EEG-fMRI study of the ictal and interictal epileptic activity in patients with eyelid myoclonia with absences

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Summary

Purpose: To investigate the blood oxygenation level-dependent (BOLD) signal changes correlated with ictal and interictal epileptic discharges using electroencephalography-correlated functional magnetic resonance imaging (EEG-fMRI) in patients with eyelid myoclonia with absences (EMA) and then to explore the pathophysiological mechanisms of epileptic discharges and their effect on brain function.

Methods: Four patients with EMA were investigated through the method of EEG-fMRI. The characteristics of BOLD signal changes linked to ictal and interictal epileptic discharges under different states of consciousness were explored.

Results: Seven sessions of EEG-fMRI scanning in the four patients were obtained. The main regions of activation included thalamus, mesial frontal cortex, middle parietal lobe, temporal lobe, insula, midline structures, and cerebellum. Deactivations were mainly in the anterior frontal lobe, posterior parietal lobe, and posterior cingulate gyrus. Thalamic BOLD change was predominantly activation in most of our cases. The distribution of activation associated with ictal epileptic discharges was wider, and the distribution of deactivation was closer to pericortex compared with the BOLD change linked with interictal epileptic discharges.

Conclusions: The activation in the thalamus may be associated with generalized spike wave in EMA; the combination of different patterns of activation with consistent pattern of deactivations (“default” pattern) in patients with EMA may prognosticate different states of consciousness in response to ictal and interictal epileptic discharges.

KEY WORDS: EEG-fMRI, Interictal period, Ictal period, BOLD, EMA.
1968; Marcus et al., 1968; Avoli et al., 2001; Blumenfeld, 2003; Timofeev & Steriade, 2004). The recently developed technique of EEG-correlated functional magnetic resonance imaging (EEG-fMRI) can obtain both electro-physiologic and metabolic information and can then be used to explore the pathophysiological mechanisms of epileptic discharges and improve the diagnosis for an epileptogenic focus. A study of blood oxygenation level-dependent (BOLD)-associated neuronal activity in patients with EMA by EEG-fMRI has not been reported. This study aimed to investigate the BOLD signal changes correlated with epileptic discharges using EEG-fMRI in patients with EMA. The BOLD signal changes were examined under different states of consciousness, and the epileptogenic zone of EMA was localized.

**Materials and Methods**

**Patients**

Inclusion criteria for the diagnosis of EMA were according to Panayiotopoulos and included eyelid myoclonia and brief absences, which were related to EEG generalized paroxysmal activity and were triggered by eye closure or by intermittent photo stimulation (IPS) (Panayiotopoulos, 2005). The study was conducted in four patients with EMA (2 males, 2 females, mean age 10.25, mean onset age 8.5, range 8–9) recruited from the epilepsy clinics at the West China Hospital for Neurology of Sichuan University between June 2005 and January 2007. All patients underwent routine clinical neuroimaging and 24-h video EEG monitoring. No structural abnormalities were found during neuroimaging, including computed tomography (CT) and MRI, but frequent and stereotypical ictal and interictal epileptic discharges were confirmed. During the experimental sessions, patients were continuously monitored to detect seizure occurrence inside the scanner. In the EEG-fMRI scanning sessions of ictal activity, when patients presented with clinical symptoms such as eyelid myoclonus and absence, motor activity did not induce image artifacts during the seizure. Patients with mental disorder or cognitive handicaps were excluded. This study was approved by a responsible governmental agency at the Sichuan University. Informed consent for the study was obtained from each subject.

**EEG acquisition**

The EEG was recorded using a 10-20 system with 21 Ag/AgCl electrodes soldered to 12 kV current-limiting resistors applied on the scalp with conductive cream. The EEG device was an EBNeuro Mizar 40 (EBNeuro, Florence, Italy) with 32 channels adapted for MR and a sampling rate of 4 kHz, which allowed suitable time resolution for detecting the switching effect of the readout gradient in the high slew rate condition. The EEG dynamic range was ±65.5 mV in order to prevent MRI artifact waveforms from saturating the EEG/electrocardiogram (ECG). The amplifier was connected to the recording computer outside the scanner room via a fiber-optic cable. The MR artifact was filtered online (Garreffa et al., 2003). The pulse artifact was minimized by using a locked arrangement of particular wires and an elastic cap. If no spikes were found in one session, that run’s fMRI data was excluded in the future analysis.

