Review Article

Methods and utility of EEG-fMRI in epilepsy

Louis André van Graan[1,2], **Louis Lemieux**[1,2], **Umair Javaid Chaudhary**[1,2]

[1]Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK; [2]MRI Unit, Epilepsy Society, Chalfont St. Peter SL9 0RJ, UK

Correspondence to: Louis André van Graan. MRI Unit, Epilepsy Society, Chalfont St. Peter SL9 0RJ, UK. Email: umair.chaudhary@ucl.ac.uk.

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

Submitted Dec 04, 2014. Accepted for publication Jan 22, 2015.
doi: 10.3978/j.issn.2223-4292.2015.02.04
View this article at: http://dx.doi.org/10.3978/j.issn.2223-4292.2015.02.04

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.

Disclosure: The authors declare no conflict of interest.

References

1. Laufs H. Functional imaging of seizures and epilepsy: evolution from zones to networks. Curr Opin Neurol 2012;25:194-200.
2. Koepp MJ. Neuroimaging of drug resistance in epilepsy. Curr Opin Neurol 2014;27:192-8.
3. Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry 2004;75:1376-81.
4. Burch J, Marson A, Beyer F, Soares M, Hinde S, Wieshmann U, Woolacott N. Dilemmas in the interpretation of diagnostic accuracy studies on presurgical workup for epilepsy surgery. Epilepsia 2012;53:1294-302.
5. Centeno M, Carmichael DW. Network Connectivity in Epilepsy: Resting State fMRI and EEG-fMRI Contributions. Front Neurol 2014;5:93.
6. Mulert C, Lemieux L. eds. EEG-fMRI: Physiological Basis, Technique and Applications. Berlin, Heidelberg: Springer, 2010:153-71.
7. Chaudhary UJ, Duncan JS, Lemieux L. Mapping hemodynamic correlates of seizures using fMRI: A review. Hum Brain Mapp 2013;34:447-66.
8. van Houdt PJ, de Munck JC, Leijten FS, Huiskamp GJ, Colon AJ, Boon PA, Ossenblok PP. EEG-fMRI correlation patterns in the presurgical evaluation of focal epilepsy: a comparison with electrocorticographic data and surgical outcome measures. Neuroimage 2013;75:238-48.
9. Chaudhary UJ, Carmichael DW, Rodionov R, Thornton RC, Bartlett P, Vulliemoz S,Micallef C, McEvoy AW, Diehl B, Walker MC, Duncan JS, Lemieux L. Mapping preictal and ictal haemodynamic networks using video-electroencephalography and functional imaging. Brain

