EEG-fMRI study of the interictal epileptic activity in patients with partial epilepsy☆

Yonghong Liu a,1, Tianhua Yang a,1, Xuhong Yang a, Iing Liu a, Wei Liao b, Su Lui c, Xiaoqi Huang c, Huafu Chen b, Qiyong Gong c, Dong Zhou a,*

a Department of Neurology, West China Hospital, Si Chuan University, Chengdu, Sichuan, P. R. China
b School of Life Science and Technology/school of Mathematics, University of Electronic Science and Technology of China, Chengdu, Sichuan, P. R. China
c Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, PR China

Received 22 July 2007; received in revised form 18 November 2007; accepted 21 November 2007
Available online 11 January 2008

Abstract

Purpose: To investigate Blood Oxygen Level Dependent (BOLD) responses to interictal epileptic discharges (IEDs) during EEG-correlated functional MRI (EEG-fMRI) in patients with partial epilepsy.

Methods: We studied eight patients who had a diagnosis of partial epilepsy and active spiking on routine scalp EEG recording. Sessions of continuous EEG-fMRI were recorded, and spikes (identified after online artifact removal) were used as events in the fMRI analysis. Regions of BOLD signal change in response to interictal epileptic discharge were assessed and epileptogenic zone localization was electroclinically identified.

Results: Eight patients with partial epilepsy were recruited (6 males, 2 females, mean age 18.5, mean onset age range 0.5-29). Two who underwent EEG-fMRI were excluded from further analysis: one due to absence of epileptic discharges, the other due to excessive head motion. Eight sessions of EEG-fMRI scanning in 6 patients were obtained: 6 with activation and deactivation, one with activation only, and one with deactivation only. Focal activations corresponding to electroclinical localization occurred in 7 sessions, 5 of which were maximal.

Conclusions: Maximally activated areas detected by EEG-fMRI in patients with partial epilepsy appear to be concordant with epileptogenic areas as defined by electroclinical localization data. In most patients with focal epilepsy, positive BOLD responses seem to be mainly in epileptogenic zones and the corresponding contralateral areas. Responses to deactivation seem less associated with IEDs. So EEG-fMRI is a useful tool to study the pathophysiological mechanisms of epilepsy and may assist in presurgical evaluation of epilepsy.

© 2007 Elsevier B.V. All rights reserved.

Keywords: EEG-fMRI; Blood oxygen level-dependent; Partial epilepsy

1. Introduction

As a tool for diagnosis of epileptic disorders, EEG has high temporal resolution and sensitivity but lacks spatial resolution. At the same time, fMRI has high spatial resolution and can localize cerebral metabolic changes noninvasively. So the combination of EEG and fMRI has more technical advantages. Because it integrates both electro-physiologic and metabolic information, EEG-fMRI can be used to obtain Blood Oxygen Level Dependent (BOLD) responses to epileptic discharges and improve the localization of epileptogenic foci.

It has been reported that EEG-fMRI delineates regions of interictal epileptic discharges (IEDs) that are correlated with
BOLD responses in 60–70% of patients [1–6]. In addition, it allows the identification of functionally disturbed areas affected by IEDs, in particular the irritative zone [7], which is the area responsible for generating interictal epileptiform activity. Localization of functionally disturbed cortical areas can facilitate identification of the epileptogenic zone (the cortical area indispensable for generating epileptic seizures) and assist in presurgical evaluation of epilepsy [8].

In some patients with partial epilepsy and no abnormal findings in clinical neuroimaging, it is difficult to localize the epileptogenic focus, and localization is an important aspect of diagnosis and therapy in these cases. Previous reports suggest that EEG-fMRI studies performed in patients with focal epilepsy could provide localizing information non-invasively about the epileptogenic zone, but the degree of concordance with the presumed epileptic generator has varied [2,9–11]. Here, we used an event-related EEG-fMRI design to analyze interictal epileptiform activity, with simultaneous acquisition of EEG and fMRI as recently described [9,12]. The purpose of this study was to investigate Blood Oxygen Level Dependent (BOLD) responses to IEDs using EEG-fMRI recordings in patients with partial epilepsy, and to assess the concordance between the regions of BOLD signal changes in response to IEDs and the electro-clinical localization of the epileptogenic zone.

