher sensitivity to detect the epileptic foci, but it is an invasive method. Compared with EEG, MEG has superior spatial and temporal resolution by using magnetic field positioning to detect epileptogenic zones, but it is insensitive to radial sources and is limited by its high cost and low penetration [2].

Disorder in brain neural activity is a significant characteristic of epilepsy. It has been known that increased neural activity results in changes in cerebral blood flow. However, until the end of the twentieth century, the effects of neuronal activity on cerebral blood flow could be observed in situ due to the development of fMRI. Changes in the vascular concentration of deoxyhemoglobin can be measured by fMRI. Increased blood flow in active areas of the brain results in higher concentrations of oxyhemoglobin relative to deoxyhemoglobin, then leads to a local increase in the magnetic field homogeneity and an increased signal relative to the resting state [3]. Even though no epileptic symptoms occur, abnormal discharge still exists in epileptic focus of brain during epileptic interval. The abnormal discharge can cause changes in regional cerebral blood flow, cerebral blood volume and cerebral oxygen consumption rate, thus leading to changes in BOLD signals. This confirms that epilepsy is very suitable to be observed and studied by fMRI technology.

This paper reviews the localization methods of epileptic foci and epileptic activity in rs-fMRI to provide valuable recommendations and references for further research. These methods were broadly divided into data-driven approaches, deconvolution algorithms, epileptic foci localization with brain functional network connectivity, etc. Table 1 summarizes the methods used in localizing epileptic foci and activities. With more effective methods emerging, fMRI can be further applied in clinical localization of epileptogenic foci alone and may also include infrequent epileptic events, ultimately improving the localization of epilepsy foci in a non-invasive manner.

2. Approaches to localize epileptic foci with fMRI

The researches of epilepsy fMRI mainly focus on the analysis of BOLD effect attributes caused by epilepsy events, such as the construction of characteristic blood flow response model. With researchers' deeper understanding of epilepsy and the progress of fMRI technology, fMRI data analysis methods become mature gradually. fMRI analysis methods primarily include hypothesis model and data-driven based approaches.

Hypothesis model approach selects hypothesis model in advance. For example, general linear model (GLM) is one of the most traditional methods [4]. This model can be used to show relationship between measurement of blood oxygen level dependent (BOLD) responses and experimental paradigm by using hemodynamic response function as pulse function of linear time invariant systems. However, not all brain activities could be simulated through prior simulation functions. For example, spontaneous interictal epileptiform discharges (IEDs) are unpredictable events, which cannot be established by corresponding model in advance. Unusual events, such as epileptiform activities, are often beyond control of experimenters and determined by resting-state behavior during scanning. Therefore, hypothetical model approach is not suitable to locate epileptic foci [5].

Data-driven model is independent on priori assumptions or restrained parametric modeling for identifying such relations. Such methods include temporal clustering analysis (TCA) [6], principal component analysis (PCA) [7], independent component analysis (ICA) [8] and new data-driven temporal anti-correlation. As novel fMRI data analysis methods, deconvolution algorithms such as TA and blind deconvolution approach are also applied to explore the underlying activity-inducing signal of the BOLD signal, demonstrating good abilities for the study of non-stationary dynamics of brain activity.

fMRI maps related to IEDs often show multiple regions or “networks”, rather than focal singularities, and thus effective connectivity approaches such as autocorrelation function method, Pearson Correlation Coefficient have been proposed to identify which brain regions drive the generation of seizures within the epileptic network.

2.1. Data-driven approaches

2.1.1. TCA

TCA was used to detect BOLD responses in epileptic events at unknown time. It explores maximal signal intensity responses in brain through BOLD signal [9,10]. Such exploration is performed by expressing three-dimensional image space into one-dimensional value by creating a histogram showing the number of voxels reaching maximum signal intensity at each time point in the series. Each voxel has equal probability of maximal signal intensity; this probability is independent of time unless stimulus is introduced as basis of this technique.

Morgan et al. adapted TCA to detect BOLD responses to epileptic events when the timing and location of the activation are completely unknown [6]. Researchers hypothesized that using TCA or variations of TCA with rs-fMRI can be used to determine timing of IEDs and subclinical ictal discharges; then, conventional event-related fMRI analysis can be used to create activation maps corresponding to spontaneous epileptic brain activity. Data demonstrated that this technique is potentially useful for both temporal and extra temporal lobe epilepsy.

However, Hamandi et al. discovered that these TCA techniques are highly sensitive to other signal changes, such as motion and physiological noise, during fMRI data acquisition [11]. Morgan et al. developed two-dimensional TCA technique (2dTCA) to solve this problem by detecting and organizing separate BOLD responses, which were assumed to be from different sources [12].