2012;135:3645-63.
10. Thornton R, Laufs H, Rodionov R, Cannadathu S, Carmichael DW, Vulliemoz S, Salek-Haddadi A, McEvoy AW, Smith SM, Lhatoo S, Elwes RD, Guye M, Walker MC, Lemieux L, Duncan JS. EEG correlated functional MRI and postoperative outcome in focal epilepsy. J Neurol Neurosurg Psychiatry 2010;81:922-7.
11. Chaudhary UJ, Carmichael DW, Rodionov R, Vulliemoz S, Scott C, Mcevoy AW, Micallef C, Diehl B, Walker MC, Duncan J, Lemieux L. Mapping the irritative zone using simultanoeus intracranial EEG-fMRI and comparison with postsurgical outcome. Epilepsia 2012;53:14.
12. Thornton R, Vulliemoz S, Rodionov R, Carmichael DW, Chaudhary UJ, Diehl B, Laufs H, Vollmar C, McEvoy AW, Walker MC, Bartolomei F, Guye M, Chauvel P, Duncan JS, Lemieux L. Epileptic networks in focal cortical dysplasia revealed using electroencephalography-functional magnetic resonance imaging. Ann Neurol 2011;70:822-37.
13. Zijlmans M, Buskens E, Hersevoort M, Huiskamp G, van Huffelen AC, Leijten FS. Should we reconsider epilepsy surgery? The motivation of patients once rejected. Seizure 2008;17:374-7.
14. Pittau F, Dubeau F, Gotman J. Contribution of EEG/fMRI to the definition of the epileptic focus. Neurology 2012;78:1479-87.
15. Salek-Haddadi A, Diehl B, Hamandi K, Merschhemke M, Liston A, Friston K, Duncan JS, Fish DR, Lemieux L. Hemodynamic correlates of epileptiform discharges: an EEG-fMRI study of 63 patients with focal epilepsy. Brain Res 2006;1088:148-66.
16. Marrosu F, Barberini L, Puligheddu M, Bortolato M, Mascia M, Tuveri A, Muroni A, Mallarini G, Avanzini G. Combined EEG/fMRI recording in musicogenic epilepsy. Epilepsy Res 2009;84:77-81.
17. Mórocz IA, Karni A, Haut S, Lantos G, Liu G. fMRI of triggerable aurae in musicogenic epilepsy. Neurology 2003;60:705-9.
18. Salek-Haddadi A, Mayer T, Hamandi K, Symms M, Josephs O, Fluegel D, Woermann F, Richardson MP, Noppeney U, Wolf P, Koepp MJ. Imaging seizure activity: a combined EEG/EMG-fMRI study in reading epilepsy. Epilepsia 2009;50:256-64.
19. Vaudano AE, Carmichael DW, Salek-Haddadi A, Rampp S, Stefan H, Lemieux L, Koepp MJ. Networks involved in seizure initiation. A reading epilepsy case studied with EEG-fMRI and MEG. Neurology 2012;79:249-53.
20. Vaudano AE, Di Bonaventura C, Carni M, Rodionov R, Lapenta L, Casciato S, Fattouch J, Egeo G, Pantano P, Nucciarelli V, Maraviglia B, Prencipe M, Lemieux L, Giallonardo AT. Ictal haemodynamic changes in a patient affected by "subtle" Epilepsia Partialis Continua. Seizure 2012;21:65-9.
21. Jacobs J, Levan P, Moeller F, Boor R, Stephani U, Gotman J, Siniatchkin M. Hemodynamic changes preceding the interictal EEG spike in patients with focal epilepsy investigated using simultaneous EEG-fMRI. Neuroimage 2009;45:1220-31.
22. Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. Proc Natl Acad Sci U S A 2005;102:15236-40.
23. Salek-Haddadi A, Lemieux L, Merschhemke M, Friston KJ, Duncan JS, Fish DR. Functional magnetic resonance imaging of human absence seizures. Ann Neurol 2003;53:663-7.
24. Carney PW, Masterton RA, Harvey AS, Scheffer IE, Berkovic SF, Jackson GD. The core network in absence epilepsy. Differences in cortical and thalamic BOLD response. Neurology 2010;75:904-11.
25. Archer JS, Abbott DF, Waites AB, Jackson GD. fMRI "deactivation" of the posterior cingulate during generalized spike and wave. Neuroimage 2003;20:1915-22.
26. Moeller F, Siebner HR, Wolff S, Muhle H, Boor R, Granert O, Jansen O, Stephani U, Siniatchkin M. Changes in activity of striato-thalamo-cortical network precede generalized spike wave discharges. Neuroimage 2008;39:1839-49.
27. Vulliemoz S, Carmichael DW, Rosenkranz K, Diehl B, Rodionov R, Walker MC, McEvoy AW, Lemieux L. Simultaneous intracranial EEG and fMRI of interictal epileptic discharges in humans. Neuroimage 2011;54:182-90.
28. Cunningham CB, Goodyear BG, Badawy R, Zaamout F, Pittman DJ, Beers CA, Federico P. Intracranial EEG-fMRI analysis of focal epileptiform discharges in humans. Epilepsia 2012;53:1636-48.
29. Laufs H, Daunizeau J, Carmichael DW, Kleinschmidt A. Recent advances in recording electrophysiological data simultaneously with magnetic resonance imaging. Neuroimage 2008;40:515-28.
30. Laufs H. A personalized history of EEG-fMRI integration. Neuroimage 2012;62:1056-67.
31. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R. Dynamic magnetic resonance

imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci U S A 1992;89:5675-9.
32. Ogawa S, Lee TM, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn Reson Med 1990;14:68-78.
33. Vulliemoz S, Lemieux L, Daunizeau J, Michel CM, Duncan JS. The combination of EEG source imaging and EEG-correlated functional MRI to map epileptic networks. Epilepsia 2010;51:491-505.
34. Logothetis NK, Wandell BA. Interpreting the BOLD signal. Annu Rev Physiol 2004;66:735-69.
35. Ekstrom A. How and when the fMRI BOLD signal relates to underlying neural activity: the danger in dissociation. Brain Res Rev 2010;62:233-44.
36. Friston KJ, Frith CD, Turner R, Frackowiak RS. Characterizing evoked hemodynamics with fMRI. Neuroimage 1995;2:157-65.
37. Aguirre GK, Zarahn E, D'esposito M. The variability of human, BOLD hemodynamic responses. Neuroimage 1998;8:360-9.
38. Lindquist MA, Meng Loh J, Atlas LY, Wager TD. Modeling the hemodynamic response function in fMRI: efficiency, bias and mis-modeling. Neuroimage 2009;45:S187-98.
39. Schacter DL, Buckner RL, Koutstaal W, Dale AM, Rosen BR. Late onset of anterior prefrontal activity during true and false recognition: an event-related fMRI study. Neuroimage 1997;6:259-69.
40. Bagshaw AP, Aghakhani Y, Bénar CG, Kobayashi E, Hawco C, Dubeau F, Pike GB, Gotman J. EEG-fMRI of focal epileptic spikes: analysis with multiple haemodynamic functions and comparison with gadolinium-enhanced MR angiograms. Hum Brain Mapp 2004;22:179-92.
41. Glover GH. Deconvolution of impulse response in event-related BOLD fMRI. Neuroimage 1999;9:416-29.
42. Lindquist MA, Wager TD. Validity and power in hemodynamic response modeling: a comparison study and a new approach. Hum Brain Mapp 2007;28:764-84.
43. Lemieux L, Laufs H, Carmichael D, Paul JS, Walker MC, Duncan JS. Noncanonical spike-related BOLD responses in focal epilepsy. Hum Brain Mapp 2008;29:329-45.
44. Thornton RC, Rodionov R, Laufs H, Vulliemoz S, Vaudano A, Carmichael D, Cannadathu S, Guye M, McEvoy A, Lhatoo S, Bartolomei F, Chauvel P, Diehl B, De Martino F, Elwes RD, Walker MC, Duncan JS, Lemieux L. Imaging haemodynamic changes related to seizures: comparison of EEG-based general linear model, independent component analysis of fMRI and intracranial EEG. Neuroimage 2010;53:196-205.
45. Di X, Biswal BB. Identifying the default mode network structure using dynamic causal modeling on resting-state functional magnetic resonance imaging. Neuroimage 2014;86:53-9.
46. Lu Y, Bagshaw AP, Grova C, Kobayashi E, Dubeau F, Gotman J. Using voxel-specific hemodynamic response function in EEG-fMRI data analysis. Neuroimage 2006;32:238-47.
47. Lu Y, Grova C, Kobayashi E, Dubeau F, Gotman J. Using voxel-specific hemodynamic response function in EEG-fMRI data analysis: An estimation and detection model. Neuroimage 2007;34:195-203.
48. Jacobs J, Hawco C, Kobayashi E, Boor R, LeVan P, Stephani U, Siniatchkin M, Gotman J. Variability of the hemodynamic response as a function of age and frequency of epileptic discharge in children with epilepsy. Neuroimage 2008;40:601-14.
49. Bénar CG, Gross DW, Wang Y, Petre V, Pike B, Dubeau F, Gotman J. The BOLD response to interictal epileptiform discharges. Neuroimage 2002;17:1182-92.
50. van Houdt PJ, de Munck JC, Zijlmans M, Huiskamp G, Leijten FS, Boon PA, Ossenblok PP. Comparison of analytical strategies for EEG-correlated fMRI data in patients with epilepsy. Magn Reson Imaging 2010;28:1078-86.
51. Masterton RA, Harvey AS, Archer JS, Lillywhite LM, Abbott DF, Scheffer IE, Jackson GD. Focal epileptiform spikes do not show a canonical BOLD response in patients with benign rolandic epilepsy (BECTS). Neuroimage 2010;51:252-60.
52. Murta T, Leite M, Carmichael DW, Figueiredo P, Lemieux L. Electrophysiological correlates of the BOLD signal for EEG-informed fMRI. Hum Brain Mapp 2015;36:391-414.
53. Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-related fMRI: characterizing differential responses. Neuroimage 1998;7:30-40.
54. Pandian JD, Cascino GD, So EL, Manno E, Fulgham JR. Digital video-electroencephalographic monitoring in the neurological-neurosurgical intensive care unit: clinical features and outcome. Arch Neurol 2004;61:1090-4.
55. Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. Epilepsia 2005;46:669-76.
56. Ray A, Tao JX, Hawes-Ebersole SM, Ebersole JS. Localizing value of scalp EEG spikes: a simultaneous scalp and intracranial study. Clin Neurophysiol 2007;118:69-79.

