Identifying seizure-onset zone and visualizing seizure spread by fMRI: a case report

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ABSTRACT – Aim. To visualize by ictal, functional MRI, the initial haemodynamic change (i.e. putative seizure-onset zone) and subsequent seizure spread during an epileptic seizure. Methods. A 20-year-old woman was investigated during a simple partial seizure consisting of right-sided mouth clonus. An internal reference curve, correlated with signal change pixelwise, was applied to obtain correlation coefficient maps. The reference curve was shifted scan by scan to examine the correlation at each time point. To demonstrate seizure onset and propagation, a lag time map was produced showing the temporal sequence of activation in various brain regions. Results. fMRI analysis showed that the lower part of the insular cortex was activated first, and its signal alteration preceded the clinical beginning of the seizure (i.e. mouth clonus) by more than one minute. Most of the activations started before clinical seizure onset. The activation corresponding to the motor area of the right face showed only a 7.5 second-long, pre-ictal phase. BOLD signal alterations were also observed in the left caudate nucleus, left thalamus, along with various areas of the left cerebral and cerebellum hemispheres. Conclusions. The present study demonstrates a whole-brain activity simultaneously in time and space, during an epileptic seizure. Our results also support the existence of the pre-ictal state in epilepsy. Replication of our results would be of major interest for presurgical evaluation of patients with drug-resistant epilepsy.

Key words: epilepsy, ictal fMRI, cross-correlation, post-processing, seizure-onset zone, seizure spread

Whole-brain neuronal activity cannot be adequately visualized synchronously in time and space (Lehmann 1984, He and Lian 2002). Epileptic seizures are accompanied by abnormally large neuronal activity (Engel et al. 2007, Uhlhass and Singer, 2006). Theoretically, this abnormally large activity can be much better detected in comparison with normal neuronal processes. Consequently, spatiotemporal visualization of epileptic activity can be the first step in developing methods to demonstrate whole-brain neuronal activity in general, with adequate time and space resolution.
However, until now, no technique has been able to adequately visualize the spatiotemporal relationship of the spreading activity during epileptic seizures. Scalp EEG detects electric potential fields some distance from the source, resulting in very low spatial resolution. The invasive intracranial EEG can only measure electrical changes during epileptic seizures that are in the vicinity of the electrodes. Because the whole brain cannot be implanted by electrodes, a sampling error must always occur during intracranial recordings, thus neuronal activity distant from the electrodes remains undetected (Siegel et al. 2000).

Using ictal SPECT or PET, epileptic activity can only be visualized at the time of the tracer binding (Koepp et al. 1998). Thus, it often visualizes seizure spread but not seizure onset (Janszky et al. 2002). Magnetoencephalography (MEG) can exclusively detect an overall electromagnetic brain activity but with low spatial resolution (Knowlton and Shih 2004).


Visualization of epileptic activity in the brain with good spatial resolution is of critical importance for the presurgical evaluation of epileptic patients. To the best of our knowledge, there is no study in the literature that successfully demonstrated whole-brain, spatiotemporal, haemodynamic changes during a clinical seizure. In the present paper, an ictal fMRI investigation is reported involving a patient with drug-refractory epilepsy. Apart from postoperative lesions, the patient had no detectable epileptogenic lesions on the high-resolution, anatomical, MRI scans. Our aim was: (i) to highlight the site of the initial haemodynamic alteration (i.e. putative seizure-onset zone) during an epileptic seizure and (ii) to visualize haemodynamic changes associated with seizure propagation. Our observations may be of help in the presurgical evaluation of epilepsy.

**Methods**

**Patient history**

A 20-year-old woman, with no risk factors for epilepsy, had suffered from epileptic seizures since the age of 11. Her seizures began with a feeling of palpitations and flushing followed by loss of consciousness and distal, bilateral hand automatisms. She had received all available antiepileptic drugs and numerous drug combinations including phenytoin, carbamazepine, oxcarbazepine, valproic acid, sulphlam, clobazam, clonazepam, phenobarbital, primidon, vigabatrin, felbamate, ethosuximide, gabapentin, levetiracetam, topiramate, lamotrigine. As a consequence of drug resistance, the patient underwent presurgical evaluation in 2001. The neurological examination was normal. The patient’s global IQ was 94.

High-resolution MRI revealed no structural abnormality. Interictal EEG showed left frontal, interictal epileptiform discharges. A left frontal seizure pattern appeared during ictal scalp EEG examination. Ictal SPECT revealed left frontal hyperperfusion in frontomedial and frontobasal regions. Interictal PET examination showed left-sided hypometabolism in the frontopolar region, frontobasal, frontodorsal, temporopolar areas and in the cingulate gyrus. Electrophysiological examinations using implanted subdural electrode grids suggested a seizure-onset in the frontopolar region. On the basis of this examination, she underwent surgery in 2001: the left frontal pole was removed.