The researchers identified regions with positive transient fMRI BOLD signal fluctuations in temporal lobe epileptic patients using 2dTCA. This method can provide significant and unique information regarding localization and propagation of IEDs.

Morgan’s method has potential to detect more BOLD signal responses (interictal activity) than EEG-fMRI. There are two reasons: One is that hemodynamic response model is not assumed; the other is that 2dTCA may be sensitive to activity not detected by scalp EEG.

2.1.2. PCA

TCA of fMRI data was developed for localizing interictal epileptic activity [9], but such activities can be detected only in high-intensity epileptic events. Delayed PCA method is presented for detecting interictal epileptic activities from rs-fMRI time-course dataset [13].

PCA is data-driven approach applied widely in fMRI without the priori assumption. This method is based on assumption that activation signal is orthogonal to other variable signals to be analyzed; for example, activation signal is orthogonal to head movement and physiological signals, such as respiration [14], and has strong ability to suppress noise. Consequently, the application of PCA to analyze BOLD signal can significantly reduce noise.

Song et al. combined PCA with time-delayed t-test of weighted correlation coefficient and time courses of rs-fMRI data to determine interictal epileptic activities [13]. Specific steps are as follows: First, covariance matrix is calculated with time delay; second, singular value decomposition is performed to receive 98% of main signal component of all components; then, weighted correlation matrix is calculated, and t-test for each voxel is performed; voxel with higher threshold is regarded as potential model space of epileptic activities. Finally, remaining voxels include those with mean and standard deviation belonging to corresponding range, and space model they constitute is considered as epileptic activity area.

The data obtained by this method are consistent with the preoperative evaluation results. Nevertheless, such algorithm is mainly used to locate seizure activities, requiring further improvement to precisely locate epileptic foci.

2.1.3. ICA

ICA can successfully extract sources related to epileptic activity and epileptic foci from fMRI time series recorded during interictal period [15,16]. It is a data-driven approach that can recover signals from linear mixed signals by initially resolving blind source separation problem and therewith continually expanding definition. ICA maximizes the statistical independence of ICs based on its high-order statistics. It can be divided into spatial ICA (sICA) and time ICA (tICA), respectively, preserving spatial information at expense of temporal information in contrast to preserving time information at expense of spatial information [17]. ICA is flexible and potentially performs well under various circumstances [18]. sICA is major ICA algorithm used for analysis of fMRI data; it decomposes fMRI data into courses of maximized independent space map and their associated time courses.

Two steps are involved when using fMRI data through sICA algorithm to target epilepsy. First, interfering factors are eliminated, including noise signals, such as breathing, pulse rate, and human movement [17,19] and component of exclusive epileptic foci to acquire ICs associated with epilepsy. Second, epileptic foci are tracked from extracted ICs. Locating epileptic foci initially requires properly selecting ICs containing epileptic foci from large number of components; this issue is still unsolved and requires artificial subjective choice [16,20]. Hunyadi et al. proposed a novel approach for determining the epileptogenic zone in the presurgical evaluation of epilepsy, based on fMRI as a single modality, which aims for fully automating the procedure to select the epileptic IC from EEG-positive cases, i.e. in cases where interictal spikes were visible on the simultaneously recorded EEG. Therefore, it can extend the applicability of fMRI records to patients who cannot be performed by traditional EEG-fMRI analysis. The results show that the method provides maps which correctly indicate the EZ in several EEG-negative cases but at the same time maintaining a high specificity. In addition, they reported cases where fMRI analysis has added value to clinical decision-making compared with traditional techniques. The significance of this technology is that it is very specific and fully automated, so it can be used prospectively in clinical practice. However, the method proposed is especially beneficial in patients where no IEDs are visible in the EEG. Hunyadi et al. have shown that epileptic ICs can be found in such EEG-negative cases as well as before [18].

Clara et al. manually screened epileptogenic zone in focal epileptic patients [16]. First, noise component characteristics indicating that main noise IC activities (residual motion artifacts) [21] are not in cerebral cortex but in brain stem, eyes, or peripheral cerebral cortex. Therefore, brain boundary is marked by structural MRI, while fMRI brain voxel is detected internally or externally. Most normal resting-state brain activities are usually symmetrical, but epileptic activities can be found in unilateral cerebral hemispheres. Consequently, excluded ICs comprise those with vascular pressure, auditory events, or default mode network, which are all normal resting-state brain activities as well. After adoption of first two criteria, remaining ICs are filtered through third screening [18]. De Martino et al. discovered that significant neurophysiological components have specific time structure; thus, their frequency is usually in the range of 0.01 to 0.1Hz [22,23].

