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Scalp and Intracranial EEG-fMRI in Epilepsy

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Abstract

The choice of treatment for epilepsy patients relies on the identification and characterization of epileptic discharges and the type of epilepsy. The continued lack of a universally applied gold standard in presurgical evaluation has opened the ways to the investigation of new localizing and mapping tools in difficult cases including simultaneous EEG-fMRI, which can be used to map interical and ictal discharges-related haemodynamic networks. The rapid increase in the literature on EEG-fMRI attests to its promised contribution in understanding of epilepsy-related and physiological networks of the brain. Its applications to investigate epileptic networks in humans have evolved since the mid 1990's, and has yielded a better knowledge of the generation, propagation and particularly localisation of epileptic discharges, as well their interaction with the physiological and pathological brain networks. Here, we review the published literature to raise the awareness of different concepts pertaining to the applications of simultaneous EEG-fMRI in epilepsy and discuss their potential impact on our understanding of epilepsy and its clinical management. We also describe our perspectives regarding possible future roles of the technique in epilepsy.

Abbreviations: AED: Antiepileptic Drugs; BOLD: Blood Oxygen Level Dependent; DMN: Default Mode Network; ECG: Electrocardiogram; EEG: Electroencephalography; EEG-fMRI: Simultaneous Electroencephalography and Functional Magneticresonance Imaging; EOG: Electro-occulogram; EZ: Epileptogenic Zone; fMRI: Functional Magnetic Resonance Imaging; GLM: General Linear Model; GSWDs: Generalized Spike and Wave Discharges; HRF: Haemodynamic Response Function; ICA: Independent Component Analysis; ictal-SPECT = Ictal Single Photon Emission Computed Tomography; icEEG: Intracranial EEG; icEEG fMRI: Intracranial Electroencephalography and Functional Magneticresonance Imaging; IEDs: Interictal Epileptiform Discharges; IGE: Idiopathic Generalized Epilepsy; ILAE: International League Against Epilepsy; IZ: Irritative Zone; MEG: Magneto-encephalography; MR-compatible: Magnetic Resonance compatible; MRI: Magnetic Resonance Imaging; PCA: Principal Component Analysis; PET: Positron Emission Tomography; RF: Radio Frequency; SOZ: Seizure Onset Zone; SPM: Statistical Parametric Mapping; T: Tesla; TCI: Transitory Cognitive Impairment; video-EEG: Simultaneous Video and Scalp Electroencephalography

Background

Epilepsy can be broadly classified into generalised and focal epilepsy. Some 30% of patients with epilepsy remain refractory to antiepileptic medications requiring further assessment for the control of seizures [1]. In refractory focal epilepsy, surgery has proved a valuable intervention. The success of epilepsy surgery depends, for the most part, on the precise identification of the area of seizure onset (seizure onset zone: SOZ) and the area deemed necessary to be resected to render the patient seizure free (epileptogenic zone: EZ) during presurgical assessment. The current approach to localize the SOZ and EZ is consensus, based on the results from a combination of non-invasive (magnetic resonance imaging (MRI), long term video-electroencephalography (video-EEG) monitoring, magnetic-encephalography (MEG), positron emission tomography (PET) and ictal single photon emission computed tomography: ictal-SPECT) and invasive (intracranial electroencephalography: icEEG) investigations. There is, however, no agreement as to which tests should constitute this combination, and the combination of tests used varies considerably across institutions as well as studies [2]. Furthermore, in current clinical practice, there is no true 'gold standard' localization technique; though in major centres icEEG tends to be the last and most reliable tool to localize the SOZ and EZ prior to surgery.

Against this backdrop, the introduction of simultaneous EEG and functional MRI (EEG-fMRI) has allowed the localization of haemodynamic changes associated with epileptic discharges on EEG for both focal [3] and generalized epilepsy [4-6] and thereby provided unique information on the associated brain networks. It is unique because of the nature of the measured effect, but also in the way that localization is achieved, using fMRI which does not have the fundamental limitations of EEG (or MEG) based localization techniques. EEG-fMRI albeit "technically very challenging," has "furnished the greatest insights into the relationship between fast neuronal dynamics and their spatially resolved haemodynamic correlates" [7] providing a multilateral view of the structure and function of brain.

