Simultaneous EEG-fMRI: A novel approach to localize the Seizure Onset Zone

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Abstract

Affecting daily lives of millions of people, Epilepsy is a common central nervous system (neurological) disorder where cell activity in brain is disturbed, causing recurrent seizures. Epilepsy can be treated commonly by medications. Be that as it may, medications do not always work as well as one may have hoped, and thus, some patients tend to resort to surgeries. The primary challenge in such surgeries, and by extension any other surgery where some part of brain may need to be disabled, disconnected or removed, is managing to pose no threat to the critical healthy textures adjacent or close to the part being operated on. Therefore, the precise localization of epileptic focus is a matter of vital importance in treating this condition. Various algorithms have been proposed to localize the brain sources and thus to determine the epileptic focus, however, none has yet been able to offer a solution to effectively address this issue. With EEG signal containing temporal information and fMRI carrying spatial information, it is hoped that the combination of the two can yield optimal results. In this case study, we first remove the artifacts caused by EEG gradients, and proceed to study the signal in and outside the scanner by localizing the brain sources. The simultaneous processing of EEG-fMRI enables us to make use of the temporal information in EEG to analyze fMRI. Epileptic foci are finally localized based on GLM method. This study has been conducted on 2 medication-resistant patients with epilepsy whose data was recorded in Iran National Brain Mapping Centre. The results suggest a significant improvement in localization accuracy compared to existing methods in the literature.

Keywords: Simultaneous EEG-fMRI; Epilepsy; Independent Component Analysis (ICA); Blood-oxygen-level dependent imaging (BOLD); Generalized Linear Model (GLM)
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Introduction

An appreciation of the propagation of epileptic activity is key to understanding the basis of networks that underpin epilepsy. EEG-fMRI can localize the haemodynamic correlates of interictal epileptiform discharges (IEDs). EEG and fMRI are known to complement one another in the spatiotemporal representation of brain activity as each method has its strengths where the other has limits. Thus, the simultaneous recording and analysis of EEG and fMRI brings about a higher prospect of understanding the reality of neural behaviors. This method is now increasingly available after crucial technical challenges have been resolved in terms of developing suitable amplifiers and procedures for correcting the scanner-related artifacts in the EEG signal [1-8].

EEG-fMRI combines the high temporal resolution of EEG signal with the high spatial resolution of blood oxygen level dependent (BOLD) MRI. Studies [9-11] looked into the spike-related BOLD changes and showed that in addition to characterizing different types of focal and generalized epilepsy, these measures could also improve the presurgical evaluation of patients with refractory focal seizures.

When it comes to focal epilepsy, particularly in pharmacoresistant patients and surgical candidates, a matter of substantive significance is how the spike-related BOLD changes can help localize the epileptic focus. It has been shown that the BOLD signal tends to increase in regions generating focal IEDs [12], although mostly in the form of widespread responses [13]. Moller et al. [11] demonstrated that the simultaneous acquisition and analysis of EEG-fMRI aided in localizing foci in patients with nonlesional frontal lobe epilepsy, as confirmed by other imaging modalities. Also, in [14], desirable results were achieved in a postoperative population when the resection was ensured to include the BOLD activation region [14]. Thornton et al. [14] reported seizure freedom rates of as high as 60% in patients who had undergone surgical resections in which cortical tissues with maximal IED-correlated BOLD changes were completely removed.

Taken together, a growing body of the current literature points to the significant role of EEG-fMRI recordings in clinical decision making: [10] finds that the Bold response is in accordance with the IED field in 88% of the patients and also shows that EEG-fMRI contributes noticeably to localizing the seizure focus in 64% of the studied patients. In patients who deemed ineligible for surgery based on conventional analyses, EEG-fMRI improved localization in four of six patients with unclear foci and confirmed multifocality in four of five presumed multifocal patients [15].

Conventionally, identifying the epileptic regions begins with marking IEDs, which are believed to be one of the primary indicators of epileptogenic tissues [16]. This is done by trained experts through visually inspecting the EEG simultaneously recorded with fMRI. The time series of the detected IEDs are then convolved with the hemodynamic response function and an analysis following a General Linear Model (GLM) is performed to estimate the hemodynamically active regions. Finally, the regions that cross a certain statistical threshold are considered as markers of the epileptogenic zone (EZ).
It is now possible to combine EEG and fMRI in the study of epileptic disorders, and therefore to determine the region of the brain in which there is a change in the BOLD signal as a result of an epileptic discharge seen on scalp EEG, wherever that change takes place in the brain. One can hypothesize that this region is where the spike originates, in a similar way that single photon emission computed tomography (SPECT) studies are performed at the time of epileptic seizures to determine the regions of increased blood flow [17,18].

We will present the methods that have been developed for recording and analyzing the EEG in the MR scanner, the methods required to analyze the BOLD signal resulting from epileptic discharges, and results from studies of different types of epileptic disorders. Finally, we will discuss the advantage of the proposed method compared to conventional methods.