Selecting epileptic ICs manually is largely a subjective factor. The researchers employ different methods, but these should be combined with characteristic differences between epileptic ICs and other components to develop viable screening program to ensure preservation of epileptic ICs and to maximize removal of noise and other non-epileptic ICs. Although several methods automatically filter epileptic ICs, they require prior knowledge of epileptic activities that differ from other normal physiological events as support. Key rationale of employing ICA is to extract correct epileptic ICs to obtain accurate positioning results. Therefore, optimal filter conditions should be developed.

Chen et al. presented a spatio-temporal ICA-based data-driven method to localize foci [24]. In spatio-temporal ICA of fMRI study, sICA is used to reduce spatial dimensionality of data from auditory response; then in located region of interest (ROI), tICA is used to show that neural activity evoked by sound is composed of sustained and transient patterns. This method was applied to fMRI data of six epileptic patients, and results were consistent with clinical assessment.

In conclusion, the research findings demonstrate the potential of spatio-temporal ICA method basing on rs-fMRI to detect and localize latent epileptic brain activities. Further verifications in more epileptic patients are needed to clinically confirm epileptogenic zones.

2.1.4. Temporal anti-correlation

Positron emission tomography (PET) and fMRI were used to study the functional imaging of normal subjects. It was found that some special areas such as posterior cingulate cortex, ventral cingulate cortex display reduction in brain functional network when performing task-induced functions. This finding hypothesizes that the activities of these regions form the default mode network. The activities increase when attention is not required externally in rs-fMRI. Default mode network principally involves spontaneous and self-referential mental activities [25]. Regardless of the level of activities or cognitive tasks, the required attention may enhance task-related brain activities and weaken regional activities of default mode network [26].

Therefore, anti-correlation may arise from time courses in both default mode network and task-induced regions. During generalized and some localized spike and waves, the advantage of this phenomenon can be used to identify specific spontaneous brain activities, such as intermittent epileptic discharge; deactivation in posterior cingulate cortex also occurs [27]. Therefore, for rs-fMRI data without auxiliary EEG, it is effective to use temporal anti-correlation test to detect epilepsy region in epileptic patients with frequent IEDs.

Wang et al. used temporal anti-correlation to target seizure area of epileptic patients with frequent IEDs [28]. First, fMRI data of epileptic patients are filtered using phase-insensitive low-pass filter (passband range 0.008 to 0.08 Hz) to reduce high-frequency physiological noise and low-frequency drift. Voxel intensity comprises voxel values divided by average of whole brain voxel value at each time point; this factor can minimize influence on overall drift at specific time points. Next, WFU-Pick Atlas software [29,30] selects node of default network, the posterior cingulate cortex, as ROI. When PET and fMRI measures require cognitive tasks of attention, posterior cingulate cortex can reliably predict brain area of reduced activities. Finally, correlation analysis is implemented on ROI. By averaging time courses of all voxels of ROI, namely, posterior cingulate cortex, average signal intensity is extracted. Calculation includes Pearson's linear correlation between resulting time course and time course of all voxels in whole brain. Mask images are obtained through correlation threshold, and selected voxel is defined as potential activation voxel. To improve the reliability and sensitivity of the localization of seizure activities, final average signal intensity is obtained by averaging the time courses of potential activation voxels again. The obtained average time courses represent hemodynamic response of activation regions. Correlation is calculated using new time course and time course of all voxels in brain to set up threshold of correlation coefficient ($P < 0.1$) to obtain final map of epileptic activities. In rs-fMRI data, algorithm can be used to identify epileptic seizures area in epileptic patients with frequent IEDs.

2.2. Deconvolution algorithms

2.2.1. TA

Substantial data-driven algorithms ensure that brain activities are explored pre-defined hemodynamic response function [31], whereas as no previous knowledge considered hemodynamic signal or type-driven activities, these data-driven algorithms are incapable of directionally recognizing "active" components; for example, ICA is applied to fMRI depending on independent statistical space.

