Imaging Epileptic Networks Using Spatial-Temporal EEG-fMRI Fusion

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Abstract. To investigate the dynamic responses of epileptic networks, the spatial-temporal EEG-fMRI fusion (STEFF) is proposed for a partial epilepsy study. Independent component (IC) analysis is applied to fMRI data, then ICs related to interictal epileptiform discharges (IEDs) are identified by fitting a hemodynamic response function (HRF) to the time courses of ICs at the time of the IEDs event. These IEDs related ICs are further classified into spatial consistent and inconsistent ones according to their contributions in EEG source imaging of IEDs. As IEDs related ICs are widespread, STEFF provides a new classifier of the fMRI ICs, which is not only considering the timing of IEDs, but also the topography of IEDs. The resulting EEG-fMRI spatial consistent ICs with early HRF peaks would be the most possible indicators of the epileptogenic focus.

Keywords: EEG-fMRI; STEFF; epilepsy; independent component analysis; EEG source imaging

1. Introduction

EEG-fMRI is a rapidly developing non-invasive technique which may be of particular interest in the presurgical evaluation of patients with epilepsy [Gotman, 2008]. In an attempt to delineate the epileptogenic focus, initial studies have investigated BOLD responses to interictal epileptiform discharges (IEDs) identified on the simultaneously recorded EEG [Salek-Haddadi et al., 2006]. The BOLD changes usually were modeled as a convolution of IEDs with a canonical hemodynamic response function (HRF) in the general linear model (GLM) [Worsley and Friston, 1995]. However it is often unclear whether the canonical HRF is an appropriate representation of pathological epileptic discharges [Benar et al., 2002]. Several reports showed variability in the shape of the HRF as a function dependent on regions, subjects, age, task, gender and sessions [Gotman, 2008; LeVan et al., 2010]. Moreover, BOLD responses to deep, asynchronous, or very focal discharges may appear non-canonical with respect to the activity visible on the scalp. The observed BOLD response may even appear to precede the occurrence of the scalp discharge [Moeller et al., 2008].

Recently, some EEG-fMRI studies have investigated the BOLD response to the scalp discharges with independent component analysis (ICA). In contrast to the model-driven analysis, ICA is a data-driven method that can be used to detect relevant patterns of BOLD signal fluctuations without a prior hypothesis on the HRF shape [McKeown et al., 1998]. It can identify regions showing a non-canonical HRF and also yield de-noised time courses of cerebral activity as a result of the separation of artifactual components [Thomas et al., 2002]. In patients with interictal discharges, it has been shown that ICA could identify similar brain regions as those identified by a GLM analysis, while separating components related to acquisition or physiological artifacts [Rodionov et al., 2007]. In ictal studies, the author used deconvolution to reconstruct the HRF function and the components were classified as a function of peak delay [LeVan et al., 2010]. BOLD response clusters associated with early HRF peaks were concordant with the suspected epileptogenic focus, while subsequent HRF peaks may correspond to ictal propagation [LeVan et al., 2010]. However, it remains to be seen whether the spatial information of IEDs could also provide additional information on the identification of the epileptogenic focus.

This study proposes an EEG-fMRI integration [Lei et al., 2010] to investigate the dynamic responses of epileptic networks. After extracting fMRI condensed components, EEG-informed HRF estimation and fMRI-constrained EEG imaging are employed successively to detect brain regions showing spatial-temporal consistent BOLD changes related to IEDs. As IEDs related components are widespread, the spatial-temporal EEG-fMRI fusion (STEFF) provided a classification of the components as a function of response sign (positive or negative), peak delay of HRF and spatial
consistency of component. One case study indicates that STEFF provides a dynamic analysis of IEDs related BOLD responses and can identify components which are concordant with the suspected epileptogenic focus.

2. Methods

2.1. Scheme Procedure

Fig. 1 illustrates the data processing in epileptic networks imaging based on spatial-temporal EEG/fMRI fusion (STEFF) [Lei et al., 2010]. The fMRI independent components (ICs) will go through the temporal and spatial models of STEFF and finally be separated into IEDs unrelated ICs, related but spatial inconsistent ICs, and spatial consistent ICs.