2. Material and methods

2.1. Patients

We selected patients with partial epilepsy from the epilepsy clinics of the West China Hospital for Neurology, Sichuan University, from January 2006 to January 2007. The study protocol was approved by the institutional review committee at Sichuan University. Informed consent for the study was obtained from each subject. All patients underwent routine clinical neuroimaging (brain MRI) and 24-hour video-EEG. EEG-fMRI data were acquired in patients who fulfilled the following criteria: a diagnosis of partial epilepsy established according to the International League Against Epilepsy recommendations, and frequent stereotyped interictal epileptiform discharges recorded on EEG. Patients who could not cooperate were excluded.

2.2. EEG acquisition

The EEG was recorded using a 10/20 system with 21 Ag/AgCl electrodes soldered to 12 kΩ current-limiting resistors attached to the scalp with conductive cream. The EEG device was a Mizar 40 amplifier (EBNeuro, Florence, Italy), with 32 channels adapted for MR. The sampling rate was set at 4 kHz, which allows a suitable time resolution for picking up the switching effect of the readout gradient in the high slew rate condition, and the EEG dynamic range was ±65.5 mV to prevent MRI artifact waveforms saturating the EEG/ECG. The EEG device inside a shielded box amplifies the signal and performs A/D conversion. The amplifier was connected to the recording computer outside the scanner room via a fiber optic cable. The MR artifact was filtered out online [13] and the software was BE-MRI Tool box (Galileo New Technology, Florence, Italy). The pulse artefact was minimized using careful arrangement of the EEG cables and an elastic cap. If no spike was found in one session of a particular run, this run of fMRI data was excluded from the analysis.

2.3. fMRI acquisition

A 3.0 T GE MRI scanner (EXCITE, Milwaukee, WI, USA) was used to acquire BOLD-sensitive echo-planar images (EPI) images with continuous, simultaneous EEG. Foam padding was used to help secure the EEG leads, minimize motion, and improve patient comfort. At the same time the ears were packed with cotton and the patients were in the resting state with eyes closed. The imaging parameters of the gradient echo EPI sequences were as follows: 30 slices, 200 volumes, TR = 2000 ms, TE = 40 ms, FOV = 24 cm, matrix = 64 × 64, in-plane resolution = 2 × 2 mm, and flip angle = 90°. The structural image was also acquired in the interval of the first and second run (TR = 8.5 ms, TE = 3.4 ms, FOV = 24 cm × 24 cm, flip angle = 12°, matrix = 512 × 512, and 156 slices). BOLD fMRI data were collected in successive runs of 6 min 40 sec, and additional sessions of scanning were acquired in the same patient if no spikes were recorded on real-time EEG in one session.

2.4. Data analysis

First, the experimental data were analyzed using SPM2 software [www.fil.ion.ucl.ac.uk/spm] [14,15]. Spatial transformation and realignment was performed using 3-D rigid-body registration to correct for head motion. Second, to increase analysis efficiency, only signals in the brain were processed. Voxels with values lower than a certain threshold were regarded as background. We set the threshold values empirically to be 1/10 of the highest intensity in the input image. Third, a spatial smoothing filter was employed for each brain 3D volume by convolution with an isotropic Gaussian kernel (FWHM = 8 mm for our data) to increase the MR signal-to-noise-ratio. Fourth, we systematically removed noise from the considered data after eliminating background noise from the fMRI data. Linear trends were removed from the data to eliminate the effect of gross signal drifts, which could be caused by scanner instabilities and/or gross physiological change in the subject. A high-pass filter with a cut-off of 128 seconds was used to remove low-frequency noise.

The fMRI data were firstly preprocessed according to the steps mentioned above. According to the EEG, the spike time was first acquired. Then the canonical hemodynamic response function (HRF) was modeled by two gamma-variate functions [16] convolved with the spike time. Finally, the canonical HRF was specified as the task regressor and included in the SPM design matrix. Six other regressors were derived from six parameters obtained by rigid-body correction of head motion.
We could calculate the special activated areas using statistical t-tests (five contiguous voxels above a t value of 3.1, uncorrected; lowest threshold, t > 3.1, p < 0.001). According to the null hypothesis, the threshold is reached when there is a significant difference at the p < 0.05 level. In fMRI data processing, all t-statistics for threshold should exceed this obvious level (p < 0.05), that is, it should be p < 0.001, with the corresponding t-threshold value being t > 3.1. The highest threshold being the maximum mean global activity (p = 0.001). According to the number of activated voxels (the true activated voxels evoked by the task) must be determined and differentiated from the number of other voxels evoked by noise. This number (5 activated voxels) was distinguishable by experiment and experience. Responses with positive t values were labeled as activations and those with negative t values were labeled as deactivations [18].