Recently, Karahanoğlu et al. proposed a spatio-temporal regularization, TA. It was used for deriving activity-inducing signal and to perform deconvolution in fMRI. Based on characteristics of temporal sparse and hemodynamic system without prior information on onset timing and duration of events, researchers discovered that TA could perform deconvolution for underlying activity-inducing signal in fMRI. TA can detect spontaneous resting-state activities in fMRI, as it does not demand timing information of paradigm. Hence, IEDs of spontaneous neural activities can be captured by TA, and sources of epileptic activities can be located using TA algorithm [32]. Activity-inducing signal is fed to hemodynamic system to obtain related activities signals, which are then added to noise signal to acquire fMRI measurement data. Therefore, TA aims to recover underlying activity-inducing signals from noisy fMRI measurements through adding structured-sparsity priors in spatio-temporal domain and then perform nonparametric hypothesis testing and other follow-up operations to locate epileptic foci.

Karahanoğlu et al. separated activity-inducing signal from fMRI to locate epileptic foci via TA [33]. Main steps are denoising for fMRI to regain related activities signal, further regaining activity-inducing signals, and nonparametric hypothesis testing of activity-inducing signals to locate detecting-zone seizures. Exact-position-detection algorithm is tested by surgical resection or intracranial measurement of conventional methods.

TA is a recently proposed method, which extremely relies on priori assumptions model and ICA algorithm. It discards the shortcomings of GLM method. Moreover, it could not be affected by hemodynamics and types of activity-induced signals. As a deconvolution algorithm, TA maintains linear model for hemodynamic system and does not require time characteristics of hemodynamics, which provides more accurate results and maximizes a posteriori assessment by appending prior sparse knowledge of underlying activity-inducing signals. In addition, by defining prior space knowledge of space activation map, TA becomes continuative standard GLM analysis.

2.2.2. Blind deconvolution approach

Studies showed significant variability in the hemodynamic response function (HRF) for different types of epileptiform discharges across subjects [34]. To solve these problems, parameterized HRF approach can be used. Parameterization separately represents different shape characteristics of HRF. This new approach adopts parameterized HRF.

Lopes presented new framework for identifying BOLD manifestations of epileptic discharges without having to record EEG [35]. First stage is based on detection of timings on epileptic events for each voxel by using dictionary of HRF in wavelet domain. Recently, Khalidov et al. introduced new dictionary called “activelets” [36]. Activelets are the wavelets for sparse representation of hemodynamic responses, which sparsify the activity-related BOLD signal. Second stage involves gathering voxels according to proximity in time and space of detected activities. Clustering technique was used for identifying regions with similar patterns of detected activation.

The research results demonstrated that maps of activation obtained from this method were more similar to those obtained by EEG-fMRI compared with those obtained by others.

2.3. Epileptic foci localization with brain functional network connectivity

By measuring the correlation degree of brain activities, functional network reflecting the connectivity of brain function can be obtained. Two brain regions with similar wave signals are considered functionally related, or that one region is affected by another, or that both are affected by third one.

In fMRI brain functional network assessment, the algorithms used are divided into two categories. One is non-directional evaluation algorithms, which are divided into correlation and partial correlation. Correlation assessment algorithm cannot determine causality and ascertain direct connectivity between nodes. Also, partial correlation cannot confirm causality between nodes but can verify direct connectivity. Another category is directive evaluation algorithms. Among these algorithms, the most common one is Granger causality analysis, which is based on delayed algorithm. When time course is delayed for another period, another time course is generated, providing direction of connectivity.

Many studies reported that the functional connectivity in the nearby areas of suspected seizures decreased [37–41], whereas some insist that it should increase [42–44]; such factors possibly differ in connectivity metric, overall patients, and small sample size. Nevertheless, given the huge difference in network between epileptic patients and normal subjects, epileptic foci can be determined through functional network connectivity analysis. Currently, with limitations of functional network construction methods, pinpointing epileptic foci is not achieved by brain functional network connectivity. However, this type of connectivity still possesses considerable potential in detecting epileptic foci.

Lately, construction methods for brain functional network connectivity were developed to determine potential location of epileptic foci with focus on correlation. Following are two common construction methods of brain functional network connectivity based on correlation.

2.3.1. Autocorrelation function method

Destruction of brain functional connectivity demonstrates abnormal dynamics. As a complex measurement method of rs-fMRI, autocorrelation function can locate deviation from optimal dynamics in epileptic patients.

Nedic et al. used autocorrelation function to analyze rs-fMRI and selected regions with non-normal dynamics as seed points; abnormal connectivity is detected through follow-ups on functional connectivity analysis between seed point and voxels [45]. This algorithm has high sensitivity and specificity to detect epileptic foci and can provide additional information on potential dynamics and other factors for patients with epilepsy.

2.3.2. Pearson correlation coefficient

Pearson correlation coefficient algorithm can detect strength of brain activities and synchronization change in BOLD signals [46]. Epilepsy is characterized by spontaneous abnormal network discharges and may cause synchronized changes in blood oxygen level and may enhance brain activities in epileptic region. Thus, Pearson correlation algorithm can detect and locate seizure activities.