57. Grouiller F, Thornton RC, Groening K, Spinelli L, Duncan JS, Schaller K, Siniatchkin M, Lemieux L, Seeck M, Michel CM, Vulliemoz S. With or without spikes: localization of focal epileptic activity by simultaneous electroencephalography and functional magnetic resonance imaging. Brain 2011;134:2867-86.
58. Elshoff L, Groening K, Grouiller F, Wiegand G, Wolff S, Michel C, Stephani U, Siniatchkin M. The value of EEG-fMRI and EEG source analysis in the presurgical setup of children with refractory focal epilepsy. Epilepsia 2012;53:1597-606.
59. Friston KJ, Ashburner J, Frith C, Poline JB, Heather JD, Frackowiak RSJ. Spatial Registration and Normalization of Images. Hum Brain Mapp 1995;3:165-89.
60. Wilke M. An alternative approach towards assessing and accounting for individual motion in fMRI timeseries. Neuroimage 2012;59:2062-72.
61. Lemieux L, Salek-Haddadi A, Lund TE, Laufs H, Carmichael D. Modelling large motion events in fMRI studies of patients with epilepsy. Magn Reson Imaging 2007;25:894-901.
62. Mullinger KJ, Morgan PS, Bowtell RW. Improved artifact correction for combined electroencephalography/functional MRI by means of synchronization and use of vectorcardiogram recordings. J Magn Reson Imaging 2008;27:607-16.
63. Liston AD, Lund TE, Salek-Haddadi A, Hamandi K, Friston KJ, Lemieux L. Modelling cardiac signal as a confound in EEG-fMRI and its application in focal epilepsy studies. Neuroimage 2006;30:827-34.
64. van Houdt PJ, Ossenblok PP, Boon PA, Leijten FS, Velis DN, Stam CJ, de Munck JC. Correction for pulse height variability reduces physiological noise in functional MRI when studying spontaneous brain activity. Hum Brain Mapp 2010;31:311-25.
65. Chaudhary UJ, Rodionov R, Carmichael DW, Thornton RC, Duncan JS, Lemieux L. Improving the sensitivity of EEG-fMRI studies of epileptic activity by modelling eye blinks, swallowing and other video-EEG detected physiological confounds. Neuroimage 2012;61:1383-93.
66. Archer JS, Waites AB, Abbott DF, Federico P, Jackson GD. Event-related fMRI of myoclonic jerks arising from dysplastic cortex. Epilepsia 2006;47:1487-92.
67. Archer JS, Abbott DF, Masterton RA, Palmer SM, Jackson GD. Functional MRI interactions between dysplastic nodules and overlying cortex in periventricular nodular heterotopia. Epilepsy Behav 2010;19:631-4.
68. Bai X, Vestal M, Berman R, Negishi M, Spann M, Vega C, Desalvo M, Novotny EJ, Constable RT, Blumenfeld H. Dynamic time course of typical childhood absence seizures: EEG, behavior, and functional magnetic resonance imaging. J Neurosci 2010;30:5884-93.
69. Berman R, Negishi M, Vestal M, Spann M, Chung MH, Bai X, Purcaro M, Motelow JE, Danielson N, Dix-Cooper L, Enev M, Novotny EJ, Constable RT, Blumenfeld H. Simultaneous EEG, fMRI, and behavior in typical childhood absence seizures. Epilepsia 2010;51:2011-22.
70. Donaire A, Bargallo N, Falcón C, Maestro I, Carreno M, Setoain J, Rumià J, Fernández S, Pintor L, Boget T. Identifying the structures involved in seizure generation using sequential analysis of ictal-fMRI data. Neuroimage 2009;47:173-83.
71. Federico P, Abbott DF, Briellmann RS, Harvey AS, Jackson GD. Functional MRI of the pre-ictal state. Brain 2005;128:1811-7.
72. Hamandi K, Salek-Haddadi A, Laufs H, Liston A, Friston K, Fish DR, Duncan JS, Lemieux L. EEG-fMRI of idiopathic and secondarily generalized epilepsies. Neuroimage 2006;31:1700-10.
73. LeVan P, Tyvaert L, Moeller F, Gotman J. Independent component analysis reveals dynamic ictal BOLD responses in EEG-fMRI data from focal epilepsy patients. Neuroimage 2010;49:366-78.
74. Tyvaert L, Hawco C, Kobayashi E, LeVan P, Dubeau F, Gotman J. Different structures involved during ictal and interictal epileptic activity in malformations of cortical development: an EEG-fMRI study. Brain 2008;131:2042-60.
75. Tyvaert L, LeVan P, Dubeau F, Gotman J. Noninvasive dynamic imaging of seizures in epileptic patients. Hum Brain Mapp 2009;30:3993-4011.
76. Detre JA, Sirven JI, Alsop DC, O'Connor MJ, French JA. Localization of subclinical ictal activity by functional magnetic resonance imaging: correlation with invasive monitoring. Ann Neurol 1995;38:618-24.
77. Jackson GD, Connelly A, Cross JH, Gordon I, Gadian DG.Functional magnetic resonance imaging of focal seizures. Neurology 1994;44:850-6.
78. Warach S, Ives JR, Schlaug G, Patel MR, Darby DG, Thangaraj V, Edelman RR, Schomer DL. EEG-triggered echo-planar functional MRI in epilepsy. Neurology 1996;47:89-93.
79. Lemieux L, Salek-Haddadi A, Josephs O, Allen P, Toms N, Scott C, Krakow K, Turner R, Fish DR. Event-related fMRI with simultaneous and continuous EEG: description of the method and initial case report. Neuroimage