![Figure 1](image_url)

**Figure 1.** Schematic representation of the data processing steps. Spatial ICA is applied on fMRI data and IEDs related ICs are identified by EEG-informed HRF estimation (the temporal model of STEFF), which also estimates an HRF with the timing of IEDs. In fMRI-constrained EEG imaging (the spatial model of STEFF), components are further classified to spatial consistent ones if they are valid prior to source reconstruct of topography of IEDs. STEFF provides a classification of the components as a function of response sign (positive or negative), peak delay of HRF and spatial consistency of component.

**Step 1: fMRI Decomposing and IEDs Extracting**

Preprocessing of fMRI data was conducted through the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm). The slice time correction, 3D motion detection and correction, spatial normalization to the MNI template supplied by SPM, and spatial smoothing using an isotropic Gaussian kernel (8 mm full width at half maximum) were included. The resulting data matrix was decomposed into $n$ components through the GIFT software (http://icatb.sourceforge.net/). To determine the number of components, dimension estimation was performed using the minimum description length criteria. The intensity values in each fMRI IC were scaled to z scores. Voxels with absolute z scores larger than 3 were considered to show activation. Negative z scores indicate that the BOLD signals are modulated oppositely to the IC waveform [McKeown et al., 1998].

The artifact-free EEG data were analyzed by a clinically experienced neurophysiologist. The timing of IEDs was used in Step 2 to identify temporal related components from fMRI ICs. To extract the topography of IEDs, multiple IEDs intervals in an fMRI scale were temporal concatenated to build the IEDs discharge matrix. Principle component analysis (PCA) was performed on discharge matrix. The different variations in the IEDs data were captured in the principal components (PCs), ordered according to the variance explained by each component. The first $m$ PCs were selected based on the amount of variance explained by these PCs was larger than 85%. The topography of IEDs was reconstructed with these PCs weighted with corresponding variance. Then, the topography of IEDs was put into Step 3 to identify spatial consistent and inconsistent components from fMRI.

**Step 2: EEG-informed HRF Estimation**

In this step, the timing of IEDs event acted as the prediction information to estimate HRF from the fMRI component time courses. HRF was modeled by a smooth waveform spanning an interval from 10 s before to 20 s after the marked events. Components with the hyperparameters of the timing of IEDs.
event significantly larger than 0 \((p<0.005)\) were considered as IEDs related fMRI ICs, and the corresponding HRF defined the hemodynamic responses for IEDs. The HRF of IEDs related ICs was investigated to determine the sign and delay of the HRF peaks. The peak was defined as the maximum absolute value of the fitted HRF. Any data outside a window of ±5 s around the peak was then considered as baseline [LeVan et al., 2010]. The sign of the peak was quantified by its relative amplitude with the mean of the baseline. The sign of the peak was then used to distinguish positive peak (BOLD activations) from negative peak (BOLD deactivations). The peak delay provides a temporal ordering of the BOLD changes and is important to distinguishing onset from propagated activity [LeVan et al., 2010].

The model in this step is based on EEG-informed HRF estimation and mathematic details can be found in [Lei et al., 2010], which is identical to the robust Bayesian GLM. Usually 1 to 4 IEDs related ICs will remain after this step, used as the input for the following procedure of Step 3.

**Step 3: fMRI-constrained EEG Imaging**

The IEDs related ICs extracted in above stage were employed as spatial priors for the inverse problem of the topography of IEDs (which reflects the average influence of IEDs during fMRI scanning). Since some EEG sources may be blind for fMRI measurements, multiple sparse priors (MSP, see [Friston et al., 2008]) were employed for the remaining source space outside the subspace generated by fMRI ICs. The spatial patterns, whose hyperparameters were significantly larger than 0 \((p<0.005)\) were considered valid priors for source imaging. This step classified the IEDs related ICs into spatial consistent and inconsistent ICs, considering the contribution in the generation of topography of IEDs. The model in this step is based on fMRI-constrained EEG imaging and mathematic details can be found in [Lei et al., 2010; Lei et al., 2011].

### 2.2. Patient and Study Protocol

A 10-year-old right-handed male patient with epilepsy participated in a simultaneous EEG-fMRI study in the epilepsy clinic of the West China Hospital of Neurology, Sichuan University. Informed consent was obtained before the patient underwent a clinical brain structural MRI and a 24-hour video EEG. A diagnosis was established according to the scheme published by the International League Against Epilepsy in 2001 [Engel 2001]. This patient experienced a seizure at 9 years of age, and was treated with sodium valproate. He was diagnosed as suffering from complex partial seizures, and secondary generalized tonic-clonic seizures. A clinical structural MRI of the brain revealed an anatomical abnormality, a left central temporal atrophy. Interictal EEG revealed paroxysmal spike waves and spike-slow-waves over the left temporal and central frontal regions. In simultaneous EEG-fMRI, the patient was instructed to simply lie inside the scanner with eyes closed. He was also required to keep awake during the experiment. No visual or auditory stimuli were presented at any time during the functional scanning.

