Spatial and Temporal EEG-fMRI Changes During Preictal and Postictal Phases in a Patient With Posttraumatic Epilepsy

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Abstract
The combined use of electroencephalography (EEG) and functional magnetic resonance imaging (EEG-fMRI) in epilepsy allows the noninvasive hemodynamic characterization of epileptic discharge-related neuronal activations. The aim of this study was to investigate pathophysiologic mechanisms underlying epileptic activity by exploring the spatial and temporal distribution of fMRI signal modifications during seizure in a single patient with posttraumatic epilepsy. EEG and fMRI data were acquired during two scanning sessions: a spontaneous critical episode was observed during the first, and interictal events were recorded during the second. The EEG-fMRI data were analyzed using the general linear model (GLM). Blood oxygenation level–dependent (BOLD) localization derived from the preictal and artifact-free postictal phase was concordant with the BOLD localization of the interictal epileptiform discharges identified in the second session, pointing to a left perilesional mesiofrontal area. Of note, BOLD signal modifications were already visible several seconds before seizure onset. In brief, BOLD activations from the preictal, postictal, and interictal epileptiform discharge analysis appear to be concordant with the clinically driven localization hypothesis, whereas a widespread network of activations is detected during the ictal phase in a partial seizure.

Keywords
ictal and postictal EEG-fMRI, interictal EEG-fMRI, BOLD signal, posttraumatic epilepsy, seizure spread

Received July 23, 2013; revised December 13, 2013; accepted January 17, 2014.

Introduction
Since the early 1980s, functional neuroimaging studies with positron emission tomography (PET), single-photon emission computed tomography (SPECT), and electroencephalography–functional magnetic resonance imaging (EEG-fMRI) have been widely applied in the evaluation of the pathophysiology and neurochemical correlates of epilepsy.1 The majority of the studies, using these noninvasive methods, were based on interictal epileptiform discharge (IED) analysis.2-4 Indeed, because of the technical limitations of seizure assessment, the risks for the patient inside the scanner, the unpredictability of ictal events, and constraints of movement, ictal and postictal phases have been rarely investigated, and little is known about the physiologic changes that occur during seizures with a motor semiology.

Fluorine-18 fluorodeoxyglucose PET, the most widely established imaging technique for the evaluation of patients with epilepsy, provides a topographic distribution of cerebral metabolism, but the long duration of steady-state uptake of glucose precludes its use during ictal events. Nonetheless, it is a valuable tool to identify, in the interictal state, the possible epileptic focus as an area of decreased metabolism.5 Conversely, 99Tc-hexamethylpropyleneamine oxime SPECT can be used to study regional cerebral blood flow (CBF) during seizures or in the immediate postictal phase. Using this technique, Duncan et al6 showed a marked increase in CBF values up to 15 minutes after seizure onset in 26 of 28 patients with intractable, complex partial seizures. In their study of 59 secondarily generalized tonic-clonic seizures during combined EEG and SPECT, Varghese et al7 found multiple activating

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Full-color figures are available online at http://eeg.sagepub.com
areas in the hemisphere of seizure onset during the generalized phase, coupled with a decrease in CBF in the contralateral hemisphere. But despite the technique’s usefulness for localizing the region of seizure onset, its main limitation remains the chance of successfully infusing the radioactive tracer in the patient as early as possible after the onset of a seizure.

Magnetic resonance (MR) images acquired during epileptic seizures without EEG recording showed activation in the presumed seizure focus. More recently, the combination of EEG-fMRI has partly overcome the limitations of PET and SPECT and provided new insights into the study of epileptic seizures, offering reliable localizing information about the cerebral areas generating IEDs, bursts of interictal discharges, and even focal epileptic seizures, both electrographic and clinical. Concentrating mainly on preictal and ictal BOLD signal modifications, these studies pointed to alterations in brain functioning, beginning from a few seconds before the start of a full-blown electroclinical seizure up to 20 minutes before seizure onset, clearly indicating activation of the suspected seizure onset zone at the beginning of the event.

