Review Article

Methods and utility of EEG-fMRI in epilepsy

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Abstract: Brain activity data in general and more specifically in epilepsy can be represented as a matrix that includes measures of electrophysiology, anatomy and behaviour. Each of these sub-matrices has a complex interaction depending upon the brain state i.e., rest, cognition, seizures and interictal periods. This interaction presents significant challenges for interpretation but also potential for developing further insights into individual event types. Successful treatments in epilepsy hinge on unravelling these complexities, and also on the sensitivity and specificity of methods that characterize the nature and localization of underlying physiological and pathological networks. Limitations of pharmacological and surgical treatments call for refinement and elaboration of methods to improve our capability to localise the generators of seizure activity and our understanding of the neurobiology of epilepsy. Simultaneous electroencephalography and functional magnetic resonance imaging (EEG-fMRI), by potentially circumventing some of the limitations of EEG in terms of sensitivity, can allow the mapping of haemodynamic networks over the entire brain related to specific spontaneous and triggered epileptic events in humans, and thereby provide new localising information. In this work we review the published literature, and discuss the methods and utility of EEG-fMRI in localising the generators of epileptic activity. We draw on our experience and that of other groups, to summarise the spectrum of information provided by an increasing number of EEG-fMRI case-series, case studies and group studies in patients with epilepsy, for its potential role to elucidate epileptic generators and networks. We conclude that EEG-fMRI provides a multidimensional view that contributes valuable clinical information to localize the epileptic focus with potential important implications for the surgical treatment of some patients with drug-resistant epilepsy, and insights into the resting state and cognitive network dynamics.

Keywords: Epilepsy; the blood-oxygen-level-dependent (BOLD); functional magnetic resonance imaging (fMRI); language; memory; electroencephalography and fMRI (EEG-fMRI); networks; connectivity

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Background

The primary clinical goal for imaging in patients with refractory epilepsy has been the identification and localization of a potential surgical target. However, the development of the concept of epileptogenic networks, in contrast to a single regional source (1), has challenged the conventional classification of focal and generalised epilepsy. This is encouraging investigators and clinicians to pay particular attention to the network dynamics of conventionally defined clinical targets, posing new challenges to treatment options (2) potentially more suited to patients that remain refractory to antiepileptic medications (3), and in light of surgical failures.

Currently, localization of the seizure onset zone (SOZ) and epileptogenic zone (EZ) is commonly performed by employing a range of techniques, including magnetic resonance imaging (MRI), long term video-electroencephalography monitoring (video-EEG), magnetic-encephalography (MEG), positron emission tomography (PET), ictal single photon emission computed tomography (ictal-SPECT) and/or intracranial EEG

(icEEG). Intracranial EEG is considered a clinical gold standard despite its limitations: limited spatial sampling and constraints regarding safety. The lack of a true gold standard (4) has further enhanced the realisation that understanding of whole brain networks is required for improved markers in patients with refractory epilepsy, specifically to aid novel and targeted interventions (1,2,5).

The development of simultaneous EEG and functional MRI (EEG-fMRI) has the potential to combine information from two spheres: electrical and haemodynamic. Albeit operating at vastly different temporal resolutions, EEG and simultaneous fMRI employs the synchrony of electrographic events and haemodynamic correlates to localise and track the evolution of activity. This approach combines our knowledge of the EEG markers of epilepsy with the whole brain sensitivity and good spatial resolution of fMRI to derive its measurements, therewith resolving the inherent limitations of EEG (and MEG) and fMRI taken individually (6).

In its most common form, simultaneous EEG-fMRI aims to measure haemodynamic changes associated with epileptiform electrical brain activity, essentially through a multifactorial correlation analysis. Scalp EEG-fMRI based localization of epileptic brain networks has been evaluated relative to that of more established methods such as scalp EEG, MRI, ictal-SPECT and icEEG (7). Therefore, a role for EEG-fMRI is indicated by virtue of its demonstrated success in localizing the SOZ/EZ for patients with refractory epilepsy undergoing presurgical assessment (8-15), and identifying syndrome-specific brain networks in patients with focal (16-21) or generalized epilepsies (22-26). However, the use of scalp EEG to predict haemodynamic signal variations related to epileptic activity, is constrained by its limited sensitivity, in particular to deep activity. In contrast, intracranial EEG has exquisite local sensitivity, and more recently simultaneous icEEG-fMRI has been shown to reveal interictal activity-related haemodynamic networks (11,27,28).