### 2.3. Simultaneous EEG-fMRI

Functional images were acquired with a 3T MRI scanner (EXCITE, GE Milwaukee, USA) using means of T2*-weighted echo planar imaging free induction decay sequences with the following parameters: echo time \((TE)\) of 30 ms; matrix size of 64×64; field of view \((FOV)\) of 240×240 mm\(^2\); in-plane voxel size of 3×3 mm\(^2\); flip angle of 90°; slice thickness of 5 mm; and no gap. Functional volumes consisted of thirty bicommissural slices, which were acquired with a volume repeat time \((TR)\) of 2 s. A total of 205 volumes were acquired, and the first five volumes were discarded to ensure steady-state longitudinal magnetization. Subsequently, a high-resolution T1-weighted structural volume was acquired via a 3D spoiled gradient recalled \((SPGR)\) sequence. The high-resolution T1-weighted structural volume provided an anatomical reference for the functional scan and the forward model of EEG imaging. The forward head model is established by matching the T1-weighted structural anatomy of the patient to the template. A lead-field matrix was computed for the canonical mesh according to co-registered electrode locations using a three-sphere head model [Lei et al., 2010].

An MR-compatible Mizar 40 system (EBNeuro, Florence, Italy) was used for EEG recordings with 32 nonmagnetic Ag/AgCl electrodes. An additional electrode was dedicated to the electrocardiogram \((ECG)\). Two other electrodes were positioned over the subject’s earlobes, with their average used as a reference. Data were collected with a sampling rate of 4096Hz, and the BE-MRI Toolbox (Galileo New Technology, Florence, Italy) was used for off-line correction of the MRI imaging artifact [Allen et al., 2000]. After visually checking for movement artifacts and noisy electrodes from the data, a method based on temporal ICA was used to reject the ballistocardiographic \((BCG)\) artifact and the residual imaging artifact from the filtered EEG recordings [Mantini et al., 2007].
2.4. Assessment of concordance

In the current study, we examined the neuroelectric and hemodynamic response of partial epileptic networks using STEFF. The value of localization and diagnosis for epileptic in STEFF was illustrated by the analysis of responses sign, peak delay of HRF and spatial consistency of component. The resulting maps were evaluated for spatial concordance with the SPM and the suspected epileptogenic focus.

3. Results

During the EEG-fMRI acquisitions, the patient had 9 interictal events. The average topography of IEDs during fMRI scanning is extracted using PCA. The topography of IEDs was illustrated in the top right panel of Fig. 2. Some positive peaks were in the left hemisphere and front area, and some negative peaks were in the right hemisphere. Fig. 2 also revealed the anatomical abnormality in the left temporal lobe.

3.1. MNE and SPM results

Minimum norm estimation (MNE) [Hamalainen and Ilmoniemi 1994] is calculated for comparison of the fMRI-constrained EEG imaging in this study. MNE has a single covariance to encode identically and independently distributed sources. This estimation asserts that all sources are active, with equal a priori probability and that none are correlated. As illustrated in the bottom left panel of Fig. 2, MNE localizes sources in the left frontopolar area and the reconstructed profile is a little superficial.

The GLM analysis was performed using the SPM8 software package. The canonical HRF was convolved with IEDs time pulse function as a regressor of interest in the SPM design matrices. Six parameters (3 translations and 3 rotations) for spatial realignment were included to model the effects of head motion. Design matrices and data were high-pass filtered with a cutoff of 128 s. The specifically activated areas were calculated using statistical t-tests with five contiguous voxels above an absolute t value of 3.14 (P < 0.001, uncorrected). As shown in the bottom right panel of Fig. 2, SPM has a negative activation in left temporal lobe and two positive activations in bilateral frontal lobes. This pattern was partially consistent with the topography of IEDs and suggests that the focally activated areas may be related to epilepsy. However, the frontal activation was distant from the presumed epileptogenic focus.