Ming Ke et al. constructed the network adjacency matrix of normal subjects and patients with tonic-clonic epilepsy by Pearson correlation method. The characteristics of brain network were compared by the properties and efficiency of small-world network [47]. Compared with normal subjects, the small-world characteristics and network efficiency of patients with tonic-clonic epilepsy are lower, suggesting that the information transmission ability of patients with epilepsy is weakened, which is caused by brain dysfunction. Owing to its ability to detect seizure activities, Pearson correlation method can be effectively utilized in clinical studies of epilepsy.

Stufflebeam et al. hypothesized that epileptogenic zone is characterized by altered connections to other brain regions even in interictal state [44]. Epileptogenic zone can be localized based on functional connectivity changes in comparison with health controls. To test this hypothesis, researchers used functional connectivity to identify epileptic foci based on Pearson correlation algorithm and compared results with invasive EEG.

Voxel-wise whole-brain correlation analysis was performed to measure the degree of local and remote functional connectivity of each voxel [48,49]. Specifically, correlation was determined between BOLD low-frequency signal time course of each voxel from subject's brain and every other voxel time course at local and remote levels. Then, Pearson correlation coefficients were averaged and assigned to given voxel. Researchers selected neighborhood strategy to define local and remote limits. For local connectivity, included voxels were found in 3 mm-radius sphere surrounding seed voxel. Remote connectivity considered all voxels outside 25 mm-radius sphere. Degree of coupling was calculated by summarizing number of voxels above correlation threshold of 0.25 at both local and remote levels. This method may benefit epileptic patients because it is noninvasive and does not require additional imaging modality. Table 1 summarizes the methods used in localizing epileptic foci and activities.

3. Discussion

Accurate preoperative localization of epileptogenic zone is the key to complete surgical resection of drug-refractory epilepsy. Based on the limitations of other localization methods and specific advantages of fMRI algorithm on positioning epileptic foci, researchers summarized algorithms used in locating epileptogenic zone and epileptic activities during rs-fMRI.

3.1. Analysis and comparison of the mentioned methods

3.1.1. Data-driven approaches

TCA and PCA are algorithms involved in detecting localization of spontaneous epileptic brain activity in data-driven algorithm. TCA is an efficient way to analyze fMRI data based on the size of a temporal cluster, which is used in detecting BOLD responses to epileptic events of unknown timing. This technique is potentially efficient because of the high temporal synchronicity associated with epileptic activity. Using TCA method can make the data processing and analysis as simple as paradigm-dependent methods. It also acquires the generalness of paradigm-independent methods. When the experimental paradigm cannot provide temporal information necessary for data processing, TCA is not a paradigm-independent method but a strategic approach of paradigm-dependent methods [10]. In the conventional TCA technique, one reference time course is created for each imaging series or subject and so BOLD responses caused by many different stimuli are added together. Using the Morgan's 2dTCA technique, voxels with similar times of signal response of interest are clustered together. In this algorithm, the number of reference time courses only depended on the number of time points in the series. This method does not need to assume hemodynamic response model and 2dTCA may be sensitive to the activity not detected by scalp EEG. Therefore, it has the potential to detect more BOLD signal responses (interictal activity) than fMRI with EEG. Compared with simultaneous EEG and fMRI recordings, the processing of 2dTCA algorithm saves lots of time, which only takes a few minutes. In addition, 2dTCA algorithm can be completely automated before the activation map is created. It is well recognized that epileptiform discharges generated in deep brain regions, discharges that have an unfavorable dipole orientation, or discharges that involve less than 6 cm^2 of cerebral cortex are difficult to be recorded by scalp EEG. 2dTCA method's sensitivity to undetected activity on the scalp may be explored in a future study, especially for the patients with no scalp EEG interictal spiking detected during fMRI acquisition. However, the EEG correlates of the 2dTCA detected activations remain unknown, which should be elucidated before clinical application [12].