**fMRI acquisition**

A 3.0 T GE MRI scanner (EXCITE, Milwaukee, WI, U.S.A.) was used to acquire BOLD sensitive echo-planar images (EPI) 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 patient’s ears were packed with cotton balls and the patient assumed a resting state with their eyes closed. The gradient echo EPI sequence’s parameters 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 a flip angle = 90°. The structural image was also acquired during the interval of the first and second run (TR = 8.5 ms, TE = 3.4 ms, FOV = 24 × 24 cm, flip angle = 12°, matrix = 512 × 512, 156 slices). BOLD fMRI data were collected in successive runs of 6 min and 40 s. Additional scanning sessions were acquired in the same patient if no spikes were recorded during the real-time EEG in one session.

**Data analysis**

The data analysis proceeded in four steps. First, the experimental data were analyzed using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm) (Friston et al., 1994, 1995). Spatial transformation and realignment were performed using a three-dimensional (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 one-tenth of the highest intensity in the input image. Third, a spatial smoothing filter was used for each brain 3D volume by convolution with an isotropic Gaussian kernel [full width at half maximum (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 s was used to remove low-frequency noise.

The fMRI data were initially preprocessed according to the steps mentioned above. According to the EEG records,
the time point at which epilepsy occurred was when the first spike-time signal was acquired. Then, EEG canonical hemodynamic response function (HRF) was modeled by two $\gamma$-variant functions (Friston et al., 1998) convolved with the spike-time signal. Finally, the canonical HRF was specified as an interested regressor in the SPM design matrix. The other six regressors were derived from the six parameters that were obtained by the rigid-body correction of head motion. The specific activated areas were calculated using the Student's $t$-test statistic with five contiguous voxels above a $t$-value of 3.1 (uncorrected). The lowest threshold ($t > 3.1, p < 0.001$) according to the Hull hypnosis theory, must satisfy the statistical difference of approximately $p < 0.05$. Generally, during fMRI data processing, thresholds should be specified to exceed the statistical significance level of $p < 0.05$, thus it was specified as $p < 0.001$, whose corresponding $t$ threshold value was $t > 3.1$, and the highest threshold that resulted in mean global maximum activity was used (Chen et al., 2005). To remove the influence of noise, in general, a number of continuously activated voxels were specified as the true activation voxels by an evoked task, otherwise, they were not specified as true activation voxels, but considered as being evoked by noise. The number of continuous voxels was specified by experimentation and experience; here it is specified as 5. Responses to positive $t$-values were labeled as activations, and those with negative $t$-values were labeled as deactivations (Archer et al., 2003).

**Results**

**Clinical features**

Four patients with EMA were recruited (2 males, 2 females, mean age 10.25, mean onset age 8.5, range 8–9). The clinical manifestations were EMA or not, and occasional generalized tonic–clonic seizures (GTCS). The seizures of the four patients occurred multiple times per day. Before the study of EEG-fMRI, 24-h video EEG was recorded. Interictal and ictal EEGs demonstrated rapid, generalized, and often irregular 2.5–6 Hz spike-waves and polyspike-waves (Fig. 1). Every patient was administered intermittent medications, but the effect was poor. Clinical details of patients were shown in Table 1.

**EEG-fMRI**

Seven sessions were produced in all during the EEG-fMRI scans. Among them, two sessions of BOLD changes associated with ictal epileptic discharges were observed in two patients (patients 1 and 2), who presented with repetitive EMA during EEG-fMRI scans. The EEG recordings of patients 1 and 2 exhibited frequent bursts of rapid, generalized, 3–4 Hz spike-waves and polyspike-waves. These wave forms were always associated with unresponsiveness and not always recalled by the patient. Before, during, and after EEG-fMRI scanning, patients 1 and 2 had frequent and repetitive seizures as described above. The mean number of interictal GSW epochs was 19.4 (range, 4–35), and

![Figure 1.](image-url)
the duration ranged from 0.7 to 4 s. The number of ictal GSW for patient 1 was nine, and for patient 2 was eight. The duration ranged from 3 to 5 s (details shown in Table 2).