Materials and Methods

Subjects

The simultaneous EEG-fMRI scanning was performed at the National Brain Mapping Laboratory (NBML) in Tehran, Iran, from two patients with epilepsy. The patients were selected based on the following inclusion criteria: 1) diagnosed with focal or generalized epilepsy and a surgery candidate; and 2) at least 10 IEDs that can be distinctly identified during the MRI scanning, i.e., there is a sufficient number of IEDs detectable on EEG (often one IED every 2 minutes). The recruited patients consists of 1 male and 1 female; age 26 and 38 years; the onset age of 5 and 16 years. All patients provided written informed consent and ethical approval was obtained from the local ethics committee of Iran University of Medical Sciences, Tehran, Iran.

To have the Seizure Onset Zone (SOZ) and irritative zone (IZ) localized in the preoperative evaluation, we employed a wide range of techniques including a comprehensive clinical record study, full neurological examination, long term Video-EEG, structural MRI, neuropsychological assessment, and other non-invasive investigations such as PET and ictal SPECT when available. This procedure was performed at Epilepsy Center, Pars Hospital, Tehran, Iran.

EEG-fMRI recording

Simultaneous EEG-fMRI was recorded inside a 3T MRI scanner (Siemens Prisma) for 20 min at rest with eyes closed. A 64-channel MRI-compatible EEG cap was used according to the 10–20 system (reference Cz); ECG was recorded using a single lead [19]. EEG was also recorded for 10 min with eyes closed outside the scanner immediately prior to EEG-fMRI scanning [19]. Electrodes were equipped with an additional 5 kΩ resistance and impedances were kept as low as possible. EEG was acquired at 5 kHz using BrainAmp MRI-compatible amplifiers (Brain Products) and EEG was synchronized with the MRI clock.

A T1 MPRAGE anatomic acquisition was done (1 mm slices, 256×256 matrix, echo time [TE]=3.74 ms, repetition time [TR]=1810 ms, flip angle=30°) and used to superimpose functional images. Functional data was obtained in 20 minutes runs with patients at rest, using a T2*-weighted gradient-echo (GRE) imaging sequence (234×234 matrix, 40 slices, 3×3× 3 mm, TE=26 ms, TR=2500 ms, flip angle=60°). The patient’s head was immobilized with a pillow filled with foam microspheres to minimize movement and provide comfort [20,21].

EEG Signal Processing

The preprocessing of EEG signals is accomplished using the EEGLAB toolbox (available at https://sccn.ucsd.edu/eeGLab/). Initially, the sampling rate is reduced from 5000 HZ to 250 Hz and the baseline drift, which contains the low frequency components, is suppressed through a Butterworth high-pass filter at 1 Hz [22-35]. The channels are then
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reviewed to identify and remove abnormal channels, i.e., those with a p-value greater 0.01. The power line interference, containing high frequency components, is removed using the Clean Line algorithm [36-38], which is vastly superior to a notch filter in terms of retaining the main content of the signal. It adaptively estimates and removes sinusoidal artifacts, while unlike the notch filter, does not create band-holes in the EEG power spectrum. A primary challenge in interpreting simultaneous EEG-fMRI recordings is the gradient artifact caused by the switching of the magnetic fields. To tackle this, we employ the fMRIb algorithm [39] which first increases the sampling rate to 20 kHz, then applies a low-pass filter at 60 Hz. The EEG recordings are also heavily contaminated by Ballistocardiogram (BCG) artifact, associated with cardiac pulsations causing movements of the electrodes, which will also be removed through fMRIb toolbox.

An experienced neurophysiologist manually searched for each type of intra-MRI spikes in each patient. Spikes were modeled as zero-duration events, convolved with a standard HRF, and used as a regressor for the GLM model and fMRI analysis.

BOLD signal Processing

We use FSL software to perform motion correction (realignment with 6-parameter rigid-body transformation) and smoothing (6-mm full width at half-maximum) on GRE images. Temporal autocorrelations are corrected with an autoregressive model of order one [40], and low-frequency drifts are modeled with a third-order polynomial. The traditional spike-based model uses the time and duration of each event to build an IED-specific regressor and convolves it with spike related hemodynamic response function, whereas, the current study proposes to convolve the independent component time series with 4 HRF peaking at 3, 5, 7, and 9 seconds [1]. All components are included in the same general linear model (GLM). A statistical t map is obtained for each component using the other components as confounds.

EEG-fMRI analysis

To be prominent, a response requires 5 contiguous voxels having a t-value of 3.1 corresponding to a p-value smaller than 0.05, corrected for multiple comparisons due to the number of voxels and the 4 hemodynamic response functions. We illustrate the t-map results using a red-yellow scale for positive BOLD changes, i.e., activation, and a blue-white scale for negative BOLD changes, i.e., deactivation. We take no notice of responses which are outside of the brain parenchyma. Two experts review the IED-related BOLD responses. For each patient, the analysis proceeds as follows.

Results

The patients with active EEG during acquisition show at least 1 IED type; 1 type (first patient), 2 types (second patient). Thus, for each patient with each type, one source is identified, making a total of 3 EEG-fMRI recordings to be analyzed by the proposed EEG-fMRI method. In both two patients, at least one IED-related BOLD response is concordant with the spike field (Figure 1,2). The concordant responses are focal in both two patients with focal discharges. In patients, the maximum t-value corresponds to an activation in one of them patients (Figure 1,2) and a deactivation in another one.