2001;14:780-7.
80. Gholipour T, Moeller F, Pittau F, Dubeau F, Gotman J.Reproducibility of interictal EEG-fMRI results in patients with epilepsy. Epilepsia 2011;52:433-42.
81. Pesaresi I, Cosottini M, Belmonte G, Maritato P, Mascalchi M, Puglioli M, Sartucci F, Bartolozzi C, Murri L. Reproducibility of BOLD localization of interictal activity in patients with focal epilepsy: intrasession and intersession comparisons. MAGMA 2011;24:285-96.
82. An D, Fahoum F, Hall J, Olivier A, Gotman J, Dubeau F. Electroencephalography/functional magnetic resonance imaging responses help predict surgical outcome in focal epilepsy. Epilepsia 2013;54:2184-94.
83. Coan A, Chaudhary UJ, Campos B, Perani S, Thornton R, Vulliemoz S, Grouiller F, Beltramini G, Diehl B, Scott C, Covolan RJ, Cendes F, Lemieux L. EEG-FMRI in the pre-surgical evaluation of temporal lobe epilepsy patients. American Epilepsy Society Conference. 2012.
84. Zijlmans M, Huiskamp G, Hersevoort M, Seppenwoolde JH, van Huffelen AC, Leijten FS. EEG-fMRI in the preoperative work-up for epilepsy surgery. Brain 2007;130:2343-53.
85. Chaudhary UJ, Perani S, Carmichael D, Rodionov R, Vulliemoz P, Thornton R, Pugnaghi M, Micallef C, McEvoy A, Scott C, Diehl B, Walker M, Duncan J, Lemieux L. Epileptic Networks using scalp and intracranial EEG-fMRI and postsurgical outcome. Epilepsy Curr 2014;14:88-89.
86. Sandhya M, Bharath RD, Panda R, Chandra SR, Kumar N, George L, Thamodharan A, Gupta AK, Satishchandra P. Understanding the pathophysiology of reflex epilepsy using simultaneous EEG-fMRI. Epileptic Disord 2014;16:19-29.
87. Avesani M, Giacopuzzi S, Bongiovanni LG, Borelli P, Cerini R, Pozzi Mucelli R, Fiaschi A. EEG-fMRI evaluation of patients with mesial temporal lobe sclerosis. Neuroradiol J 2014;27:45-54.
88. Kokkinos V, Zountsas B, Kontogiannis K, Garganis K. Epileptogenic networks in two patients with hypothalamic hamartoma. Brain Topogr 2012;25:327-31.
89. Sierra-Marcos A, Maestro I, Falcón C, Donaire A, Setoain J, Aparicio J, Rumià J, Pintor L, Boget T, Carreño M, Bargalló N. Ictal EEG-fMRI in localization of epileptogenic area in patients with refractory neocortical focal epilepsy. Epilepsia 2013;54:1688-98.
90. Meletti S, Vignoli A, Benuzzi F, Avanzini P, Ruggieri A, Pugnaghi M, Nichelli P, Canevini MP. Ictal involvement of the nigrostriatal system in subtle seizures of ring chromosome 20 epilepsy. Epilepsia 2012;53:e156-60.
91. Halász P. The concept of epileptic networks. Part 1. Ideggyogy Sz 2010;63:293-303.
92. Chaudhary UJ, Duncan JS. Applications of blood-oxygen-level-dependent functional magnetic resonance imaging and diffusion tensor imaging in epilepsy. Neuroimaging Clin N Am 2014;24:671-94.
93. Wagner DD, Sziklas V, Garver KE, Jones-Gotman M. Material-specific lateralization of working memory in the medial temporal lobe. Neuropsychologia 2009;47:112-22.
94. Campo P, Garrido MI, Moran RJ, García-Morales I, Poch C, Toledano R, Gil-Nagel A, Dolan RJ, Friston KJ. Network reconfiguration and working memory impairment in mesial temporal lobe epilepsy. Neuroimage 2013;72:48-54.
95. Stretton J, Thompson PJ. Frontal lobe function in temporal lobe epilepsy. Epilepsy Res 2012;98:1-13.
96. Hoppe C, Elger CE, Helmstaedter C. Long-term memory impairment in patients with focal epilepsy. Epilepsia 2007;48 Suppl 9:26-9.
97. Baxendale S, Heaney D, Thompson PJ, Duncan JS. Cognitive consequences of childhood-onset temporal lobe epilepsy across the adult lifespan. Neurology 2010;75:705-11.
98. Jensen FE. Epilepsy as a spectrum disorder: Implications from novel clinical and basic neuroscience. Epilepsia 2011;52 Suppl 1:1-6.
99. Binnie CD, Marston D. Cognitive correlates of interictal discharges. Epilepsia 1992;33 Suppl 6:S11-7.
100. Binnie CD, de Silva M, Hurst A. Rolandic spikes and cognitive function. Epilepsy Res Suppl 1992;6:71-3.
101. Chaudhary UJ, Centeno M, Carmichael DW, Vollmar C, Rodionov R, Bonelli S, Stretton J, Pressler R, Eriksson SH, Sisodiya S, Friston K, Duncan JS, Lemieux L, Koepp M. Imaging the interaction: epileptic discharges, working memory, and behavior. Hum Brain Mapp 2013;34:2910-7.
102. Killory BD, Bai X, Negishi M, Vega C, Spann MN, Vestal M, Guo J, Berman R, Danielson N, Trejo J, Shisler D, Novotny EJ Jr, Constable RT, Blumenfeld H. Impaired attention and network connectivity in childhood absence epilepsy. Neuroimage 2011;56:2209-17.
103. Vaudano AE, Laufs H, Kiebel SJ, Carmichael DW, Hamandi K, Guye M, Thornton R, Rodionov R, Friston KJ, Duncan JS, Lemieux L. Causal hierarchy within the thalamo-cortical network in spike and wave discharges. PLoS One 2009;4:e6475.
104. Moeller F, Muhle H, Wiegand G, Wolff S, Stephani U, Siniatchkin M. EEG-fMRI study of generalized spike and