To our knowledge, few studies have focused on the ongoing modifications of seizure after its electroclinical termination. For example, one study described only electrographic seizures, and another reported three simple partial seizures in a single patient. Both observed the persistence of BOLD activation in the same area that was active at the beginning of the seizure, with a return to baseline conditions after 30 to 120 seconds. Another more recent study investigating the postictal phase in animal models of generalized epilepsy highlighted diffuse BOLD deactivation during this stage.

Because EEG-fMRI recording during epileptic seizures is associated with technical challenges and safety issues, the majority of studies are performed during the interictal state or in epileptic patients presenting with nonmotor seizure types (ie, fixation-off sensitivity studies). Recording of ictal motor events and temporal distributions of fMRI signal changes during the interictal BOLD activation. To do this, we studied the mechanisms underlying epileptic activity and measured both the spatial and temporal distributions of fMRI signal changes during the seizure. Seizures that result from traumatic brain injuries are often difficult to treat; nonetheless, the correlations between clinical seizure, EEG activity, and BOLD information could open new therapeutic perspectives.

Materials and Methods

Patient

The patient was a 29-year-old man with drug-resistant symptomatic epilepsy, secondary to a road accident, after which he remained comatose for 17 days. During his stay in intensive care, a bone flap was removed from the skull to reduce elevated intracranial pressure, and a prosthesis was subsequently placed. Sequelae from the accident included right-sided blindness and gross asymmetry of the craniofacial area. Three years later, he began experiencing brief, complex partial seizures characterized by subtle twitching of the right arm and leg, followed by clear-cut jerkings, posturing of the arm, right head deviation, and bilateral hand fiddling, all of which the patient reported being unaware of.

MRI showed a large malacic area encompassing the right frontal lobe and the temporopolar region. On EEG, breach activity was evident over the frontotemporal right electrodes; brief runs of theta activity and occasional spikes and sharp waves over the frontal left derivations were detected.

The patient gave written informed consent to participate in the study, in accordance with the Declaration of Helsinki. The study design and protocol were approved by the local ethics committee of the Verona University Department and Hospital. The patient underwent two EEG-fMRI coregistration sessions. During the first session, the patient experienced an episode of right complex partial motor seizure, with spread to the left arm in the scanner bore, which was witnessed by the MR personnel and a neurologist. Motions inside the scanner were restrained with a head-fixation system.

Data Acquisition

EEG Data Acquisition. During MRI scanning, EEG data were acquired using an MR-compatible EEG amplifier (SD MRI 32; Micromed, Treviso, Italy) and a cap with 32 Ag/AgCl electrodes positioned according to the 10-20 system. To remove pulse and movement artifacts during scanning, two of the electrodes were used to record the electrocardiogram and electromyogram. The electromyographic electrode was placed on the right abductor pollicis brevis muscle. The reference was placed anterior to Fz and the ground posterior to Fz. EEG data were acquired at a sampling rate of 1,024 Hz using the SystemPlus software package (Micromed). To avoid saturation, the EEG amplifier was set to a resolution of 22 bits, with a range of ±25.6 mV. An anti-aliasing hardware band-pass filter was applied, with a bandwidth of 0.15 to 269.5 Hz.

fMRI Data Acquisition. Functional images were acquired using a 1.5-T MR scanner (Symphony; Siemens Healthcare, Erlangen, Germany) equipped with echo-planar imaging capability and a standard transmit/receive head coil. fMRI data were acquired with a T2*-weighted echo-planar imaging sequence (36 slices; repetition time, 3,700 ms; echo time, 50 ms; matrix size, 64 × 64; field of view, 256 × 256; voxel size, 3 × 3 × 3 mm; axial slice orientation). At the start of each fMRI acquisition, the scanner gave a trigger signal that was recorded by the EEG system and used as a volume marker. A T1-weighted anatomic scan (192 slices; repetition time, 1,990 ms; echo time, 3 ms; scanning matrix size, 512 × 512; field of view, 256 × 256; slice thickness, 1 mm; sagittal slice orientation) was also acquired.