The intrinsic contrast mechanism that fMRI relies upon, provides a means of localising function-related hemodynamic changes noninvasively. Essentially, the genesis of the fMRI signal constitutes neuronal activity induced changes in cerebral blood characteristics, including a variation in blood oxygen, detected as the blood-oxygen-level-dependent (BOLD) contrast [8,9]. Despite limitations imposed by slow temporal characteristics of the BOLD signal [10] and unresolved questions on its relationship to the underlying neural activity, fMRI has been employed widely to map brain network involved in cognition and perception [11]. The case for the utility of the BOLD signal to localize epilepsy, received its impetus and verification independent from simultaneous EEG-fMRI as shown in the initial reported cases of seizures recorded during fMRI scanning and their associated BOLD changes [12,13].

In the light of obvious interest in localizing the generators of interictal epileptiform discharges (IED) on EEG, such recordings were first performed in combination with fMRI in 1993 by Ives [14] followed by the development of EEG-triggered fMRI [15] and simultaneous and continuous EEG-fMRI [3]. Subsequently, the literature evidences development of new insights in the context of EEG-fMRI methodologies, including the intriguing involvement of specific networks including the thalamus in relation to generalized spike wave discharges (GSWDs) [6,16,17], the effects of epileptiform activity on neurovascular coupling [18], and the distinct patterns associated with interictal and ictal epileptic discharges in focal epilepsy [19-22]. In this reviewwe discuss the current trends in respect of scientific and clinical application of the technique in epilepsy.

Technical Aspects of Scalp EEG-fMRI: Data Acquisition and Artefact Correction

Recent reviews [23-25] comprehensively describe the methodological details of the EEG-fMRI data acquisition process, we offer a synopsis here. In general, standard or modified scalp electrodes (in number ranging between 19 and 92) and specially-designed battery-powered amplifiers are used to record EEG inside the scanner. Most EEG-fMRI studies of epileptic activity are performed while the patient is lying inside the scanner with their eyes closed, taking care to immobilise the head (for example using a vacuum cushion), which helps with image and EEG quality [26]. The digitised EEG signals are transmitted via fibre-optic cables to a recording computer placed in the MRI control room where EEG is displayed on a recording and display monitor using commercially available software. Functional images are typically acquired using T2*-weighted single-shot gradient-echo echo-planar images sequence, and the scanning session (6-20 minutes duration each) can be repeated once or twice to capture sufficient epileptic events. To date the majority of studies have been conducted on 1.5 and 3Tesla MRI scanners with noted advantages to the sensitivity of BOLD changes at higher field strength [27]. However, human EEG-fMRI studies have also been performed on 4T MRI scanner [28] whilst investigations into the feasibility of EEG-fMRI at 7T magnet strength are ongoing [29]. However, it has been shown that RF inhomogeneity at 3 and 7T in relation to the longer electrode leads produce a reduction in the signal intensity in images [30].

EEG recorded inside MRI scanner is obscured by heartbeat related and scanner gradient switching induced artefacts. The approach to EEG correction is determined by the nature of the events of interest, such as their frequency [31,32] and new measures are continually evaluated [33]. However, averaged artefact template subtraction is the most commonly applied method for removing MR-gradient and pulse-related artifact [34,35].

In the early EEG-triggered fMRI studies, the images were acquired at a pre-set time (corresponding to the presumed haemodynamic delay) when IEDs were observed on EEG and compared to images acquired following periods of normal (background) EEG [15,36]. This set up had a number of limitations, including the presumption of the value of the haemodynamic delay (which may be abnormal due to the pathological processes) and the difficulty of accounting for possible interactions between discharges occurring in rapid succession, and the artificial nature of the fMRI time series due to the acquisition discontinuities. In contrast, the advent of simultaneous and continuous EEG-fMRI provided 'real time' observations of BOLD relative to the epileptic activity on EEG, thereby facilitating the capture of the full range of potential BOLD signals either prior, during or after an events of interest [37,38].