Comprehensive details of the EEG-fMRI data acquisition and analysis techniques are available in relatively recent reviews (7,29,30). Therefore, we have chosen to focus on the application of EEG-fMRI as an instrument to identify and map resting, cognitive and epileptic networks, following a brief synopsis of the technique's basic principles.

Literature search methodology

We searched English language articles in PubMed from 2003 to 2014, with the following search formulation: (epilepsy AND EEG-fMRI AND networks) OR (epilepsy AND networks) OR (fMRI AND connectivity) OR [EEG-fMRI and (language OR memory OR connectivity OR networks OR resting state networks)].

Basic principles of EEG-fMRI

The epileptiform electrical brain activity comprises synchronous firing of multiple neurons generating local field potentials which are measured on EEG as interictal epileptiform discharges (IEDs: spikes) or seizures. The haemodynamic signal recorded in fMRI is the result of coupling between the neural event or response of interest and haemodynamic fluctuation (often referred to as neurovascular coupling)—i.e., variations in blood oxygenation associated with neuronal firing—specifically detected by exploiting the magnetic properties of blood [deoxy/oxy haemoglobin, the blood-oxygen-level-dependent (BOLD) contrast] (31,32). Notwithstanding the slow temporal characteristics of the BOLD signal (33) and questions on the exact nature in relation to underlying neural activity (34,35), BOLD fMRI has been used extensively to map a range of cognitive and epileptic phenomena.

In EEG-fMRI studies of spontaneous epileptic activity, the EEG is used to indicate the occurrence of events of interest in relation to the fMRI time series, and the experimenter's challenge is to accurately represent the epileptiform activity to build a model of the associated BOLD signal changes, and choose an appropriate haemodynamic convolution model. Epileptiform events such as runs of IED and seizures can be represented as a "box" function or as a "stick" function of zero-duration for single IEDs. The most commonly employed shape is the so-called 'canonical' HRF derived from, and widely used in cognitive fMRI studies (36): it comprises two gamma functions, one accounting for the peak and the other for undershoot. However, significant variation in the shape and onset of the hemodynamic responses has been demonstrated across subjects (37,38) and brain regions (39) and may be influenced by top down and bottom up processing. In epilepsy (particularly generalised discharges) there is a suggestion that the shape of the HRF can deviate from the canonical shape, resulting in significantly decreased sensitivity (40). Characterisation of HRF shape variability can be performed using more general basis function sets such as the finite impulse response (FIR) and Fourier basis

sets, which appear to make the least assumptions about the shape of the response and potentially increases the likelihood of detecting hemodynamic changes that are different from the canonical HRF. The FIR model (41) allows estimation of idiosyncratic hemodynamic response by deconvolution which may result in a different number of regressors at each point in the time series. Whilst it provides greater flexibility, FIR readily models noise. A new modelling technique, based on the superposition of three inverse logit functions (IL), compared favourably with several other popular methods, including smooth FIR models, the canonical HRF with derivatives, nonlinear fits using a canonical HRF, and a standard canonical model (42). The Fourier series basis set employs a combination of sine and cosine to model hemodynamic response. It is sensitive to identify any pattern of consistent signal changes, providing flexibility to model interictal, ictal and preictal BOLD changes (9,43,44) and low-frequency fluctuations at resting-state (45). Multiple HRFs (40,43,46-50) with variable onset and peak times have also been used to evaluate BOLD activity associated with interictal discharges. An important caveat is that neurovascular coupling may be altered in epilepsy patients due to the presence of a structural lesion (43,51) with implications for detection, localization, shape and sign of the HRF. More details about the neurobiology of HRF shape and its underlying physiology has recently been discussed (52).

It is important to note that investigations of the relationship between the shape of the HRF and sensitivity are severely limited by the fact that ground truth (extent of the generators of epileptic activity) is usually very difficult to obtain, even in cases that subsequently undergo resective surgery successfully since it is conceivable that seizure cessation can be achieved by disruption, rather than total ablation of the epileptogenic region or network; in addition, a recent study of the extent of BOLD changes using very flexible HRF models and mass averaging has revealed whole-brain involvement in relation to simple tasks. This highlights the importance of careful consideration of the objectives of fMRI mapping studies, through appropriate model specification. A compromise between allowing HRF of almost arbitrary shape and the canonical form to account for variations in response onset is obtained by adding temporal and dispersion derivatives (53).