Because seizure frequency and severity were not changed postoperatively, a second examination using subdural electrode grids was performed. This suggested a seizure onset posterior to the first resection. The patient underwent a second operation in 2002: the first and second gyri of her left frontal lobe were removed. She did not become seizure-free, but her seizure semiology changed completely: seizures consisted of right-sided clonus of the mouth, without loss of consciousness. On two occasions, they were preceded by strange throat sensations. Previous seizure types disappeared. The altered postoperatively seizure semiology may have been caused by the ictal spread activating other brain regions than those preoperatively.

At the time of investigation, seizure frequency was 5–30 focal seizures per day (10 on average) lasting for two to four minutes. She was taking carbamazepine and vigabatrin. Similarly to the preoperative ictal recordings, the postoperative ictal scalp EEG showed a left frontotemporal seizure pattern.

**Data acquisition**

The experiment was conducted with the understanding and the written consent of the patient, and the local ethical committee of University of Pécs approved the experiment. The ictal-fMRI examination was conducted using a clinical scanner operating at 1T (Siemens Magnetom Harmony). A standard, Siemens, circularly polarized head coil was used for signal excitation and detection. The patient’s head was firmly taped to the head coil to prevent involuntary movements. The ictal fMRI study employed a commercial optimized EPI sequence with the following parameters:
parameters: TR/TE = 2 500 ms/80 ms, flip angle 90°, receiver bandwidth 752 Hz, FOV 210 × 210 mm and matrix 64 × 64 yielding 3 × 3 mm in-plane resolution, and 12 sections with a thickness of 5 and 1 mm gap. With these settings we were able to acquire good coverage of the whole brain with relatively good temporal resolution of 2.5 seconds. During fMRI, the patient was observed by her neurologist. The start and the end of the seizure were detected visually by observing mouth clonus. A set of 250 EPI images, corresponding to an acquisition time of 10 m 25 s, was acquired including images before, during and after mouth clonus. Some other seizures were also recorded during further sessions, but this was the only session containing a sufficiently long, relatively stable baseline before and after the seizure. In addition, the other fMRI datasets captured during seizures in other sessions were severely corrupted due to excessive head motion that rendered the data uninterpretable. Anatomical images were also acquired for identification of brain areas. We applied a 3D FLASH-sequence with the following parameters: TR/TE = 2 110 ms/38 ms, flip angle 15°, receiver bandwidth 130 Hz, voxel 1.3mm, isotropic.

Data processing
A retrospective motion correction was performed in the k-space with an algorithm built into the commercial Siemens BOLD imaging application and the Realign function of SPM (Friston et al. 1995) was also applied. Firstly, an internal reference curve was identified by examining the signal alteration of each voxel during the whole acquisition time in the left motor area, corresponding to the right mouth clonus. As we were about to use a voxel-by-voxel analysis, a reference signal curve of a particular voxel was selected that showed a relatively flat baseline, a symmetric signal peak and an intensity alteration of 9%. The cross-correlation function using the internal reference curve was applied to assign a correlation coefficient value to each pixel. Cross-correlation function examines the similarity between the signal alteration in a given voxel and a reference curve. The reference curve was also shifted, scan-by-scan to examine the correlation at each time point, thus all signal curves showing activation can be determined regardless of the time of activation. The histograms of the correlation coefficients showed a non-Gaussian distribution, indicating that activation occurred (Kleinschmidt et al. 1995, Baudewig et al. 2003). Active pixels were pointed out if their correlation coefficients exceeded the 99.85% (equal to p value of 0.0015) percentile rank of the fitted Gaussian function, thus showing the local maxima of the corresponding activation clusters. In a second step, neighboring pixels were iteratively added to the corresponding activation clusters as long as their correlation coefficient exceeded the 95% percentile rank (equal to a p value of 0.05). The correlation coefficients corresponding to a p value of 0.0015 and 0.05 were 0.778 and 0.445, respectively. A detailed description of the analysis using the noise distribution of the correlation coefficients can be found elsewhere (Kleinschmidt et al. 1995, Baudewig et al. 2003).

As we had to define the first rising point of the BOLD signal peak in the identified activation clusters, we used the widely accepted, upper three-sigma rule (i.e. three times standard deviation) to determine a threshold from the value of the baseline (i.e. first 20 scans). According to our definition, this point can show the beginning of the haemodynamic alteration, and thus the start of putative epileptic activity in the respective brain area. The exact locations of the activated clusters were identified by an overlay of anatomical areas using IBASPM (Fischl et al. 2004).

A color-coded, lag time map was produced to demonstrate the spread (i.e. the order of activation) of the epileptic activity. It shows the rising points of BOLD signal peaks in each activation cluster during examination.