Among the data-driven approaches, ICA and PCA are all traditional localization method without requirement of prior information about experiment. ICA is increasingly recognized as a useful fMRI data-driven analysis tool. It does not rely on prior hypotheses and has the potential to identify a greater proportion of the BOLD signal variations. The main advantage of this method is that it represents the original functional time series as a set of independent components, which may separate meaningful neurophysiological sources. However, interpreting the results may be very difficult owing to the lack of a prior hypothesis. In ICA algorithm, the key step is to determine the screening criteria for ICs containing epileptic lesions, which is helpful to the accurate selection of ICs and the accurate localization of epileptic lesions. The reasonable screening criteria of ICA algorithm should be strictly determined. However, significant variation is observed in screening standards for epileptic ICs recently. Thus, setting rational screening methods should involve selecting the best key discriminative features of epileptic ICs and other ICs as filtering conditions before extracting epileptic ICs. For ICA method, just rely on the subjective decisions is unreliable because it still do not have a proper criterion for localizing epileptic foci. PCA is not affected by this problem in this respect. The PCA method assumes that the activation is orthogonal to the other signal variations such as brain motion, physiological signals (heartbeats and respiration). PCA has strong denoising ability but lacks accuracy in locating epileptic foci. It has been found that PCA can suppress noise such us reducing noise in fMRI using component analysis.

3.1.2. Deconvolution algorithms

A potential application for fMRI deconvolution methods is to detect epileptogenic regions from fMRI components since the onset timings of IEDs are unknown in advance [11]. As a spatiotemporal regularization method, total activation was proposed for detecting unpredicted neuronal activity in fMRI. TA shows that the IEDs derived from fMRI was contrary to conventional EEG derived methods. This flexible method is suitable for different types of driving signals by altering the general derivative operator; in previous studies, TA has been shown to be able to reconstruct normal form information and related resting state networks and locate the cerebral sources of IED [34].

Compared to EEG-fMRI, blind deconvolution approach has several advantages. This framework is more suitable for the assessment of patients with too few spikes due to sparsity constraint. In addition, this method has the potential to detect activity restricted to deep brain structures since the HRF is independent of brain localization. This phenomenon is evident in the application of simulated data such us detection of the activity in the hippocampal volume of interest. Finally, blind deconvolution approach may be useful for some runs without epileptic events visible on scalp EEG. Compared with 2dTCA, has better sensitivity and specificity. 2dTCA created maps describing other activity unrelated to epilepsy, while blind deconvolution approach created only one map of activity. The reason that 2dTCA has poor sensitivity and specificity may be the use of amplitude threshold to detect the activity of each time course.

3.1.3. Epileptic foci localization with brain functional network connectivity

The functional network connectivity technique is based on calculating the intrinsic correlations of spontaneous BOLD signal across the brain to identify abnormal regions. Previous studies have confirmed significant differences in connectivity patterns in many patients. Also, the scholars found that this abnormal connectivity overlaps the epileptic areas identified by invasive EEG. This method may be useful for identifying epileptic foci with the advantage of being noninvasive and having a high spatial resolution. Since the method does not explicitly depend on existence of MRI-detectable structural abnormalities, it may eventually be applied to patients with epileptic foci that are inadequately defined or poorly localized based on the most advanced neuroimaging techniques currently.

Table 1. Methods used in localizing epileptic foci and activities with fMRI.

Method	Type	Locating type	Advantages	Disadvantages	Extent of clinical validation
TCA [10,12]	Data-driven	Epileptic activity	No hemodynamic response model is assumed, and 2dTCA may be sensitive to activity not detected by scalp EEG.	Only in high-intensity epileptic events physiological interpretation is difficult	The 2dTCA results showed temporal lobe activation in 16 subjects (94%). Temporal lobe or insula activations were detected ipsilateral to the EEG focus in 64.7% (11 patients), bilaterally with no predominance in 29.4% (5 patients), and exclusively contralateral to the EEG focus in none.
PCA [13]	Data-driven	Epileptic activity	Strong ability to suppress noise no high-intensity epileptic events	Physiological interpretation is difficult	The results are in line with the foci of anatomy display.
ICA [16,18,24]	Data-driven	Epileptic activity and epileptic foci	No high-intensity epileptic events more accurate epileptic foci widely used method	Physiological interpretation is difficult	Hunyadi's method provides maps which correctly indicate the EZ in several (N = 4) EEG-negative cases but at the same time maintaining a high specificity (92%).

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Method	Type	Locating type	Advantages	Disadvantages	Extent of clinical validation
Temporal anti-correlation [28]	Data-driven	Epileptic activity	Detecting epileptic events of unknown timing	Only in high-intensity epileptic events	The results acquired from two of the subjects demonstrated that the method can be used to localize the epileptogenic zone in some patients with frequent interictal epileptiform discharges using rs-fMRI without EEG.
TA [33]	Deconvolve	Epileptic foci	No timing information of paradigm more accurate epileptic foci linear model for hemodynamic system	——	Comparing and validating the results with conventional methods performed by experts prior to surgery, it is demonstrated that TA can locate the epileptogenic regions from fMRI data.
Blind deconvolution approach [35]	Deconvolve	Epileptic activity	Detecting epileptic events of unknown timing	Only in high-intensity epileptic events	The method was able to detect effectively and consistently for response amplitude of at least 1% above baseline. For 5 runs without event read on scalp EEG, 3 runs showed an activation concordant with the clinical diagnosis.