Haemodynamic Mapping of Epileptic Activity: The Correlation Model

The conventional analysis of EEG-fMRI data is predicated on the following question: in what brain region(s) are the fMRI signal variations correlated with the occurrence of epileptic discharges on EEG? This question is answered using the General Linear Modelling (GLM) framework in which the 'model' is derived from the EEG [23]. In other words, the EEG is interpreted and the resulting set of events (of interest) is used to form a predictor of BOLD changes at every scanned location (voxel). For this, each EEG events of interest is then represented by a mathematical function, e.g. stick function of short duration, and convolved with an appropriate haemodynamic response function (HRF) which embodies the haemodynamic delay and recovery time course. The correlated BOLD changes associated with EEG events of interest are presented as thresholded statistical parametric maps (SPMs) which are overlaid onto a glass brain and/or co-registered structural scans for the purpose of anatomic localization. BOLD changes as revealed by these SPMs have been interpreted variably in different centres depending upon: the location of the most statistically significant cluster; earliest BOLD cluster; cluster size; and positive or negative BOLD changes [23].

Events of interest, in the context of EEG-fMRI studies on epilepsy include IED and seizures. Various approaches have been employed to represent epileptic discharges mathematically in the design matrix to assess the associated BOLD signal. Most commonly, single IEDs are represented as zero-duration stick functions and runs of IEDs as box-car function of variable duration depending upon the duration of the discharge [21,39-41]. Similarly, whole seizures can be represented as a single box-car function or, as proposed in [19,22,42] multiple box-car functions of variable duration, each representing a distinct seizure-related phase classified on the basis of spatiotemporal evolution of electrical activity and clinical semiology, and has been shown to provide new insight into the onset, evolution and propagation of seizure-related BOLD changes [19,22,42]. Another form of dynamic ictal imaging is obtained through the use of sequential sliding windows [43,44].

In practice the utility and sensitivity of EEG-fMRI had been limited by the unpredictability of epileptiform activity, whilst a great deal of diagnostic information can be affected or masked by confounds i.e., effects of no interest [45]. The aforementioned is juxtaposed with the clinical context of EEG-fMRI which renders significant emphasis on the best possible extraction and interpretation of the data [39]. These confounds include head motion-related artefact and physiological noise.The fact that motion even on a millimetre scale is sufficient to render fMRI unusable has resulted in a range of means and algorithms to explain motion in the design matrix to improve modeling [46,48]. Physiological noise includes the effects of respiration, changes in oxygenation and brain tissue volume during cardiac cycle [49,50-52] background physiological brain rhythms such as alpha, beta, theta, delta activity and various activities performed by patients during EEG-fMRI acquisition such as swallowing and eye blinks which can be identified using simultaneous video recording [39,53]. Accounting for signal variations associated with these confounds in the fMRI modelling procedure is essential to regress out their effect on the data in order to identify signal variations, specifically, related to the epileptiform discharges.

A crucial question relates to the choice of the HRF. The suitability of the commonly so-called 'canonical'HRF (derived from, and widely used in cognitive fMRI studies to epileptic activity, in view of possible

pathology-related alterations has been tested by using variations of it Fourier basis set, multiple HRFs, finite impulse responsefunctions and gamma functions [19,22,42,50,54-57]. These have revealed some deviations from the canonical shape, mostly in relation to generalised discharges.

Another approach which does not require a priori hypothesis of predicted BOLD response associated with an event of interest is Independent Component Analysis (ICA)which has been applied in a number of fMRI studies of epileptic activity revealing interesting patterns, not found using conventional EEG-based correlation [5,42, 56,58-60] confirmed positive, overlapping as well as distinctive results for either approach.

The Sensitivity of EEG-fMRI

The potential advantages of simultaneous scalp EEG-fMRI over scalp EEG, PET and ictal-SPECT as localization techniques include higher spatiotemporal resolution and non-invasive nature [23,24,61] . However, as noted previously the technique's dependence on scalp EEG to capture and identify epileptic discharges during EEG-fMRI has been a major limitation resulting is reduced sensitivity, in part by the lack of IEDs during fMRI, with roughly 40% of cases showing no clear IED, but also because of sub-optimal modelling of the fMRI signal, with 30% of cases with IED not showing significant BOLD changes [45]. Recent advances in modelling by explaining previously un-modelled physiological activities have resulted in increased sensitivity; for example by correlating topographic map features derived from epileptic activity recorded during long-term video-EEG monitoring with the EEG recorded during fMRI.In turn, using the strength of this correlation as a predictor, one can obtain seemingly epileptic patterns of BOLD change even in cases without clear epileptic discharges recorded during fMRI, thereby doubling the technique's sensitivity to around 80% [62,63].