### Table 1

Clinical details of patients

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (yrs)</th>
<th>Etiology</th>
<th>Seizure type</th>
<th>Interictal EEG</th>
<th>Abnormality in neuroimaging</th>
<th>Medication</th>
<th>Areas of localization defined by electroclinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>Encephalitis</td>
<td>SPS, SGTCS</td>
<td>Sparse spikes over left parietal regions</td>
<td>Mild atrophy of left temporoparietal lobe and ENF</td>
<td>CBZ, PB, PH, TPM, VPA</td>
<td>L tempoparietal</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>Cryptogenic</td>
<td>CPS</td>
<td>Bilaterally paroxysmal spikes over temporal and occipital regions, R&gt;L</td>
<td>ENF in left temporoparietal lobe</td>
<td>CBZ, PB, PH, TPM, VPA</td>
<td>L tempoparietal</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>Brain injury</td>
<td>SPS, SGTCS</td>
<td>Spikes and slow-waves over left frontotemporal regions</td>
<td>Negative</td>
<td>None</td>
<td>R, T</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>Brain injury</td>
<td>SPS, SGTCS</td>
<td>Bilaterally paroxysmal sharp and slow waves, R=L</td>
<td>Negative</td>
<td>C seize, PB, PH, TPM, VPA</td>
<td>R T</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>Cryptogenic</td>
<td>SPS, SGTCS</td>
<td>Bilaterally paroxysmal spikes, polyspikes and slow waves, R&gt;L</td>
<td>Negative</td>
<td>CBZ, VPA, VPA</td>
<td>R, F</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>Cryptogenic</td>
<td>SPS, SGTCS</td>
<td>Right mid-frontal spikes and slow waves, polyspikes and slow waves</td>
<td>Negative</td>
<td>None</td>
<td>R, F</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>Cryptogenic</td>
<td>SPS, SGTCS</td>
<td>Widespread paroxysmal spikes and polyspikes and slow waves with left frontoparietal predominance</td>
<td>Negative</td>
<td>None</td>
<td>L frontoparietal</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>Birth asphyxia</td>
<td>SPS, SGTCS</td>
<td>Bilaterally continuous sharp waves over parietal temporal and occipital regions</td>
<td>Left frontotemporal and occipital regions</td>
<td>CBZ, PB, PH, TPM, VPA, DZ</td>
<td>L, F and T</td>
</tr>
</tbody>
</table>

Abbreviations: DZP, diazepam; CBZ, carbamazepine; PB, phenobarbitone; PHT, phenytoin; TPM, topiramate; VPA, sodium valproate; LTG, lamotrigine; TCM, traditional Chinese medicine; Bil, bilateral; CPS, complex partial seizure; SPS, simple partial seizure L, left; R, right; T, temporal; F, frontal; C, central; P, parietal; O, occipital; Cere, cerebellum; HG, hippocampal gyrus; CG, cingulate gyrus; LN, lenticular nucleus; MTG, midtemporal gyrus; ITG, inferior temporal gyrus; SFG, superior frontal gyrus; and MFG, midfrontal gyrus.