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Method	Type	Locating type	Advantages	Disadvantages	Extent of clinical validation
Autocorrelation function method [45]	FC	Epileptic foci	Additional information on potential dynamics	No more accurate epileptic foci	In Nedic's study of 90 patients, autocorrelation decay rates differentiated, with 100% accuracy, between patients and healthy controls on a subject-by-subject basis within a leave-one-subject out classification framework.
Pearson Correlation Coefficient [44,47]	FC	Epileptic activity and epileptic foci	Additional information on brain functional connectivity	No more accurate epileptic foci	The results of Ming Ke’s analysis for 15 patients participated showed the "small world" property and network efficiency of GTCS group were decreased compared to the controls.

*: TCA: temporal clustering analysis; PCA: principal component analysis; ICA: independent component analysis; TA: total activation.

For the ACF method, it has several advantages compared with conventional analysis method such us power spectral scale invariance analysis. First, ACF decay times represent the self-similarity over different lengths of time (in seconds). This have physiologically intuitive meaning and can provide some information for clinical reference. Second, since ACF do not need to use linear least squares fitting on log-log scale, it has an improved model fits for fMRI time-series compared with other analysis methods [46].

Pearson correlation coefficient reflects the time synchronization of BOLD signal and activity intensity of EEG. In addition, the enhancement of Pearson correlation coefficient suggests that the brain area is related to the occurrence and transmission of epileptic activities. Long term repetitive discharge of the whole brain can lead to damage of the default network. The results are consistent with those of other methods. Pearson correlation method can detect the seizure activity of generalized tonic and clonic seizure, which can be effectively used in clinical research of epilepsy [48]. In summary, the fMRI method of targeting network dynamics is expected to provide a new and clinically valuable tool for the identification of epileptic foci.

Although the research results have already demonstrated the potential of these techniques to localize epileptic foci, further researches are still required. These methods can be applied to more challenging cryptogenes cases only if they are verified in patients with clinically well-defined focal regions. This also points out the direction for our future research in this field.

3.2. Other novel methods

Although these modified conventional methods can increase preoperative positioning accuracy in fMRI of epileptic patients, still require other numerous novel methods for correct positioning. Based on previous studies, series of significant conclusions are exploited, proposing novel methods, such as TA, to locate epileptic foci using activity-induced signal detection on epileptogenic zone, and assuming linear model for hemodynamic system. TA does not require timing information of paradigm nor hemodynamic time characteristics and avoids disadvantages of non-directed research on ICA and other data-driven algorithms.

A new approach is proposed for identifying timing of epileptic events in fMRI BOLD signals; this approach detects epileptic activities in each voxel based on activelets dictionary and sparse representation and uses spatio-temporal clustering to gather voxels according to timing of detected activity and spatial information.

Temporal anti-correlation utilizes few nodes of default mode network, demonstrating negative activation when seizure activities occur. Hence, according to correlation, detecting epileptic foci is possible. Emergence of these new locating methods considerably enhances ability to pinpoint epileptogenic zone in fMRI. Therefore, based on previous research findings, researchers concluded that significant benefits result from innovation of novel positioning algorithms for epilepsy prior to surgery.

3.3. Functional network connection indicates significant potential in detection of epileptogenic zone

Previous studies indicated that functional network connectivity detects abnormal functional connectivity in entire epileptic network, as reported in previous fMRI studies. Functional network connectivity technique is based on calculating intrinsic correlations of spontaneous BOLD signal across the brain to identify regions with abnormal degree of functional connectivity. After measurement, abnormalities in functional connectivity patterns offer complementary approach for identifying epileptic cortex. Therefore, we believe in significant potential of using brain functional network connectivity to detect epileptogenic zone.