Figure 2. The MRI, topography of IEDs, MNE and SPM result. The structure reveals an left central temporal atrophy. Topography of IEDs has positive peaks at left temporal and central frontal regions. MNE, the distributed EEG inversion, localizes sources in the left frontopolar area. EEG-informed SPM result shows sources with different sign.
3.2. STEFF result

The ICA method decomposed the fMRI data into 32 components with the minimum description length criteria. After fitting an HRF to the component time courses, there were 3 components in which hyperparameters were significantly larger than 0, indicating that these components were related to the IEDs activity.

The IEDs related ICs was employed as spatial prior for the EEG inverse problem. After imaging the sources of the topography of IEDs, two spatial patterns showed hyperparameters that were significantly larger than 0 and they were spatial consistent IEDs related ICs. This step also reconstructs the EEG source distribution of IEDs during fMRI scanning. The top left panel in Fig. 3 shows the largest activated areas in left temporal lobes. In fact, STEFF revealed three focally activated areas corresponding to the bilateral frontal and temporal lobes. Compared with the result of MNE, these areas are more interpretable with the topography of IEDs and are consistent with the SPM result in Fig. 2.

Fig. 3 shows the spatial consistent and inconsistent fMRI ICs. The HRFs deconvolved from the time courses are also shown on the right. The maximum intensity projections indicated some dispersed activated regions in the inconsistent component, and the associated HRF has many spikes. The largest peak delays at approximately 5 s. Restricting the HRF to the canonical shape prevented the detection of this component in SPM (see Fig. 2). The spatial consistent ICs identified similar brain regions as those identified by SPM. The left temporal area was concordant with the suspected epileptogenic focus. However, BOLD responses were negative in this area and HRF peaking between 2 and 4 s (TR: 2 s). The bilateral frontal areas had a positive HRF peaking between 6 and 8 s. Both spatial consistent components were helpful in facilitating EEG imaging, while the frontal clusters associated with subsequent HRF peaks may correspond to interictal propagation.

Figure 3. Imaging epileptic networks using STEFF. Both fMRI-informed EEG imaging and EEG-constrained HRF estimation are implemented in STEFF. EEG source imaging shows the largest activation in left temporal lobes (top left). IEDs related components were classified to spatial inconsistent fMRI IC (top right) and consistent fMRI ICs (bottom). For each fMRI component, the sagittal, coronal and axial views of the spatial map and the HRFs deconvolved from the time courses are shown. The thin line in the background of waveform describes the SPM canonical HRF, amplitude arbitrary. The spatial maps are scaled to z scores and shown in maximum intensity projection format. Yellow to black represent the range of z values from 3.0 to max.

4. Discussion

To investigate the dynamic responses of epileptic networks, spatial-temporal EEG/fMRI fusion (STEFF) is used in this study. The case investigation shows the ability of STEFF to detect brain regions showing spatial-temporal consistent BOLD changes related to IEDs. As IEDs related
components are widespread, STEFF provided a classification of the components as a function of response sign (positive or negative), peak delay of HRF and spatial consistency of component. The spatial consistent component with early HRF peak may associate with epileptogenic focus.

Previous investigation on ictal EEG-fMRI data found that ICA can detect similar regions of BOLD response as the standard GLM approach [LeVan et al., 2010]. By imposing clear peak constraint on the HRF, they detected regions with early HRF peak likely corresponds to the epileptogenic zone. However the spatial information of IEDs is little discussed. With recent advances in methodology and clinical validation, EEG source imaging may add more detail to map epileptic activity. A few studies have evaluated the concordance between various EEG source imaging and EEG-fMRI results in focal epilepsy [Benar et al., 2006]. They found simultaneous source imaging and EEG-fMRI analysis may be able to distinguish areas of BOLD response related to initiation of IEDs from propagation areas [Vulliemoz et al., 2010]. As an integration of EEG-informed HRF estimation and fMRI-constrained EEG imaging, STEFF enables information one modality to be utilized as priors for the other and hence improves the spatial (for EEG) or temporal (for fMRI) resolution of the other modality [Lei et al., 2010]. The combination in STEFF provides new opportunities for investigating epileptic networks.

Acknowledgements

This project was funded by grants from the National Nature Science Foundation of China #60736029, the 973 project 2011CB707803 and the PCSIRT project. The authors are grateful to Huaxi MR Research Center, West China Hospital for providing the data.

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