Sensitivity of EEG-fMRI

Scalp EEG-fMRI depends on epileptiform events to be captured during recording sessions to detect associated BOLD changes. However, routine clinical scalp EEG recording lasting 20-30 minutes has low sensitivity (~30-50%) to capture epileptiform activity (54). It is possibly related to the fact that at least 6-10 cm^2 area of the brain is required to be activated to produce an IED to be captured on scalp EEG (55,56) and epileptiform events that are of smaller magnitude may remain undetected.

It has been shown that 40% of cases showed no clear IED during studies, another 30% of cases where IED has been identified and modelled there has been no significant BOLD change which reflects limitations in the modelling of the fMRI signal (15). In order to improve the sensitivity of technique, Grouiller *et al*. have suggested the construction of topographic maps from IEDs recorded during long-term video-EEG monitoring (57). In turn these topographic maps are correlated with the EEG recorded during fMRI and used to evaluate BOLD changes associated with epileptic activity. This approach has increased sensitivity of EEG-fMRI to around 80% (57,58). In addition, fMRI is affected by motion which has resulted in several approaches to characterise motion in the design matrix to improve sensitivity (59-61). Other forms of physiological noise have also been addressed to explain unknown variance in fMRI data and improve the sensitivity of the technique including: cardiac pulse (40,62,63), respiration (64), and a variety of patient movements: swallowing and eye blinks (65). In contrast to scalp EEG-fMRI, a limited number of icEEG-fMRI studies have shown 100% sensitivity to identify IED-related BOLD changes (11,27,28).

The sensitivity of ictal EEG-fMRI studies to capture a seizure varies from 10-100% and the sensitivity to reveal seizure-related BOLD changes if a seizure is captured during the recording session ranges between 66-100% (9,18,24,44,66-75). The range of sensitivity observed in these studies may be due to the patient selection criteria, differences in the concordance criteria used to assess localization of BOLD changes, as well as differences in modelling approaches.

Clinical utility: localisation of the epileptic focus or network

Initial fMRI studies, without simultaneous EEG, investigating seizure-related BOLD changes helped localizing the seizure focus (76,77). Spike-triggered EEG-FMRI studies (78) added diagnostic information in the pre-surgical context. Later, simultaneous and continuous EEG-fMRI showed spike-

related BOLD changes in the epileptic focus (79).

IED-related BOLD localization (8,80,81) has been found to be more specific than scalp EEG for localizing invasively defined epileptic focus (14). It has also shown that widespread and discordant IED-related BOLD changes are associated with poor postsurgical outcome (10,12,82) thus showing promise as a technique to predict surgical outcome non-invasively. Coan *et al*. have shown that localization of IED related BOLD changes within 2 cm of the EZ/area of surgical resection has a positive predictive value of 78% and negative predictive value of 81% (83). The localization of IED-related BOLD changes has also resulted in reconsideration of surgical intervention following negation of the surgical option in the context of other investigations (13,84). Simultaneous intra-cranial EEG-fMRI studies have shown significant BOLD changes for very focal spikes identified on icEEG (27,28), both in close proximity to and remote from the EZ, and also in regions that could not be sampled by icEEG (27). Moreover, the ability of scalp EEG-fMRI to predict postsurgical outcome has also been mirrored by icEEG-fMRI studies (85).

Mapping seizure-related BOLD changes using EEG-fMRI (76,77) has offered an alternative to ictal-SPECT in principal. Due to the rarity and unpredictability of seizures most studies have only been case reports (19,86-88) or fortuitous recording of seizure (44,73-75,89) during interictal EEG-fMRI studies. However, following specific selection criteria based on seizure frequency and seizure types, our group has published the largest ictal case series showing that seizure onset-related BOLD maps have the highest degree of concordance with independently defined invasive and/or noninvasive SOZ, providing localization at sub-lobar level (9). These findings are in accordance with ours and others previous findings (44,70,73-75,89). Moreover, EEG-fMRI can separate ictal-onset, propagation and preictal related BOLD changes (9,19,90).

Interictal and seizure-related BOLD maps are frequently poorly understood due to the multiplicity of BOLD clusters within a single map. Therefore, a number of concordance schemes have been developed (7) based on the location of statistically most significant or clinically most relevant cluster. These multiple clusters are seen in the EZ/SOZ, seizure propagation related areas, symptomatogenic zone as well as resting state areas, which is more consistent with network involvement as opposed to mere spatial zone delineation (1,91). These studies indicate that non-invasive spike and seizure related BOLD localisation provided by scalp EEG-fMRI can be useful for guiding implantation of intracranial electrodes in patients who requires invasive evaluation prior to surgery.