Results
Mouth cloni were observed during the examination from scan 87 (3 m 37.5 s) to scan 185 (7 m 42.5 s). A realigned function of the SPM provided maximum values of 0.2 mm and 0.4° for residual translational and rotational movements, respectively. Seizure involved only mouth clonus, hence we observed no rough movement via the cine loop. It is obvious that surgical interventions had a considerable effect on images (figures 1, 2). The signal void, due to increased susceptibility, is apparent at the site of the brain parenchyma resection and also close to burr holes used for craniotomies (compare figure 1 and figure 2). The rising points of the BOLD signals, corresponding to the activated areas, are color-coded according to time and are shown in figure 2.

Nine activated regions were selected and are presented in figure 3 to demonstrate haemodynamic changes. The regions can be identified on figure 2 by the same activation time appearing on color-coded, lag time maps. The rising point of the BOLD signal is indicated with a vertical line, while the box above the horizontal axis shows the time of the clinical seizure. The relative signal alteration was about 9% in the active brain regions. The haemodynamic change generally lasted for three minutes from the rising point, reaching the maximum and a slightly shorter time to return to the baseline. It can be clearly seen that the lower part of the insular cortex was activated first and its signal alteration preceded the clinical start of the seizure (i.e. mouth clonus) by more than one minute (figures 2, 3). Most of the activations started before clinical seizure-onset. The activation corresponding to the motor area of the right face showed only a 7.5 s-long, pre-ictal phase. However, for instance, the upper part of the insular cortex was activated 90s later than the lower part, and showed
post-ictal activation (figure 3). BOLD signal alterations were also observed in the left caudate nucleus, left thalamus, and various areas of the left cerebral and cerebellar hemisphere (figure 2). MRI signals from contralateral, non-activated regions showed a relatively flat baseline during the whole investigation (figure 3).

After the fMRI investigation, the patient received a new antiepileptic drug regime (a combination of 1 800 mg valproic acid, 225 mg topiramate, and 600 mg ethosuximide), and seizure frequency was considerably reduced (one seizure per month). Thus, no epilepsy surgery or further presurgical evaluation was performed.

Figure 1. High resolution, T₁-weighted, anatomical images of the patient’s brain. Obvious signs of previous operations are visible in the left frontal lobe. The images were used to identify anatomical regions on the low resolution EPI images (figure 2).

Figure 2. Lag time map shows the activation sequence during the seizure under investigation. The rising points of BOLD signals according to the activation are color-coded. The color bar indicates the activation time relative to seizure-onset. Nine regions are labeled with accurate activation times relative to seizure-onset, and the change to their BOLD signal is demonstrated in figure 3. Asterisk shows the motor area of the face.
Discussion

Only a few ictal fMRI studies have been presented in the literature so far (Jackson et al. 1994, Detre et al. 1995, Detre et al. 1996, Kubota et al. 2000, Krings et al. 2000, Federico et al. 2005, Salek-Haddadi et al. 2002, Kobayashi et al. 2006). Despite the advantage of high spatial resolution, ictal fMRI is only applicable to epilepsy patients under special circumstances: frequent seizures, preserved consciousness, no rough ictal movements. To the best of our knowledge, the present study is the first in the literature that visualizes the seizure-onset zone and spread of an epileptic seizure without any detectable epileptogenic lesion. The seizure spread included diverse subcortical and cortical activations (figure 2) that provides new insight into the pathophysiology of seizure spread. Further, an anatomical region showing the initial activation was determined, thus providing guidance for invasive examinations to identify the putative seizure-onset zone. It was especially important because the patient had already undergone two unsuccessful surgeries on the basis of invasive electrophysiological findings. However, it is obvious that more ictal fMRI examinations would be necessary to prove the uniformity of the seizure onset.

Previous ictal fMRI studies have been mostly carried out on patients with known epileptogenic lesions, including Rasmussen’s encephalitis (Jackson et al. 1994), chronic gliosis (Detre et al. 1995, Detre et al. 1996), brain tumors (Kubota et al. 2000, Krings et al. 2000) or gray matter nodular heterotopia (Kobayashi et al. 2006). Moreover, no subcortical activation was observed in these studies except for a study conducted by (Detre et al. 1996). However, no overt seizure was reported during the examination which puts into question the real background of the BOLD signal change (Detre et al. 1996). A recent EEG-fMRI study of a subclinical EEG seizure (Salek-Haddadi et al. 2002) tried to analyze the seizure spread. However the

Figure 3. The BOLD signal alterations of nine activation clusters labeled on figure 2 are displayed. The horizontal axis represents time and the box above the axis indicates the duration of the seizure. The vertical dotted line represents the rising point of the BOLD signal (i.e. the beginning of the hemodynamic change). BOLD signals from contralateral, non-activated regions are also displayed in the last row.
BOLD signal alteration lasted for only several seconds, with a percent change of 2.5%.