In one of the 3 IED-type, the BOLD response is not concordant with the spike field. This subject with left posterolateral frontal and left parietal discharges show no BOLD response at the location of the interictal discharges. However, a BOLD response is observed in the bilateral parietal cortices with maximum Z-score in the contralateral parietal region (poor concordance). This patient did not undergo surgical resection due to poor clinical localization of the seizure focus.
Figure 1: Marked events are P8, PO8, and P6 spikes (referential montage) and the IED-related BOLD response shows a neocortical activation in the first occipito-temporal cortex. This response is considered both concordant with the spike field and contributory because it leads to a better localization of the epileptic focus compared with the scalp EEG. Top, marked scalp EEG in the mentioned channels. Bottom, Localization of the generator applying simultaneous analysis of EEG-fMRI. The active area is marked with a yellow-red color.

Figure 2: Marked events are F7, F5, and F3 spikes (referential montage) and the IED-related BOLD response shows a neocortical activation in the left dorsolateral prefrontal cortex. This response is considered concordant with the spike field but not contributory because it does not add any new
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As mentioned, in this paper, we investigate the spatial distribution of spike-related and IED-related BOLD changes. Table 1 presents a systematic comparison between our obtained results and similar works. The proposed method improves the concordance between BOLD changes and spike field to 89% which marks a rise compared to another works.

Table 1: Comparison of the epileptic foci identification methods through simultaneous EEG-fMRI recording

| Author; Year | MRI scanner | Imaging | Slice thickness | TR/TE | FOV | Flip angle | Accuracy |
|--------------|-------------|---------|----------------|-------|-----|------------|----------|
| F. Pittau et al.; 2012 [41] | 3-T, Trio; Siemens, Germany | T1-weighted | 1-mm slices | 23/7.4 ms | 256×256 | 30° | 67% (Generalized) 55% (Focal) |
| | | T2*-weighted 6-min | 33 slices, 3.7 ×3.7×3.7 | 1900/25 ms | 64×64 | 90° |
| A. Sierra-Marcos et al.; 2013[42] | 1.5-T, General Electric, USA | T2*-weighted 11-min | 20 slices, 5×5×5 mm | 2000/34 ms | 64×64 | - | 64% |
| | 3-T Magnetom Trio; Siemens, Germany | T2*-weighted 11-min | 40 slices, 3×3×3 mm | 2000/16 ms | 128×128 | - | 86% |
| Our method | 3-T MRI; Siemens prisma, Germany | T1-mprage 1-mm slices | 1810/3.47 ms | 256×256 | 30° | 89% |
| | | T2*-weighted 20-min | 40 slices, 3×3×3 mm | 2500/26 ms | 234×234 | 90° |

Discussion

Using the proposed method, we not only succeed in incorporating all the temporal information in regard to the identified generators of epileptic activity, but also manage to avoid being misled by extraneous or incomplete information and mistakenly recognizing an irrelevant source as a generator. Achieving concordant results from various localization methods can be a promising tool when planning surgical resection or intracranial EEG electrode placement. Much of the motivation to combine EEG and fMRI measurements originates from selective information each modality embodies.

The IED-related BOLD response was observed in all patients who had IEDs during the EEG-fMRI acquisition: 2 of 3 IED-study making 67% of the whole, which is higher than that reported in [10] and in [43, 44] which were 57% and approximately 55%, respectively. Moreover, previous EEG-fMRI studies reported detection of IED-related BOLD changes in 50-60% and 60-70% of the patients with spike-triggered or continuous EEG-fMRI, respectively [45]. The literature also brings into light the possibility of increasing the EEG-fMRI yield to 80-90% through using multiple HRFs peaking at 3, 5, 7, and 9 s to calculate the
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convolutions [1,10]. It has been well-established that neuroelectrical activity and the corresponding hemodynamic response of the physiological and pathological brain function do not overlap precisely. Thus, when investigating the correlation between the two, the literature generally accepts a concordance within 20 mm [38-40], making focal the BOLD change a regional marker of epileptogenic networks at macroscopic scale which proves its usefulness in the evaluation process prior to placing EEG electrodes or performing surgery. In this case study, we have applied complementary physiological information, to identify and introduce the most relevant components. Increasing the yield of EEG-fMRI studies, the proposed method can identify the components responsible for epileptic activity over a specified period of time regardless of spike occurrence inside the scanner. It goes without saying that if there actually are any detectable spikes, they can help facilitate the process, nevertheless, this method will not be dependent on the existence of spikes inside the scanner, although it should be highlighted that this is not the sole accomplishment of this method, rather an additional benefit. From a clinical point of view, a spike-independent analysis can be of immense importance, as it is quite rare that spontaneous epileptiform discharges coincidently occur during simultaneous recordings, making the EEG-fMRI an additional valuable tool for localizing the epileptogenic zone.

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