EEG-fMRI investigation of cognitive networks in epilepsy

Loss of consciousness or cognitive impairment during seizures is a universally known fact. Also, cognition is impaired during the course of epilepsy (92) depending upon the type and location of epilepsy and structural abnormalities, and type of cognitive process i.e., language and memory (93-96). However, there are limited number of studies investigating the acute and immediate effects of IEDs on cognition and cognitive networks in patients with epilepsy. A common clinical manifestation of IEDs (97,98), known as transient cognitive impairment (TCI) is particularly associated with generalised spike and wave discharges (GSWD) lasting more than 3 sec (99,100).

Attention (68,69) and working memory (101) related BOLD networks are altered as an effect of GSWD. Reduction in resting functional connectivity in the medial frontal cortex together with poor attention task performance is associated with decreased activation of medial frontal cortex in children with absence epilepsy (102). A causal link is implied between such patterns and the cognitive ("downstream") or facilitation ("upstream") effects of GSWD (103)—a question underlined by a case report (104) in a patient without cognitive impairment during GSWDs which revealed GSWD-related BOLD changes in a similar cortico-subcortical network. This finding is established with additional cogency by the observations of impoverished architecture and connections in resting state networks (RSNs) associated with task impairment such as poor verbal memory retention (105-107). These result indicate that EEG-fMRI can potentially be deployed to observe functional changes in brain networks which otherwise might not be detectable clinically (101).

Epileptic networks observed using EEG-fMRI

When multiple regions are shown to be activated or deactivated in relation to a specific type of epileptic event, it is common to refer to such a pattern as a network, with each activated cluster representing a node (at least conceptually). In this section we re-interpret some of the commonly observed epileptic activity-related BOLD maps as putative networks, which we believe can be particularly

justified when these are considered in relation to, and found to incorporate some aspects of brain networks, identified in different contexts and using different methods, such as resting-state fMRI functional connectivity and PET studies.

In generalized epilepsy, a number of EEG-fMRI studies have demonstrated a common pattern which comprises BOLD increases in the thalamus and BOLD decreases in medial as well as lateral frontal, superior parietal, posterior cingulate, precuneus (22,23,25,26) and caudate (22,23,72,108,109), and the reticular formation (24). This cortico-subcortical network also involves the default mode network (DMN) which reflects physiological processes that undergirds attention and working memory (110). Alteration in the activation/deactivation of BOLD changes in the DMN (111) suggest that the normal brain activation/rest balance is apparently disturbed due to GSWDs (112-114) which in turn may be the reflection of changes in awareness. These findings indicate the importance of cortico-subcortical connectivity in producing and maintaining GSWDs which is consistent with the cortical focus theory (115), and BOLD changes in the precuneus (part of the DMN) may act to facilitate the occurrence of GSWDs (103,116). Different GSWD-related BOLD patterns have been demonstrated in Valproate responsive and resistant generalized epilepsy (117,118). Moreover, the duration of GSWD is linearly related to the amplitude of BOLD changes with no universal threshold effect of its duration (119).

Seizure-related BOLD decreases in the DMN have also been observed in focal epilepsy suggestive of the mechanism responsible for changes in awareness (9,75,120). Other networks are also recruited in refractory focal seizures e.g., RSNs (9), a visual attention network in children with photo paroxysmal response (21,121), musicogenic seizure-related networks (16,17), a reading epilepsy-related network (18,19) and epilepsia partialis continua-related networks (20). In some conditions such as Dravet Syndrome, a syndrome-specific epileptic network has not been identified, albeit specific thalamic and DMN-related regions demonstrated BOLD changes (122).

EEG-fMRI has provided interesting observations of the temporal window of BOLD changes associated with seizures. Several studies have reported BOLD changes prior to the onset of electrical changes on EEG during seizures. These preictal changes are relatively more widespread (9,70,71) than BOLD changes prior to the onset of IED (21).

In related observations, typically functional connectivity based on EEG/electrophysiology reveals increased FC in epileptic regions. In contrast fMRI BOLD measures reveal decreases in functional connectivity in epileptic regions (123,124). A recent study confirmed these connectivity patterns using simultaneous icEEG-fMRI data specifically for depth electrodes. However, higher within-zone BOLD functional connectivity, i.e., pathological zones, was found for grid electrodes in contrast to the results for depth electrodes.