**BOLD change in response to epileptic discharges**

The regions of BOLD signal changes (activation and deactivation) linked to epileptic discharges were bilaterally and symmetrically distributed over the cerebral hemispheres. BOLD signal changes were shown in the following sequence: parietal lobe (seven times), frontal cortex (six times), temporal lobe (six times), posterior cingulate gyrus (seven times), occipital lobe (five times), cerebellum (five times), thalamus (five times), insula (two times), brain stem (two times), and basal ganglia (one time). The activation in the thalamus was positive in four sessions, and there was predominant biphasic activation in one session.

**BOLD change in response to IEDs**

The map of activation and deactivation in response to interictal epileptic discharges (IEDs) possessed unique characteristics. Activation regions involved the entire brain, including the thalamus and brain stem with symmetrical and submedian distributions (seen in Figs. 2, 3, and 4). The main regions of activation included the thalamus, mesial frontal cortex, middle parietal lobe, temporal lobe, insula, midline structures, and cerebellum. However, the maximum activation area was not fixed, two sessions demonstrated activation in occipital lobe, scattered in parietal lobe, frontal cortex, or cingulate gyrus. Deactivations were mainly in the anterior frontal lobe, parietal area, and cingulate gyrus where they were in close vicinity to the regions of activation in the cortex. Deactivation was only related to IEDs in the second session of patient 3 and occurred symmetrically and bilaterally in the temporal lobe, parietal lobe, occipital lobe, posterior cingulate gyrus, and insula.

### Table 1. Clinical details of patients studied based on ILAE diagnostic categories

<table>
<thead>
<tr>
<th>Patient ID no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Seizure type</th>
<th>Frequency of GSW (Hz) and accompanied symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>Male</td>
<td>Eyelid myoclonus accompanied with absence or not, 5–8/d (8)</td>
<td>PB, VPA, 3–6, Eyelid myoclonus absence</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>Male</td>
<td>Eyelid myoclonus accompanied with absence or not 5–8/d (8); GTCS 1/y (11)</td>
<td>PB, VPA, 3–6, Eyelid myoclonus absence</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>Female</td>
<td>Eyelid myoclonus accompanied with absence or not 2–5/d (10)</td>
<td>VPA, 3.5, Eyelid myoclonus absence</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>Female</td>
<td>Eyelid myoclonus accompanied with absence or not 2–5/d (9)</td>
<td>TCM, 2.5–4, Eyelid myoclonus absence</td>
</tr>
</tbody>
</table>

International League Against Epilepsy (ILAE) diagnostic categories show age and sex of the patients, seizure type and frequency, age of onset, medication at time of study, and frequency of GSW and accompanying symptoms.

GTCS, generalized tonic–clonic seizures; d, day; y, year; CBZ, carbamazepine; PB, phenobarbitone; VPA, sodium valproate; TCM, traditional Chinese medicine; GSW, generalized spike-wave.

### Table 2. Summary of results for all sessions during which GSW activity occurred; detailing number and duration of GSW epochs, and regions of significant BOLD signal change

<table>
<thead>
<tr>
<th>ID no.</th>
<th>Number of GSW</th>
<th>Duration of GSW (s)</th>
<th>Thalamus</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Temporal</th>
<th>Occipital</th>
<th>Posterior cingulate</th>
<th>Cerebellum</th>
<th>Brain stem</th>
<th>Insula</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>3–5</td>
<td>↑</td>
<td>↑</td>
<td>↓m↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>2a</td>
<td>8</td>
<td>3–6</td>
<td>↑</td>
<td>↓</td>
<td>↓↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>□</td>
</tr>
<tr>
<td>2b</td>
<td>2</td>
<td>2–3</td>
<td>↑L</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>□</td>
</tr>
<tr>
<td>2c</td>
<td>35</td>
<td>2–3</td>
<td>↓</td>
<td>↓m↓</td>
<td>↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>□</td>
</tr>
<tr>
<td>3a</td>
<td>24</td>
<td>0.7–1.5</td>
<td>↑</td>
<td>↓</td>
<td>↓↑↑</td>
<td>↓↑↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>3b</td>
<td>25</td>
<td>0.7–1.5</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>1–4</td>
<td>↑</td>
<td>↓</td>
<td>↑□</td>
<td>↓□</td>
<td>↑</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>—</td>
</tr>
</tbody>
</table>