The sensitivity of ictal studies is generally greater varying between 66 and 100% for cases in whom at least one seizure was captured, possibly reflecting the greater magnitude of the BOLD changes for these events compared to IED [16,19,20,22,42,44,58,64-70]. This wide range of sensitivity largely depends on the variable patient selection criteria, various modelling approaches and concordance criteria to assess localization of BOLD changes.

Localization of Epileptic Focus during Presurgical Assessment: Clinical Value

As it is conventional for the evaluation of novel localization techniques in epilepsy, their value is evaluated in comparison with other, more established methods such as scalp EEG, MRI, ictal-SPECT and icEEG when available [23].

The potential clinical contribution of EEG–fMRI has been demonstrated by reports of patient groups who were reconsidered for surgery after undergoing EEG-fMRI despite previous rejection as surgical candidates in whom the technique revealed BOLD changes in areas which were amenable to surgery [41,71]. Moreover, EEG-fMRI can corroborate negative evidence regarding surgical candidacy and may suggest poor postsurgical outcome, especially when IED-related BOLD networks are widespread in patients with focal cortical dysplasia [21,41]. Moreover, IED-related BOLD localization of the epileptic focus (defined on icEEG) is more specific than scalp EEG alone, with implications for the implantation strategy [72-74].

Early fMRI studies (without EEG) showed that it has valuable role in mapping seizure-related BOLD changes potentially surpassing ictal-SPECT, PET and EEG [12,13]. These initial reports were followed by a large number of case reports showing the utility of EEG-fMRI in localizing the SOZ. However more recent, relatively larger, studies of seizures (captured either fortuitously in the course of studies focused on interictal activity or intentionally have shown that EEG-fMRI can localize the SOZ at sub-lobar level (better than scalp EEG) in a large (~85%) proportion of cases. In addition, it can also separate seizure onset-related BOLD changes from propagation-related BOLD changes [19,22,42,44,58,75,76]. The potential clinical role of ictal studies using EEG-fMRI is constrained by the rarity and unpredictability of seizures and the potential impact of seizure-related motion artefact on data quality. These localizing findings in interictal and ictal studies which can be used during presurgical assessment may render EEG-fMRI a potentially viable clinical tool.

In addition to mapping IED and seizure-related BOLD networks for localization of the EZ, EEG-fMRI has been used to explore BOLD changes associated with asymmetric delta activity in a patient with refractory focal epilepsy. The delta activity related BOLD changes localized the EZ as defined by icEEG and cortical stimulation even in the absence of clear IEDs on EEG [77].

Epileptic Networks in Generalised and Focal Epilepsies

The first deployment of continuous EEG–fMRI in a case of generalized epilepsy with frequent absence seizures and later studies revealed a common pattern of BOLD increases in the thalamus and widespread BOLD decreases in medial and lateral frontal, superior parietal, posterior cingulate, precuneusand caudate and posterior brainstem (reticular formation) [4,6,68,78,79]. This provided further evidence of the importance of cortico-subcortical connectivity and suggested a role for the default mode network (DMN) during GSWDs [80]. The DMN essentially describes an organized network in which there is a balance of relative activity/inactivity distributed amongst brain regions during the (admittedly ill defined) 'resting state' or 'resting wakefulness'[80]. The suggestion is that this balance is altered in the context of function/epileptic discharges-related activity reflected as BOLD changes in the DMN [61,81,82].

Since the DMN is thought to be intimately engaged in processes of attention and working [83], it has been suggested that epileptic activity-related BOLD decreases in this network reflect transient changes in awareness or consciousness [4,81,82,84]. Also, in patients with refractory focal seizures BOLD decreases in the DMN are found to be significantly correlated with the loss of consciousness [19]. Taking the opposite causal viewpoint, it has also been shown that BOLD changes in the precuenus (part of the DMN) may act to facilitate the occurrence of GSWDs [85-87] which can be seen as consistent with the cortical focus theory of initiation of absences.