wave discharges without transitory cognitive impairment. Epilepsy Behav 2010;18:313-6.

105. Holmes M, Folley BS, Sonmezturk HH, Gore JC, Kang H, Abou-Khalil B, Morgan VL. Resting state functional connectivity of the hippocampus associated with neurocognitive function in left temporal lobe epilepsy. Hum Brain Mapp 2014;35:735-44.
106. Pizoli CE, Shah MN, Snyder AZ, Shimony JS, Limbrick DD, Raichle ME, Schlaggar BL, Smyth MD. Resting-state activity in development and maintenance of normal brain function. Proc Natl Acad Sci U S A 2011;108:11638-43.
107. Wang Z, Lu G, Zhang Z, Zhong Y, Jiao Q, Zhang Z, Tan Q, Tian L, Chen G, Liao W, Li K, Liu Y. Altered resting state networks in epileptic patients with generalized tonic-clonic seizures. Brain Res 2011;1374:134-41.
108. Hamandi K, Laufs H, Nöth U, Carmichael DW, Duncan JS, Lemieux L. BOLD and perfusion changes during epileptic generalised spike wave activity. Neuroimage 2008;39:608-18.
109. Aghakhani Y, Bagshaw AP, Bénar CG, Hawco C, Andermann F, Dubeau F, Gotman J. fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. Brain 2004;127:1127-44.
110. Raichle ME, Mintun MA. Brain work and brain imaging. Annu Rev Neurosci 2006;29:449-76.
111. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A 2001;98:676-82.
112. Laufs H, Hamandi K, Salek-Haddadi A, Kleinschmidt AK, Duncan JS, Lemieux L. Temporal lobe interictal epileptic discharges affect cerebral activity in "default mode" brain regions. Hum Brain Mapp 2007;28:1023-32.
113. Laufs H, Lengler U, Hamandi K, Kleinschmidt A, Krakow K. Linking generalized spike-and-wave discharges and resting state brain activity by using EEG/fMRI in a patient with absence seizures. Epilepsia 2006;47:444-8.
114. Logothetis NK. What we can do and what we cannot do with fMRI. Nature 2008;453:869-78.
115. Meeren H, van Luijtelaar G, Lopes da Silva F, Coenen A. Evolving concepts on the pathophysiology of absence seizures: the cortical focus theory. Arch Neurol 2005;62:371-6.
116. Benuzzi F, Mirandola L, Pugnaghi M, Farinelli V, Tassinari CA, Capovilla G, Cantalupo G, Beccaria F, Nichelli P, Meletti S. Increased cortical BOLD signal anticipates generalized spike and wave discharges in adolescents and adults with idiopathic generalized epilepsies. Epilepsia 2012;53:622-30.
117. Szaflarski JP, Lindsell CJ, Zakaria T, Banks C, Privitera MD. Seizure control in patients with idiopathic generalized epilepsies: EEG determinants of medication response. Epilepsy Behav 2010;17:525-30.
118. Szaflarski JP, Kay B, Gotman J, Privitera MD, Holland SK. The relationship between the localization of the generalized spike and wave discharge generators and the response to valproate. Epilepsia 2013;54:471-80.
119. Pugnaghi M, Carmichael DW, Vaudano AE, Chaudhary UJ, Benuzzi F, Di Bonaventura C, Giallonardo AT, Rodionov R, Walker MC, Duncan JS, Meletti S, Lemieux L. Generalized spike and waves: effect of discharge duration on brain networks as revealed by BOLD fMRI. Brain Topogr 2014;27:123-37.
120. Fahoum F, Zelmann R, Tyvaert L, Dubeau F, Gotman J. Epileptic discharges affect the default mode network--FMRI and intracerebral EEG evidence. PLoS One 2013;8:e68038.
121. Moeller F, Siebner HR, Ahlgrimm N, Wolff S, Muhle H, Granert O, Boor R, Jansen O, Gotman J, Stephani U, Siniatchkin M. fMRI activation during spike and wave discharges evoked by photic stimulation. Neuroimage 2009;48:682-95.
122. Moehring J, von Spiczak S, Moeller F, Helbig I, Wolff S, Jansen O, Muhle H, Boor R, Stephani U, Siniatchkin M. Variability of EEG-fMRI findings in patients with SCN1A-positive Dravet syndrome. Epilepsia 2013;54:918-26.
123. Bettus G, Guedj E, Joyeux F, Confort-Gouny S, Soulier E, Laguitton V, Cozzone PJ, Chauvel P, Ranjeva JP, Bartolomei F, Guye M. Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. Hum Brain Mapp 2009;30:1580-91.
124. Bettus G, Ranjeva JP, Wendling F, Bénar CG, Confort-Gouny S, Régis J, Chauvel P, Cozzone PJ, Lemieux L, Bartolomei F, Guye M. Interictal functional connectivity of human epileptic networks assessed by intracerebral EEG and BOLD signal fluctuations. PLoS One 2011;6:e20071.
125. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995;34:537-41.
126. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 2005;360:1001-13.
127. Fox MD, Raichle ME. Spontaneous fluctuations in brain

activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007;8:700-11.

128. Doria V, Beckmann CF, Arichi T, Merchant N, Groppo M, Turkheimer FE, Counsell SJ, Murgasova M, Aljabar P, Nunes RG, Larkman DJ, Rees G, Edwards AD. Emergence of resting state networks in the preterm human brain. Proc Natl Acad Sci U S A 2010;107:20015-20.
129. Raichle ME. The brain's dark energy. Sci Am 2010;302:44-9.
130. Supekar K, Uddin LQ, Prater K, Amin H, Greicius MD, Menon V. Development of functional and structural connectivity within the default mode network in young children. Neuroimage 2010;52:290-301.
131. Zielinski BA, Gennatas ED, Zhou J, Seeley WW. Network-level structural covariance in the developing brain. Proc Natl Acad Sci U S A 2010;107:18191-6.
132. Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 2006;103:13848-53.
133. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 2009;106:13040-5.
134. Hyder F, Rothman DL. Neuronal correlate of BOLD signal fluctuations at rest: err on the side of the baseline. Proc Natl Acad Sci U S A 2010;107:10773-4.
135. Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, Beckmann CF, Adelstein JS, Buckner RL, Colcombe S, Dogonowski AM, Ernst M, Fair D, Hampson M, Hoptman MJ, Hyde JS, Kiviniemi VJ, Kötter R, Li SJ, Lin CP, Lowe MJ, Mackay C, Madden DJ, Madsen KH, Margulies DS, Mayberg HS, McMahon K, Monk CS, Mostofsky SH, Nagel BJ, Pekar JJ, Peltier SJ, Petersen SE, Riedl V, Rombouts SA, Rypma B, Schlaggar BL, Schmidt S, Seidler RD, Siegle GJ, Sorg C, Teng GJ, Veijola J, Villringer A, Walter M, Wang L, Weng XC, Whitfield-Gabrieli S, Williamson P, Windischberger C, Zang YF, Zhang HY, Castellanos FX, Milham MP. Toward discovery science of human brain function. Proc Natl Acad Sci U S A 2010;107:4734-9.
136. Shehzad Z, Kelly AM, Reiss PT, Gee DG, Gotimer K, Uddin LQ, Lee SH, Margulies DS, Roy AK, Biswal BB, Petkova E, Castellanos FX, Milham MP. The resting brain: unconstrained yet reliable. Cereb Cortex 2009;19:2209-29.
137. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, Vogel AC, Laumann TO, Miezin FM, Schlaggar BL, Petersen SE. Functional network organization of the human brain. Neuron 2011;72:665-78.
138. Chai XJ, Castañón AN, Ongür D, Whitfield-Gabrieli S. Anticorrelations in resting state networks without global signal regression. Neuroimage 2012;59:1420-8.
139. Zhang Z, Liao W, Zuo XN, Wang Z, Yuan C, Jiao Q, Chen H, Biswal BB, Lu G, Liu Y. Resting-state brain organization revealed by functional covariance networks. PLoS One 2011;6:e28817.
140. Golland Y, Golland P, Bentin S, Malach R. Data-driven clustering reveals a fundamental subdivision of the human cortex into two global systems. Neuropsychologia 2008;46:540-53.
141. Moeller F, LeVan P, Gotman J. Independent component analysis (ICA) of generalized spike wave discharges in fMRI: comparison with general linear model-based EEG-fMRI. Hum Brain Mapp 2011;32:209-17.
142. Rodionov R, De Martino F, Laufs H, Carmichael DW, Formisano E, Walker M, Duncan JS, Lemieux L. Independent component analysis of interictal fMRI in focal epilepsy: comparison with general linear model-based EEG-correlated fMRI. Neuroimage 2007;38:488-500.
143. Kozák LR, van Graan LA, Chaudhary UJ, Szabó Á, Lemieux L. Describing Epilepsy-related BOLD Changes in the Framework of Resting State Functional Networks. 20th Annual Meeting of the Organization for Human Brain Mapping. Hamburg, Germany, 2014.
144. Yu JM, Tyvaert L, Levan P, Zelmann R, Dubeau F, Gotman J, Kobayashi E. EEG spectral changes underlying BOLD responses contralateral to spikes in patients with focal epilepsy. Epilepsia 2009;50:1804-9.
145. Mantini D, Perrucci MG, Del Gratta C, Romani GL, Corbetta M. Electrophysiological signatures of resting state networks in the human brain. Proc Natl Acad Sci U S A 2007;104:13170-5.
146. van Dellen E, Douw L, Hillebrand A, de Witt Hamer PC, Baayen JC, Heimans JJ, Reijneveld JC, Stam CJ. Epilepsy surgery outcome and functional network alterations in longitudinal MEG: a minimum spanning tree analysis. Neuroimage 2014;86:354-63.
147. Wilke C, Worrell G, He B. Graph analysis of epileptogenic networks in human partial epilepsy. Epilepsia 2011;52:84-93.
148. Amini L, Jutten C, Achard S, David O, Kahane P, Vercueil L, Minotti L, Hossein-Zadeh GA, Soltanian-Zadeh H. Comparison of five directed graph measures for identification of leading interictal epileptic regions. Physiol Meas 2010;31:1529-46.