The patient was positioned supine on a bed inside the scanner bore, with elbows flexed at 120° and hands pronated in a relaxed position; the head was stabilized on both sides with
adjustable padded restraints. During fMRI acquisition, the patient was instructed to keep his eyes closed and remain as still as possible throughout the procedure. A total of 140 volumes for each session were acquired.

Preprocessing

EEG Preprocessing. The EEG artifact induced by the magnetic field gradient was digitally removed offline using an adaptive filter,\textsuperscript{21} while the EEG artifact associated with pulsatile blood flow, ballistocardiogram, was removed using an averaging procedure, both of which were implemented in SystemPlus. The data were processed using an average reference. EEG recordings were band-pass-filtered from 1 to 30 Hz using a finite impulse response filter.

fMRI Preprocessing. Before statistical analysis, the functional data were preprocessed using Brain Voyager software (Brain Innovation, Maastricht, The Netherlands). The MR images were realigned to reduce the effect of head motion (3-dimensional motion correction with sinc interpolation). To correct for the different acquisition times, slice scan time correction was used in an ascending, interleaved scanning order with linear interpolation over time. The data were then preprocessed with linear trend removal (to remove all drifts and with a temporal high-pass filter (3 cycles in time course) to reduce the effect of breathing and physiologic noises. Spatial Gaussian smoothing was used with Gaussian kernel 6 mm full width at half maximum.

Data Analysis

GLM of Preictal, Ictal, and Postictal Phases. The EEG abnormalities recorded inside the scanner did not differ from those usually recorded during either standard or video EEG. They consisted of brief, recurrent runs (<2 seconds) of theta activity that were usually intermingled with sharp waves over the left anterior temporal derivation. Only occasionally was an isolated spike detected over the same leads. To ensure the reliability of BOLD results, only epochs that contained clear-cut sharp waves, or spikes whenever possible, were selected for the preictal analysis. The ictal phase was determined on the basis of the EEG signal (abrupt EEG shift, with appearance of a sharp wave with inversion over T3/F7, followed a few milliseconds later by a definite high-amplitude spike with a maximum over the same region) that was paralleled by the beginning of motor activity as monitored by the neurologist through a mirror system in the scanner bore. Finally, the postictal phase was defined as the clinical resolution as monitored by the neurologist.

During the first fMRI recording, the seizure was classified according to EEG epoch selection in relation to the clinical semiology in blocks of different latencies: 7 single-volume blocks in the preictal phase (nos. 37-43), a block of 17 volumes in the ictal phase (nos. 44-60), a block of 10 volumes in the postictal phase after clinical seizure termination (nos. 61-70), and 3 other single-volume blocks in the postictal phase (nos. 71-73). Each block was used as an independent regressor in the design matrix (ie, each column of the design matrix corresponded to one period of the seizure).\textsuperscript{22}

Included in the design matrix was a baseline regressor of volumes at the beginning of the recording and without abnormal activity (IED) unrelated to the seizure. The hemodynamic response to each block was modeled by linear convolution of a canonical hemodynamic response function (HRF). The dynamic analysis of the epileptic activity represents the fit of a regressor for each epoch considered and of a relative statistical map.

The six motion parameters derived from fMRI preprocessing were used as confounding covariates in the design matrix to remove any residual artifacts.\textsuperscript{23} During EEG-fMRI scanning, the patient exhibited head movements <1 mm in the baseline, preictal and postictal phase. A significant head movement was noted in the ictal phase. Activated voxels were identified with a single-subject GLM approach for the time-series data.\textsuperscript{24} Brain activation was detected by comparing the signal intensity of active images (IED activity) with that of resting images on the basis of the changes in local BOLD signals and on a voxelwise Student’s \(t\) test, with a threshold of \(P < .05\) (uncorrected). A low-threshold correction was used because each active volume was individually compared with the baseline, resulting in low statistical robustness. \(Z\)-score maps representing brain activation were then generated from \(t\) maps. The results were displayed as parametric statistical maps, on which the pixel \(Z\) value is expressed on a colorimetric scale. To assess effects of interest, we contrasted each column of the design matrix to the baseline regressor. Finally, the statistical maps were overlaid on the anatomic MR images.