In addition to the BOLD changes in the DMN, EEG-fMRI has also shown BOLD changes in other networks in different types of epilepsy, playing its role in moving the debate forward from 'zones' to 'networks' [88]. In fact, EEG-fMRI studies have shown the involvement of various resting state networks and symptomatogenic areas in refractory focal seizures [23], visual attention network in children with photo paroxysmal response [89,90] musicogenic network in musicogenic seizures [91,92]. Reading epilepsy-related network [70,76] and motor network in epilepsiapartialis continua of the hand [93]. However in children with Dravet Syndrome, thalamic andDMN-related regions were shown to reveal BOLD changes though a syndrome-specific epileptic network could not be identified [94]. BOLD changes have also

been revealed prior to the onset epileptic discharges on EEG, which are found to be more focal for IED [89] and more widespread for seizures [19,20,69].

The presence of BOLD changes from the conventionally identified epileptic focus, during and prior to the seizure onset on EEG, is consistent with epileptic network hypothesis [95-97]. BOLD changes in apparently non-pathological cortex may reflect the fluctuations in baseline resting state networkactivity either that are necessary as part of the initiation process through interactions with the pathological region/network oras a result of the epileptic activity, such as recruitment of these areas in seizure generation or propagation [19,98]. Moreover, relatively widespread preictal (defined by scalp EEG and clinical manifestations) BOLD decreases followed by increases, prior to the electrical activity seen on scalp EEG may reflect active inhibitory circuits [99-101] which are subsequently overtaken by the increase in neuronal activity at the seizure onset [102] or projected neuronal activity not visible in the EEG [103,104].

In relation to the characterisation of the connectivity between different nodes of these epileptic networks [105-107] effective connectivity studies have also helped to identify areas involved in seizure facilitation [108] and propagation[109]. Changes in resting state functional connectivity have been observed in the orbitofrontal cortex [110,111], thalamus [112,113] and the DMN [111,114] in children with absence epilepsy pointing to further investigations of the interaction between cognition and GSWDs-related networks.

One of the early motivations for fMRI studies in generalised epilepsies was the possibility of identifying syndrome-specific BOLD patterns for IGE and secondary generalized epilepsy [16]. Recently, patients with idiopathic generalized epilepsy who are refractory or responsive to Valproate treatment were shown to have different GSWD-related BOLD patterns [115,116]. Similarly, in different focal epilepsies, syndrome specific IED-related BOLD patterns have been identified which involve the DMN-related and non-DMN related areas [117].

Cognitive Studies in Conjunction with EEG-fMRI

Cognitive impairment affects a large proportion of epilepsy patients and is reported as one of the primary clinical manifestations of pathological interictal behaviour [118,119]. IEDs can be associated with transitory cognitive impairment (TCI) especially for cognitively demanding tasks and >3sec long GSWDs [120,121]. Using attention [66,67] and working memory [122] tasks during EEG-fMRI studies alterations in the respective cortico-subcortical BOLD attention and working memory networks secondary to the presence of GSWDs during the performance of the task were demonstrated. These findings suggest that EEG-fMRI can detect functional changes in the underlying brain networks which might not be detected when tested clinically for a behavioural correlate [122]. Another relatively larger study in children with absence epilepsy also showed decreases in resting functional connectivity in medial frontal cortex implicated in the attention network, whereas impaired performance on attention task was correlated with decreased activation of medial frontal cortex [123]. Conversely, a case report [124] in a girl without cognitive impairment during GSWDs revealed GSWD-related BOLD changes in a similar cortico-subcortical network, raising the question of the causal link between such patterns and the cognitive ('downstream') or facilitation ('upstream') effects of GSWD [89].

Simultaneous Intracranial EEG-fMRI

The limitations of using scalp EEG to predict BOLD signal

variations related to epileptic and to other types of activity, throughout the brain include the EEG's limited sensitivity and lack of regional specificity. Furthermore, despite developments that have resulted in important increases in sensitivity [125,126] the lack of significant BOLD changes associated with (sometimes abundant) epileptic discharges in a significant proportion of cases and the sometimes complex IED-related patterns remain unexplained. The possibility of recording intracranial EEG and fMRI simultaneously may help us answer these questions.