149. Varotto G, Tassi L, Franceschetti S, Spreafico R, Panzica F. Epileptogenic networks of type II focal cortical dysplasia: a stereo-EEG study. Neuroimage 2012;61:591-8.
150. Kim JY, Kang HC, Kim K, Kim HD, Im CH. Localization of epileptogenic zones in Lennox-Gastaut syndrome (LGS) using graph theoretical analysis of ictal intracranial EEG: a preliminary investigation. Brain Dev 2015;37:29-36.
151. van Diessen E, Otte WM, Braun KP, Stam CJ, Jansen FE. Improved diagnosis in children with partial epilepsy using a multivariable prediction model based on EEG network characteristics. PLoS One 2013;8:e59764.
152. Chavez M, Valencia M, Navarro V, Latora V, Martinerie J. Functional modularity of background activities in normal and epileptic brain networks. Phys Rev Lett 2010;104:118701.
153. Vlooswijk MC, Vaessen MJ, Jansen JF, de Krom MC, Majoie HJ, Hofman PA, Aldenkamp AP, Backes WH. Loss of network efficiency associated with cognitive decline in chronic epilepsy. Neurology 2011;77:938-44.
154. Vaessen MJ, Braakman HM, Heerink JS, Jansen JF, Debeij-van Hall MH, Hofman PA, Aldenkamp AP, Backes WH. Abnormal modular organization of functional networks in cognitively impaired children with frontal lobe epilepsy. Cereb Cortex 2013;23:1997-2006.
155. Bernhardt BC, Hong S, Bernasconi A, Bernasconi N. Imaging structural and functional brain networks in temporal lobe epilepsy. Front Hum Neurosci 2013;7:624.
156. Guye M, Bettus G, Bartolomei F, Cozzone PJ. Graph theoretical analysis of structural and functional connectivity MRI in normal and pathological brain networks. MAGMA 2010;23:409-21.
157. Onias H, Viol A, Palhano-Fontes F, Andrade KC, Sturzbecher M3, Viswanathan G, de Araujo DB. Brain complex network analysis by means of resting state fMRI and graph analysis: will it be helpful in clinical epilepsy? Epilepsy Behav 2014;38:71-80.
158. Minati L, Varotto G, D'Incerti L, Panzica F, Chan D. From brain topography to brain topology: relevance of graph theory to functional neuroscience. Neuroreport 2013;24:536-43.
159. van Diessen E, Diederen SJ, Braun KP, Jansen FE, Stam CJ. Functional and structural brain networks in epilepsy: what have we learned? Epilepsia 2013;54:1855-65.
160. Deligianni F, Centeno M, Carmichael DW, Clayden JD. Relating resting-state fMRI and EEG whole-brain connectomes across frequency bands. Front Neurosci 2014;8:258.

Cite this article as: van Graan LA, Lemieux L, Chaudhary UJ. Methods and utility of EEG-fMRI in epilepsy. Quant Imaging Med Surg 2015;5(2):300-312. doi: 10.3978/j.issn.2223-4292.2015.02.04