GLM of Interictal Activity. In the second fMRI recording, the analysis was based on visual identification of the IEDs on scalp EEG. The convolution of these EEG events, represented as stick functions, with the HRF provided the regressor for the GLM analysis of fMRI data.\textsuperscript{25} The six motion parameters derived from fMRI preprocessing were used as confounding covariates in the design matrix, although the patient exhibited head movements <0.6 mm during the second scan. Activated voxels were identified with a single-subject GLM (false discovery rate corrected, \(q < .05\)). \(Z\)-score maps representing brain activation were generated from \(t\) maps. To assess effects of interest, we contrasted the IED activity regressor of the design matrix to the baseline regressor. Finally, the statistical maps were overlaid on the anatomic MR images.

Results

EEG inside the MR scanner showed its typical ictal and interictal activity over the frontotemporal electrodes (F7–T3). Two continuous EEG-fMRI sessions were performed.

BOLD Signal Changes During the Preictal, Ictal, and Postictal Phases

During the first fMRI scanning session, a spontaneous critical episode, stereotypical for the patient, and lasting about one
minute, was recorded (Figure 1). The Figure shows the time evolution from 15 seconds before clinical seizure onset, the motor ictal phase (63 seconds), and 48 seconds of the artifact-free postictal phase. Clinical resolution of the seizure was paralleled by the appearance on the EEG of delta rhythmic sequences over the left frontal regions (late significant pattern). BOLD localization across the preictal phase (volumes 40-43) and in the late, artifact-free postictal phase (volumes 72-73) was concordant with the localization identified from the interictal activity, which pointed to left perilesional cortex (Figure 2). During the ictal event (volumes 44-60), gross BOLD activation spread to the whole of the left prefrontal area (supplementary motor area), reaching the lesional margin on the contralateral hemisphere, with an adjunctive BOLD increase over the right temporal lobe. In this stage, BOLD deactivation appeared over the left sensory motor area. This pattern reversed 63 seconds later, with deactivation over the previously active zones (left prefrontal, right frontal lesional margin) and an increased signal over the left sensory motor area. The inversion was temporally related to resolution of the clinical seizure, with a gradual fading off of the residual diffused BOLD activity over a time span of roughly 37 seconds and persistence of the initial left prefrontal BOLD signal. Although the time series of the translation and rotation parameters estimated during motion correction were modeled as effects of no interest in the GLM analysis, residual motion-related effects in this ictal phase could have been present.

**BOLD Signal Changes During Interictal Activity**

During the second fMRI session, only interictal events were recorded and used for the second GLM analysis (Figure 2). EEG showed isolated large-voltage paroxysms on the left frontotemporal electrodes with phase reversal in T3/F7. These elements did not tend to spread contralaterally. Significant BOLD changes were localized over the perilesional and frontal areas bilaterally, FDR corrected ($q < .05$).

**Discussion**

Concomitant EEG-fMRI seizure recordings permit a better estimation of the epileptogenic zone than interictal activity alone and provide a deeper understanding of ongoing modifications before and during a seizure. Because of the hazards associated with recording motor ictal events inside the scanner bore, reports of this kind of seizure are less common than for other seizure types; even rarer are studies of possible cerebral lesions generating motor ictal events. Because of the unpredictability of ictal events and safety issues, patients are generally investigated during interictal activity or frequent short ictal events unassociated with the presence of movement, as, for example, in subclinical electrographic seizures without clinical symptoms.