### Table 2

Summary of EEG-fMRI results for all sessions during which spikes occurred

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Presumed location of epileptic focus</th>
<th>Number of spikes</th>
<th>Activation</th>
<th>Deactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum activation</td>
<td>Other activation</td>
</tr>
<tr>
<td>1</td>
<td>L tempoparietal regions</td>
<td>7</td>
<td>L, P postcentral gyrus</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>R, T</td>
<td>12</td>
<td>R, LN</td>
<td>R, LN; R, ITG; R, SFG; L, ITG</td>
</tr>
<tr>
<td>3</td>
<td>L tempoparietal lobe</td>
<td>6</td>
<td>L, MTG</td>
<td>L,O; R, MTG; R, O</td>
</tr>
<tr>
<td>4</td>
<td>R frontotemporal lobe</td>
<td>7</td>
<td>R, MTG</td>
<td>R, MFG</td>
</tr>
<tr>
<td>5a</td>
<td>R, F</td>
<td>5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5b</td>
<td>R, F</td>
<td>8</td>
<td>R, F</td>
<td>L,F; thalamus; CG; L, P</td>
</tr>
<tr>
<td>6</td>
<td>R, F</td>
<td>No epileptic discharges</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7a</td>
<td>L frontotemporal lobe</td>
<td>4</td>
<td>L, Cere</td>
<td>B, P</td>
</tr>
<tr>
<td>7b</td>
<td>L frontotemporal lobe</td>
<td>6</td>
<td>L, P</td>
<td>R, P</td>
</tr>
<tr>
<td>8</td>
<td>L, F and T</td>
<td>Head movement</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Notes: Id no.—identification number, corresponds to that in Table 1. (a) and (b) are given for those studied with two sessions.

--, no response; B, bilateral; L, left; R, right; T, temporal; F, frontal; C, central; P, parietal; O, occipital; Cere, cerebellum; HG, hippocampal gyrus; CG, cingulate gyrus; LN, lenticular nucleus; MTG, midtemporal gyrus; ITG, inferior temporal gyrus; SFG, superior frontal gyrus; and MFG, midfrontal gyrus.

### 3. Results

#### 3.1. Clinical features

Eight patients with partial epilepsy were recruited (3 with organic brain lesions; 6 males, 2 females, mean age 18.5, onset age range 0.5–29). The sites of seizure activity were...
mainly in 1 or 2 unilateral brain lobes. Of the 8 patients, 5 took many antiepileptics with little effect and 3 took no medications when first diagnosed. EEGs (24-hour videoelectroencephalograms) and clinical manifestations were used to localize epileptogenic sites. Clinical details of our patients are shown in Table 1.

3.2. EEG-fMRI results

Two of the eight patients who underwent EEG-fMRI were excluded from further analysis: one due to lack of epileptic discharges, the other due to excessive head motion. Eight sessions of EEG-fMRI scanning in 6 patients were obtained...
The mean number of interictal spikes was 6.86 (range, 4–12). The ballistocardiogram artifact and MRI gradient artifact were removed from all EEG recordings.

All studies showed responses: six had activation and deactivation responses (Figs. 2 and 3), one had only activation responses, and one only deactivation responses (Fig. 4). Maximal activation responses were concordant with the sites of electroclinical localization in five of seven studies with activation responses (Figs. 1–3). In patients 5 and 7, the BOLD responses were not concordant with spike topography in the first session, but were in the second session. In 5 sessions of the 8 studies, weak activations were noted in the homologous region contralateral to the lesion sites. Activations were mainly in cortex and subcortex in one study. In 2 studies (patients 1 and 3) with abnormal MRIs, the BOLD responses were in perilesional regions (Fig. 2). In patient 1, with mild atrophy of the left temporoparietal lobe containing an area of encephalomalacia, the largest activation was in the left parietal lobe and postcentral gyrus. In patient 3, with encephalomalacia in the left temporoparietal lobe, the site of highest activation was in perilesional regions in the left posterior mid-temporal gyrus. In addition, in patient 5 who suffered from repetitive seizures before the test, activation was also in the thalamus and cingulate gyrus (Fig. 3).

4. Discussion

This study demonstrates that BOLD responses in partial epilepsy reflect both activations and deactivations, mostly activations. This result agrees with that of previous reports [11]. Maximal activations were concordant with the electroclinical localization in five studies. Activation rather than maximal activation was found in regions of electroclinical localization in two studies. In 7 of the 8 studies, activations occurred in the areas of electroclinical localization. Therefore activations tend to be highly concordant with at least the lobe of presumed seizure activity, while deactivations appeared to be much less concordant with these areas. This finding is inconsistent with those of other studies [19,20–22]. So EEG-fMRI can provide localizing information noninvasively and objectively in a large proportion of patients with focal epilepsy and frequent IEDs. In addition, it can offer some degree of confirmation of the epileptogenic zone defined by electroclinical data.