Resting-state networks and epilepsy

The literature evidences increasing examination of spatially coherent, low frequency correlations or RSNs in the brain (125,126). These are spatially segregated areas representing underlying functional connectivity (127) which is important for development, maintenance, and function of the brain (106,110,128-131). As functional units they are active and synchronised both at rest and while performing a task (132,133). Fascination has been expressed in the contemplation of neuronal features responsible for these slow modulations—"Is it a small fraction of the population undergoing large variations or a large portion undergoing small deviations?" (134). These networks can be identified reliably across imaging sessions (135,136) and between subjects (132,136).

Several RSNs have been identified. However, two large anti-correlated systems corresponding to task engagement and task disengagement have been of more interest. One includes the DMN and the other is composed of task-based networks: somatosensory, visual, or attention RSNs (137-140). These networks are identified in several studies investigating BOLD changes associated with epileptic activity (44,73,141,142). The connectivity within these networks is altered possibly as an effect of epilepsy (5).

An effort has been made to quantify the involvement of different RSNs (143). It has also been found that there is an increase in the recruitment of RSNs during seizures as compared to IEDs, whilst the type and quantity of recruited RSNs also varies during seizures and IEDs. These BOLD networks in apparently healthy (non-affected) structure, away from conventionally defined epileptic areas, are thought to reflect projected neuronal activity not visible on EEG (56,144). Alternatively they can be interpreted as a reflection of the engagement of normal RSNs during epileptic activity, perhaps in the context of initiation or propagation of seizure activity (9,145).

Evolving the metrics in EEG-fMRI

We conclude by offering perspectives from the literature

that are likely to evolve both methodology and utility of EEG-fMRI, specifically in relation to its contribution to the current body of knowledge on epileptic networks. Graph representations of network features derived from data obtained with fMRI and EEG/MEG separately are obviously and naturally elaborated by the access to electrographic and BOLD signals provided simultaneously by EEG-fMRI (5). The technique provides a uniquely powerful method to elucidate the relationship between EEG and BOLD and through its capacity to reveal activity over the entire brain, to provide further insight into network dynamics.

Graph theory analysis approaches have been used to study the network properties of EZ/SOZ. EEG studies have shown that networks of patients who became seizure-free after surgery have specific characteristics (146) e.g., resection of network nodes with high centrality is associated with a more favourable outcome (147). Also, hub-like structures in a network further elaborate spreading of seizure activity, specifically in relation to high-frequency electrographic activity (148-150) and have shown predictive value for diagnosis of epilepsy in children after an initial seizure-like event (151). Network characteristics such as modularity and clustering co-efficient have been identified, in fMRI-BOLD studies, to be associated with cognitive impairment in patients with absence epilepsy (152), cryptogenic localization-related epilepsy (153) and frontal lobe epilepsy (154).

It is our hope and expectation that EEG-fMRI will play a crucial role in addressing unresolved issues such as the nature of the differences between ictal and interictal networks and the role of specific network elements (hubs) in the initiation and evolution of seizures in humans. The exploration of the relationship between simultaneously recorded BOLD and EEG measures of network dynamics in terms of graph representations may provide useful insights for future treatment options, especially epilepsy surgery (155-159).

In this review we posited simultaneous EEG-fMRI as a unique network investigative tool that provides a multidimensional metric by virtue of simultaneously recording that in principle can help us investigate brain activity further than the array of uni-modal EEG and fMRI studies. Whereas EEG and EEG-fMRI allow for network changes to be attributed to ictal or interictal activity based on vast established knowledge of the EEG manifestations of epilepsy, more work will be required to better understand the fMRI manifestations of the same activity and thereby help us elucidate the distinct contributions of transient or permanent network abnormalities to abnormality in epileptogenic, cognitive and sensory processing networks (5). These differences pose significant research challenge to EEG-fMRI: One that will facilitate a convergence of haemodynamic and electrographic information to a mutual lexicon such as graph theory and connectivity measures for evolving greater insight into epileptic networks (160). The exploitation of EEG-fMRI ability to identify different features of many networks simultaneously (143) during seizures as well as interictally may allow the integration of multidimensional data for potential identification of clinical biomarkers in epilepsy.

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