To our knowledge, these data are among the first to describe the epileptic networks underlying not only the beginning and
spread of a partial motor seizure but also its resolution. Identifying the epileptic networks that activate during seizures instead of those activated during the interictal period can further our understanding of epilepsy and open innovative treatment options for such patients.

In this patient with posttraumatic epilepsy, the EEG changes acquired inside the magnet were analyzed in a volume-by-volume sequence to compare the volume of interest with the volumes recognized as rest period and acquired some minutes before the ictal phase, resulting in a full time course of the crisis of the fMRI sequence. In this way, a phase model based on the observation of the early ictal phase, the clinical ictal phase, and the late ictal phase could provide a more physiologically informed model than those that represent seizures as one-by-one continuous blocks or a series of uniform-length blocks. Here, the preictal phase was decomposed into single-volume blocks to identify the temporal evolution of activations. Although this results in weaker statistics, the activation remains stable in these first volumes. Despite a lower temporal resolution, the postictal phase was averaged in multiple blocks to obtain more robust statistics. The ictal phase, characterized by some motion artifacts, although sufficiently controlled, was analyzed in a single block.

Here we observed focal BOLD activation concordant with the presumed seizure onset zone. It appeared roughly 26 seconds before the full-blown clinical seizure, during which the initial activation spread to the whole frontal area, the residual contralateral homologous cortex, and the right temporal lobe, with deactivation over the left sensory motor cortex. These activations could be seen as being congruous with seizure semiology (arm posturing, head version, fiddling), although the time scale of the data does not allow us to disentangle the specific activations related to each motion. We observed an inversion of the previously described pattern after roughly one minute, with the most active areas now depicted as BOLD deactivations. Overall, this complex of activations and deactivations gradually resolved within a couple of minutes, revealing the persistence of a BOLD-positive signal over the same zone that generated the seizure onset.

This picture points to widespread metabolic changes, in a complex partial seizure, that begin well before seizure onset and persist long after its electroclinical termination. In patients with unsuccessful surgical resection, these networks could be communication pathways across brain regions that should be severed to disrupt the pathologic flow of information. Furthermore, because posttraumatic brains develop peculiar vicarious and vicious connections, investigations need to be tailored to the specific patient. Of interest in our patient, the widespread pattern of activation and deactivation we observed provides clues to peculiar, possibly abnormal connections: during the ictal phase, the prefrontal activation was coupled with temporal activation prevailing on the right side and a sensory-motor deactivation ipsilateral to the original lesion. This pattern was preserved, with an inversion of active and inactive areas, also during the postictal phase, as proof of the soundness of such connections. The functional correlation of the contralateral temporal lobe, with the epileptogenic frontal focus, probably reflects a kindling activity of the residual left temporal lobe that is partially malacic. Interpretation of the left sensory-motor area deactivation is subtler and not unequivocal: the seizure semiology is compatible with a premotor area pattern with an almost immediate spread to the temporal lobe. Visualization of contemporary activation of the prefrontal areas and deactivation of the motor cortex proper might simply reflect the physiologic function of the premotor area, the activation of which targets subsequent motor area activation.

**Figure 2.** Interictal activity recorded during the second fMRI scanning session. EEG acquired during interictal activity (selected volumes are visualized: 95, 96, 123, and 124) and EEG-fMRI results from the GLM analysis. Corrected P value (false discovery rate [FDR], q < .05) is visualized, and the color bar shows the Z-score scale.
Conclusions

Our findings suggest that during a partial motor seizure, the changes in BOLD signal are visible several seconds before seizure onset and persist up to a few minutes after resolution of clinical seizure. BOLD activations from the preictal, postictal, and IED analysis were concordant with the clinically driven localization hypothesis, whereas a widespread network of activations was detected during the ictal phase. The identification of “epileptogenic” networks opens potential therapeutic perspectives, indicating communication pathways across brain regions that should be severed to interrupt pathologic information flow.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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