3.4. Clinical potentials of fMRI in epileptic foci localization

At present, fMRI has been widely used for preoperative planning and judgment of postoperative effects. It includes the localization of task-correlated language and memory function, and the localization of ictal and paroxysmal phenomena. Language lateralization assessment from fMRI provides comparable results to intracarotid amobarbital test. The recent development of fMRI data analysis approaches has widened new applications in seizure localization. In Morgan's TCA experiment, BOLD fMRI images of 17 TLE patients were acquired and compared to EEG. The results found that 16 patients showed apparent temporal lobe activation and mesial temporal activation could be found in 13 patients [12]. As an important method of deconvolution algorithms, blind deconvolution approach can detect response amplitude of at least 1% above baseline effectively and consistently. For 5 runs without event read on scalp EEG, 3 runs showed an activation concordant with the clinical diagnosis [36]. Furthermore, advances in fMRI combined with network analysis approaches have demonstrated great potential non-invasively. In Nedic's autocorrelation study on 90 patients, autocorrelation decay rates differentiated, with 100% accuracy, between patients and healthy controls on a subject-by-subject basis within a leave-one-subject out classification framework [45].

3.5. Localization of seizure foci in different types of epilepsy

Neuroimaging assessment is very important for the preoperative localization of epileptic focus in patients with drug-resistant focal epilepsy. Although the continuous improvement of structural and functional cranial MRI makes it possible to find the previously neglected lesions, there are still a large proportion of epileptic patients whose lesions cannot be found in the preoperative evaluation of cranial MRI. 20–30% of patients with temporal epilepsy and 20–40% of those with extra temporal epilepsy received surgical treatment do not have clear lesions on MRI [50–52]. Under these circumstances, additional information from neuroimaging modalities plays an indispensable role, such as fluorodeoxyglucose positron emission tomography (FDG-PET), single photon emission computed tomography (SPECT), and the more recently developed subtraction ictal SPECT coregistered to MRI (SISCOM). The validity of these technologies has been proven in epileptic patients [53]. Functional imaging is usually used in the treatment of intractable focal epilepsy to find the undetected lesions in patients when there is no positive finding on MRI. And the location of epileptogenic focus can be determined by combining with other technologies, such as video electroencephalography (VEEG).

However, different functional imaging technologies have their own limitations. PET results are reliable when lateralizing the temporal epileptic area, while its efficacy is lower for extratemporal cases. Instead, SISCOM is just on the contrary. In the same way, the spatial location of FDG-PET is not ideal. Therefore, the combination of multimodal technologies is particularly important. For example, MRI, especially high-resolution head MRI which can be reconstructed into three-dimensional images, has the characteristics of high spatial resolution and tissue resolution. If FDG-PET is combined with MRI, it can combine the high detection sensitivity and high tracer specificity of FDG-PET with the characteristics of high spatial resolution and high tissue resolution of MRI, so it can locate the low metabolism area more sensitively and accurately. These advantages make the combined technique have high diagnostic value for small and early lesions [54].In addition, if we can find the small lesions consistent with the clinical electrophysiology and other clinical information, it will significantly change the clinical decision-making, which is to choose surgical treatment or buried intracranial electrode EEG for further evaluation.

4. Conclusion

Successful surgical resection requires accurate localization of epileptic foci and well understanding of adjacent functional cortex to avoid iatrogenic disability. More and more studies tried to combine fMRI techniques with analysis algorithms to locate epileptic activity and focus accurately. This review covers data-driven approaches, important algorithms and functional network connection applied to localization of epileptic foci or regions of epileptic activities.

Although epileptic activities and foci can be correctly detected by some existing localization algorithms with rs-fMRI, more effort is needed to pursue more precise localization on epileptogenic zone. In future studies, ICA algorithm should be perfected for precise localization of epileptogenic zones, and it may still be significant in locating epilepsy in short term. Nevertheless, rapid development of novel methods is inevitable encouraged. Furthermore, brain functional network connectivity is expected to become an important method for localization of epileptogenic zone which may play irreplaceable role in the future.

Over the past several years, the theoretical researches about epileptic foci localization mainly focused on methods with invasive nature and limited spatial extent such us intracranial electroencephalography and direct cortical stimulation. Until recent years, more and more scholars divert attention to the application of non-invasive examinations. fMRI is an important method of them in epileptic foci localization for presurgical planning. With a lot of researches and comparisons, we can find that the number of literatures using fMRI in epileptic foci localization is small. One of the important reasons is that using fMRI to locate epileptic foci is still in the stage of academic research, which is still not widely used in clinical diagnosis. However, some existing research findings have confirmed that epilepsy is very suitable to be observed and studied by fMRI technology. For example, uniting with mathematical network approaches, fMRI have demonstrated great potential to study brain networks non-invasively in a variety of populations. So, we write this review focusing on the application of fMRI for epilepsy localization and eloquent cortex mapping, with an emphasis on some important algorithms used in fMRI data analysis. In the future, we hope this work can provide a reference for presurgical planning.

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Conflict of interest

The authors declared they have no competing interests. The authors alone are responsible for the content and writing of the paper.

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