In all of our studies, BOLD changes at the time of IEDs were all multifocal, and in 5 sessions of our 8 studies, weak activations occurred in the homologous regions contralateral to the lesion sites. This was previously observed by other groups [23–25] studying patients with lesional focal epilepsy using EEG-fMRI. The involvement of areas surrounding the lesion distinguished the lesion from the region of seizure.
onset and this may suggest that epileptic discharges from perilesions underly the epileptogenic process. These responses observed in remote areas such as homologous regions in the contralateral hemisphere suggest that the lesion may affect remote regions not directly involved in the epileptic process without generating synchronous EEG discharges [23,25,26]. Most studies showed predominantly neocortical activation, which may be due to epileptic discharges mainly coming from the neocortex [27]. But in some studies, responses such as in patient 2 appeared in the subcortex; this may suggest that epileptic discharges originate both subcortically and cortically.

Deactivation appeared in 6 of our sessions, and it often occurred in areas outside the site of EEG spike onset. At the same time, no concordance was found between the areas of deactivation and electroclinical findings. This phenomenon may be due to inhibition at a distance [28,29]. In the first session of patient 5, the BOLD response was only deactivation bilaterally over frontotemporoparietal lobe and cerebellum (Fig. 4). The patient was diagnosed with simple partial seizure (SPS) and secondary generalized tonic–clonic seizure (SGTCS), with the EEG showing bilaterally paroxysmal spikes, polyspikes, and slow waves. Raichle et al. introduced the concept of a “default” state of brain activity to explain deactivations because these regions (mainly including the bilateral mesial and dorsolateral parieto-occipital regions, anterior frontal regions, and the posterior cingulate gyri) show a consistent decrease in the BOLD signal during various stimuli and tasks [30]. So the deactivation in patient 5 may be related to bursts of generalized epileptic discharges and stand for the temporary suspension of normal brain function in the resting state [31]. But this remains to be elucidated.

In patient 5, we observed activation in thalamus and cingulate gyrus. The role of the thalamus in partial epilepsy is less clear. It has been confirmed that most patients with idiopathic generalized epilepsy (IGE) and generalized spike and wave (GSW) discharges show thalamic fMRI responses [32]. Some studies suggested that thalamic activation seen in EEG-fMRI represent subcortical activity necessary for the maintenance of GSW discharges [33], while other studies suggested that thalamic or cingulate BOLD responses are due to spike-and-wave discharges [32,34] in patients with idiopathic generalized epilepsy. That the thalamus might have a role in seizure propagation has been supported by research using animal models with thalamic lesions [35] and a few patients with intractable partial epilepsy [36]. The EEG of patient 5 showed bilateral paroxysmal spikes, polyspikes, and slow waves, so we thought the thalamic activation may be related to widespread epileptic discharges. Possibly, common circuits are sometimes activated in focal and widespread discharges. The thalamus seems to play a prominent role in the occurrence of bilateral discharges in patients with partial epilepsy [37].

In addition, in this study, we used a real-time filtering technique to remove EEG artifacts and so we were able to

---

Fig. 4. The fMRI results of first session of patient 5. The BOLD response was only deactivation and its pattern was similar to the “default” mode.
constantly monitor the EEG and the patient’s clinical behavior during the fMRI data acquisition. Therefore the duration of fMRI acquisitions was 6 min 40 sec, which is comparatively short and has been adopted by other groups [37]. Additional scanning sessions can be performed in the same patient if no spikes are recorded on real-time EEG in one session. This can save time and be useful when no activity on fMRI is observed. Thus, real-time filtering combined with an optimal EPI protocol is a good tool to investigate BOLD responses to IEDs, may assist in presurgical evaluation of epilepsy through localizing the epileptogenic zone, and is potentially useful in clinics.

In summary, activated areas detected by EEG-fMRI in patients with partial epilepsy were well concordant with areas defined as epileptogenic by electroclinical data. In most patients with focal epilepsy, positive BOLD responses were mainly seen in epileptogenic zones and also in the corresponding contralateral areas. Deactivations were less associated with IEDs. So EEG-fMRI is a useful tool to study the pathophysiological mechanism in epilepsy.

References