It appears that, as in the present study, BOLD signals show a regular peak over minutes in clinically detectable seizures and a relative signal change of 4-9% (Jackson et al. 1994, Kubota et al. 2000, Krings et al. 2000). This means presumably that a much stronger haemodynamic response is present in manifest seizures than those observed during interictal activity or in standard motor/visual/cognitive paradigms. Further, the analysis of ictal data is hampered by the fact that no model haemodynamic response function is known during seizure. This is the reason why an internal reference function was chosen that was similar to those “ictal” BOLD responses published in the literature. The “ictal” BOLD response appears to have a bell-shaped form without an obvious plateau (Jackson et al. 1994, Kubota et al. 2000, Krings et al. 2000), which is observed in the repetitive motor/visual or cognitive paradigms. The application of a low magnetic field for ictal fMRI in the present study was necessary due to the susceptibility artifacts that occurred near to the operated brain areas. The observed BOLD signal change of 9% was well within the range of other studies performed at higher field strength. It also supports the observation that BOLD signal changes in low and high magnetic fields can be comparable, if the measuring parameters and post-processing are optimized (Lundervold et al. 1995, Santosh et al. 1995).


Beside color-coded images in the published papers, only a few BOLD signal changes are displayed originating from 1-3 volumes of interests. In the present study, it was important that several BOLD signal changes should be demonstrated, reflecting the reliability of the post-processing technique applied (figure 3).

We localized: (i) the lower anterior part of the insular cortex as a seizure-onset zone for epileptic activity, (ii) the motor cortex responsible for the mouth clonus and (iii) numerous other areas acting in the epileptic network. Interestingly, activation was found in the left (i.e. ipsilateral to the involved motor cortex) cerebellar hemisphere, but no activation was found in the right (figures 2, 3), though it was expected (Van Paeschen 2004). However, Blumfeld and coworkers have found significant positive correlation in the ipsilateral medial cerebellar cortex in their SPECT study (Blumenfeld et al. 2004).

According to our findings, there is a type of seizure spread that can be measured in seconds to minutes, which is in agreement with other, intracranial studies (Lieb et al. 1991, Kim et al. 2004). Although, there is an antero-posterior and baso-apical tendency in the spread, the activation did not seem to spread radially at the time resolution of 2.5 s, suggesting complex connection between the structures. For example, there is about a one and half minute delay between the activation of the lower and the upper part of the insular cortex, suggesting that either there is a blockage within the insular cortex and the activation comes via other structures, or somehow, the activation spread is slower within the insular cortex. Conversely, a seizure spread shorter than 2.5 s cannot be detected by the present method, which is one of the limitations of our study.

Our results also support the existence of the pre-ictal state that can vary from seconds to minutes (Federico et al. 2005, Baumgartner and Aull-Watschinger 2005). Although, the motor cortex responsible for mouth clonic seizure during the seizure showed only a 7.5 s long pre-ictal phase, the activation in the lower part of the insular cortex occurred 80 seconds before the clinical seizure-onset. In addition, some regions became activated after clinical onset, suggesting a post-ictal activation. Of course, assuming that the BOLD signal changes are usually delayed by several seconds in comparison to neuronal activity changes, the real pre-ictal phase may be several seconds longer than the recorded pre-ictal phase, according to the delay.

**Limitations**

It should be noted that no simultaneous EEG-fMRI was performed, which would have helped in determining of the seizure-onset zone. Thus, there is no direct evidence that all regions with BOLD responses (i.e. haemodynamic change) are involved in the evolution of the seizure. However, the magnitude of the BOLD signal (4-8%) indicates that the haemodynamic response is much stronger than those usually seen in motor, visual, or cognitive paradigms (i.e. 2-4%). The other limitation of the study originates from the analysis: the use of an internal reference curve may exclude other BOLD responses that last for considerably longer or shorter intervals. However, a BOLD response in clinically detectable seizures lasts for minutes according to literature data (Jackson et al. 1994, Kubota et al. 2000, Krings et al. 2000). The other uncertainty is the detection of the precise timing in the activation of a particular area. It is obvious from figure 3 that in several areas there is gradual, monotonous signal increase similar to those found in the pre-ictal state (Federico et al. 2005). So the determination of the rising point of a gradually increasing BOLD signal can be difficult.

**Conclusion**

To our knowledge, this is the first study that describes, simultaneously in time and space, whole-brain haemody-
namic changes during an epileptic seizure. Our observations might contribute to a better understanding of the pathophysiology of seizure spread. Moreover, the identification of the putative seizure-onset zone can be crucial for presurgical evaluation of epilepsy patients. In the case presented, the putative seizure-onset zone could have been validated by successful surgery. However, the frequency and severity of the patient’s seizures have been considerably reduced, and she refused to undergo further invasive investigations.

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