Id no., identification number corresponding to that in Table 1. (a), (b), and (c) are given for those studied with three sessions. The BOLD changes of 1 and 2a were in response to ictal electroclinical activity. ↑, activation; ↓, deactivation; ↑↓, activation predominantly; ↓↑, deactivation predominantly, —, no response, B, bilateral L, left; R, right; m, global maxima.
Notably, during this session, the patient had no complaints or clinical symptoms, although the frequency of GSW increased to 35 Hz in the EEG.

**BOLD change in response to ictal electroclinical activity**

The BOLD changes associated with electroclinical activity were bilaterally symmetrical. The activations were predominantly in the middle parietal lobe, temporal lobe, midline structures, and secondarily in the thalamus and occipital lobe. Deactivations were mainly in the frontal lobe, anterior and posterior cortex of the parietal lobe, and cingulate gyrus (shown in Fig. 4). Ictal EEGs showed bursts of rapid, generalized, 3–4 Hz spike-waves and polyspike-waves with a high amplitude and a duration of 3–5 s (shown in Fig. 5). The BOLD change correlated with ictal electroclinical activity of patient 1 who manifested repetitive eyelid myoclonus with absence as shown in Fig. 4.

**Discussion**

**Map and pattern of BOLD signals associated with epileptic discharges in EMA**

The patterns of activation and deactivation were as follows: (1) activation and deactivation were bilaterally symmetrical; (2) activation in most of our cases was predominantly in the thalamus and occipital lobe; and (3) the BOLD signal in the posterior cortex was mainly deactivation and that in the parietal cortex was varied. The maximum activation area was not fixed, and the distribution of deactivation was correlated with a “default” pattern of brain activity in the baseline brain activity state (Figs. 3 and 4) (Raichle et al., 2001), which was inconsistent with other reports (Aghakhani et al., 2004; Gotman et al., 2006). The patterns of activation and deactivation associated with epileptic discharge in EMA were bilaterally symmetrical, which was similar to that previously reported in IGE. Therefore, our results support that EMA belongs to IGEs.

**Activation linked to epileptic discharges in EMA**

The thalamus has long been considered to be related to the paradoxical discharges of IGE and interacts with the brain cortex, which has been confirmed by several studies (Aghakhani et al., 2004; Gotman et al., 2006; Hamandi et al., 2006). Some studies suggested that the thalamic activation seen in EEG-fMRI represented subcortical activity necessary for the maintenance of GSW (Avoli et al., 2001). This study found that the thalamus exhibited predominant activation associated with epileptic discharges in most of our cases. Therefore, our results suggest that the thalamus may play an important role in the generation and maintenance of GSW in EMA. Nevertheless, we also found that the thalamus showed deactivation without activation in patient 3, whose BOLD change manifested deactivation throughout the whole brain (Fig. 3, bottom panel). Therefore, the thalamic deactivation may relate to the whole brain deactivation; however, this response...
remains to be elucidated. In addition, activation was found in the mesial midfrontal region concomitant with the bilateral insula and cerebellum in our patients with EMA. The mesial midfrontal region was associated with the propagation and generalization of epileptic discharges in focal epilepsy and IGE. In addition, the predominant activation in the frontoparietal region was concordant with the frontocentral predominance of epileptic discharges seen in the EEG. The insula is a region of convergence of multisensory inputs and has been shown to be pertinent to partial epilepsy (Isnard et al., 2004) rather than IGE; however, it is connected with the thalamus extensively, and this may contribute to the activation shown in the insula in our patients (Mesulam & Mufson, 1985). The activation in the cerebellum may be due to hyperperfusion in IGE (Bohnen et al., 1998). Previously, it was not recognized that cerebellar neuronal activity contributes to spike-and-wave EEG patterns, until it was found that the cerebellum was involved in the spike-and-wave discharges in an experimental model (Kandel & Buzsáki, 1993). The presence of activation in the frontal cortex, temporal lobe, and parietal lobe was correlated with the propagation of epileptic discharges between the lobes of the brain through callosal fibers.