Typically icEEG using subdural grids and depth electrodes is performed to localise the SOZ, EZ and eloquent cortex during presurgical assessment in refractory focal epilepsy [127] after a thorough assessment including detailed clinical history and examination, epilepsy protocol MRI, long-term scalp video-telemetry, neuropsychology and neuropsychiatry assessments and language fMRI [128]. Initial feasibility and safety studies [129-132] have been performed for simultaneous icEEG-fMRI at 1.5T and 3T suggesting this new investigation technique can be employed without posing any significant additional health risks if a strict protocol is followed. fMRI signal degradation is observed within 1cm of the electrode contacts and is orientation dependent [132]. Simultaneous icEEG-fMRI has the potential advantage over scalp EEG-fMRI of much higher electrophysiological sensitivity and regional specificity, particularly for depth electrodes [133]. Moreover, it may also circumvent limited spatial sampling of icEEG. Significant IED-related BOLD changes both close and remote from the most active electrode contacts were observed [134,135]. In one patient, IED-related BOLD network included regions that could not be sampled by icEEG and were neither resected, a finding which offered notional explanation for the persistence of seizures after surgery [135].

Future Perspectives for EEG-fMRI

Functional MRI combined with EEG and video [136] is a unique and powerful tool for the study of epileptic activity in humans and over the time multiple studies have shown its utility in mapping BOLD changes associated with interictal and ictal discharges [19,21,22,27,42,45,47,71,73,137,138]. However, certain questions remain to be answered in future studies. For example: Is there a single focus or a network responsible for a particular type of epileptic activity and does it have an impact on the surgical outcome? How do seizures and antiepileptic medications affect physiological brain networks in epilepsy? What measures can be taken to improve the clinical utility of the technique? What is the impact of epileptic discharges on cognition/consciousness and can it be measured using EEG-fMRI? What are the neuronal correlates of BOLD networks distributed across pathological as well as healthy cortex as revealed by scalp EEG-fMRI? Here, we present our perspective to address these questions in future.

Recent scalp EEG-fMRI studies point towards the existence of a network associated with IED and seizures [19,117,139]. Moreover, current clinical gold standard i.e., icEEG has its own limitations such as limited spatial sampling; comparison of IED and seizure-related BOLD networks across whole brain with postsurgical outcome will reflect the predictive power and true specificity of the technique.

It has shown that frontal piriform cortex ipsilateral to the presumed focus of epilepsy might be a common area involved in the epileptic activity in different types of epilepsy [140]. Future group studies in subtypes of epilepsy exploring the existence of a common IED and seizure-related BOLD network in patients with good versus poor postsurgical outcome may help to identify if a single area/focus or a network is responsible for the generation and propagation of epileptic activity.

Recently, it has been shown in a pilot study that BOLD changes in

DMN related areas during performance of a cognitive task are different under the influence of Topiramate as compared to other AEDs [141]. This is an interesting observation. IED-related BOLD changes have been shown in DMN related areas previously [142], therefore, it will be valuable to investigate the effect of different AEDs on IED related BOLD networks.

EEG-fMRI studies performed during performance of a cognitive task have suggested that it may be able to show a functional signature for loss of awareness associated with seizures and possibly with IEDs. This would require a thorough assessment of awareness during EEG-fMRI studies of epileptic activity. This will not be an easy undertaking and study design may have many possible confounding factors: type of epilepsy, nature and number of epileptic discharges and sensitivity of the task being performed to assess the awareness. This will require a careful selection of an appropriately sensitive task to detect loss of awareness in the future studies of EEG-fMRI on seizures. More specifically icEEG-fMRI studies can be more helpful to assess the relationship between awareness and IEDs as they do not suffer from the low sensitivity of scalp EEG.

However, the clinical application of the technique seems to remain limited, probably highlighting the diverse data analysis and concordance assessment schemes used by different research groups which need to be standardized for clinical purposes. In an effort to devise such scheme we propose a flowchart diagram to highlight a proposed scheme of data analysis and interpretation (Figure 1). Furthermore, a comparison of the localisation sensitivity of EEG-fMRI with other non-invasive imaging techniques: PET, ictal SPECT and MEG, and its role in planning the placement of intracranial electrodes prospectively will demonstrate its true utility during the presurgical evaluation of patients with refractory focal epilepsy.

Simultaneous and synchronised recording of video during EEG-fMRI [136] have shown to help in event identification and representation [19] and to increase sensitivity by modelling physiological activities in the design matrix [39]. In the future, the identification and labelling of

physiological activities such as: eye blinks, chewing and respiration can be automated by adding extra electrodes around the eyes for electro-occulography and around the face for EMG and using respiration belt respectively. Moreover, EMG recordings can also be very beneficial to investigate BOLD correlates of myoclonus [143].

The current approaches to analyse seizure-related data can show BOLD changes in areas recruited during the whole seizure or during different ictal phases represented in the design matrix as variable duration blocks; however it cannot show the evolutionary recruitment of these areas on a temporal scale within a single ictal phase. Further exploration of seizure-related fMRI data with dynamic modelling approaches e.g., real-time ICA [144] or with dynamic causal modelling to understand the connectivity between these regions can improve our knowledge regarding seizure spread and associated mechanisms. In the context of seizure spread, the GLM based group analysis approach for seizures may also highlight a common area or network.

Other limitations of current EEG-fMRI studies on seizures include: motion during seizures as a confounding factor to deteriorate data quality and to increase false positive results, and low temporal resolution of fMRI (~3 seconds) being unable to separate propagation related BOLD changes from onset related BOLD changes if occurring too fast. Future studies using fMRI sequences with online motion correction [145] and higher temporal resolution [146] may map activity patterns over the entire brain at the second time scale and improve our understanding of seizure initiation and propagation and help us answer clinically relevant questions. However, it remains to be explored if simultaneous recording of EEG during scanning will be compatible with fMRI sequences with online motion correction and higher temporal resolution.

Simultaneous icEEG-fMRI is potentially useful but only for the relatively small number of patients who undergo invasive evaluation prior to surgery. Future studies comparing BOLD localisation on scalp EEG-fMRI, using combination of conventional GLM based analysis and topographical map correlation based analysis [63], with that of icEEG-fMRI may reveal if the former has the same power and can guide implantation of intracranial electrodes. The application of icEEG-fMRI has also opened new horizons to investigate epileptic activity specific to icEEG such as high frequency oscillations. Evaluation of the transfer function (coupling) linking BOLD changes to IEDs on icEEG will be an important avenue of future research.

In conclusion, application of EEG-fMRI in epilepsy holds great promise in future to address multiple relevant scientific questions and the possibility of being employed as a clinical investigation tool in presurgical assessment for refractory focal epilepsy. However, further larger multicentre studies are required to assess the potential of the technique as a clinical investigation tool and its cost-effectiveness with standardized methods of data collection, analysis and interpretation.

Acknowledgements

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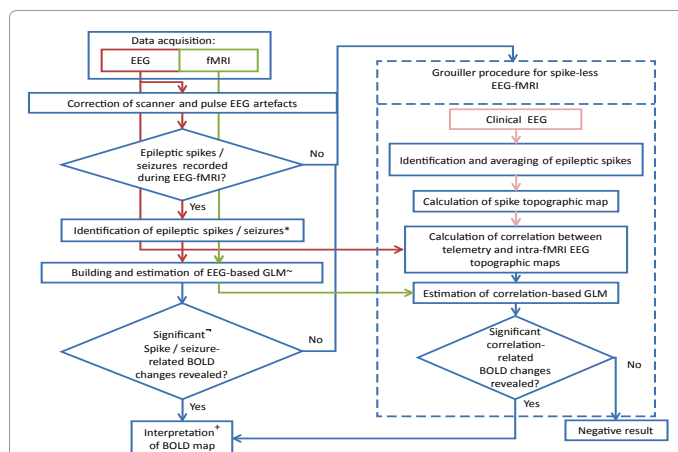

Figure 1: UCL interictal and ictal scalp EEG-fMRI analysis flowchart
*Seizures identified and divided into phases according to their spatiotemporal evolution
~One GLM for epileptic spikes and seizures which also includes additional regressors
explaining effects of no interest such as: motion, pulse and physiological activities
¬Statistically significant at $p<0.05$ family wise error corrected or $p<0.001$ uncorrected
+Evaluation of concordance of global maximum and other BOLD clusters with the SOZ

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