Deactivation associated with epileptic discharges in EMA and the default pattern of brain activity

Deactivations have been reported in areas directly or indirectly involved in stimulus processing or task completion (Born et al., 2002; Czisch et al., 2004), as well as task-independent stimulus processing (Raichle et al., 2001). Deactivations in the bilateral posterior cingulate gyrus and parietooccipital areas superimposed with other

Figure 3.
The BOLD signal of patient 3 during two EEG-fMRI scans. (Top panel) The first fMRI session showed that the main activation clusters were located bilaterally in the thalamus, periparietal lobe, occipital lobe, and predominantly in the right frontal lobe. Bilateral deactivation clusters were observed in the anterior frontal cortex, middle parietal lobe, cingulate gyrus, in addition to some in the thalamus. (Bottom panel) The second session of fMRI showed deactivation located bilaterally in the frontal cortex, parietal lobe, temporal lobe, occipital lobe, thalamus, cingulate gyrus, cerebellum, and insula.

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signals in our study were consistent with the default pattern of brain activity. This phenomenon, related to GSW, has been reported in several previous reports (Archer et al., 2003; Aghakhani et al., 2004).

Deactivation in the default areas may relate to bursts of generalized epileptic discharges and represent the temporarily suspended normal brain function in the resting state (Gotman et al., 2006; Kobayashi et al., 2006) and are not necessarily indicative of the region responsible for the generation of the epileptic discharge (Aarts et al., 1984). Patients do not always manifest a clinical absence in every burst of spike-and-wave activity in clinics, but responsiveness is often impaired during such bursts (Gloor, 1986). At the same time, the level of cognitive impairment increases when discharges become longer (McKiernan et al., 2003). Thus, this suspending of the default state combined with the delay of sensory signal inputs and the degradation of reactive potency resulting from the activation of thalamus, middle frontal regions, and insula can explain the state of altered consciousness related to GSW.

**BOLD change in response to ictal and interictal epileptic discharges and conscious states**

The BOLD change in response to IEDs was manifested by two distinct patterns. One was shown in Fig. 3, top panel, which was the most common type of BOLD in our study. The other pattern was shown in Fig. 3, bottom panel. These two patterns occurred in different sessions in patient 3 on the same day with no clinical manifestations. Whether the two patterns of BOLD change indicate the epileptic process or not remains to be determined. The ictal BOLD changes during EMA were different from that observed in response to IEDs, as shown in Figs. 4 and 5. During the EEG-fMRI sessions, these patients showed EMA. The ictal activation was different from the interictal activation, which
may be due to different types of seizure and states of consciousness.

The distribution pattern of deactivations during ictal and interictal epileptic discharges in our patients were similar and were consistent with the default pattern of brain function (Mazoyer et al., 2001; Raichle et al., 2001). Nevertheless, the distribution of activation showed no fixed pattern. According to the clinical manifestations of subjects during the EEG-fMRI scanning, we propose that consistent patterns of deactivation combined with different patterns of activation may prognosticate different types of conscious states related to epileptic discharges. Other studies (Archer et al., 2003; Aghakhani et al., 2004; Laufs et al., 2006) also showed an alteration of activity in these regions during GSW, which would be consistent with the clinical manifestation of absence seizures. Therefore, the BOLD signals observed in this study (Figs. 3 and 4) may reflect different states of consciousness, such as a mild cognitive handicap, staring, and absence associated with GSW. Nevertheless, this needs further study with larger sample sizes.

In conclusion, activation in the thalamus and cortex may be associated with generalized spike-waves in EMA, while deactivation in the anterior frontal regions, parietal lobe, and cingulate gyrus might be suspending the default state induced by spike-wave and slow-wave complexes. The combination of consistent patterns of deactivation and varied patterns of activation in patients with EMA may prognosticate different types of states of consciousness in response to ictal and interictal epileptic discharges.

Acknowledgments

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest: The authors have no conflicts of interests to disclose.

References


