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Simultaneous EEG and functional MRI of epileptic activity: a case report

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Abstract

Objectives: Attempts to localize the source of epileptic activity by linking electroencephalographic (EEG) abnormalities to blood oxygenation level-dependent (BOLD) magnetic resonance imaging (MRI) signal alterations are hampered mainly by EEG distortions during MRI, subject motion, and unknown hemodynamic response characteristics.

Methods: Using T2*-weighted echo-planar imaging at 2.0 T (2 s temporal resolution, $2 \times 2 \times 4$ mm^3 spatial resolution), this work demonstrates strategies to alleviate some of these problems while studying a patient who had ideopathic generalized epilepsy with poly-spike and slow-wave complexes.

Results: Continuous EEG recordings during dynamic MRI (500 ms scanning, 1500 ms delay) and post-examination derivation of an EEG reference function for MRI analysis revealed positive BOLD MRI responses with temporal characteristics similar to those obtained for functional challenges.

Conclusions: The ability to map focal epileptic activity and/or associated cognitive processing provides new potential for both epilepsy research and clinical patient management.

Keywords: Magnetic resonance imaging; Electroencephalographic; Epilepsy; Functional brain activation

1. Introduction

During recent years, functional magnetic resonance imaging (fMRI) of the human brain has been developed as a non-invasive tool for the detection of focal changes of neuronal activity. Beyond the sensitivity of blood oxygenation level-dependent (BOLD) MRI sequences to functional challenges, it seems possible to map abnormal brain activation elicited by pathologic processes. In particular, fMRI approaches have the potential to detect regions of epilepsy-induced activity changes identified by simultaneous electroencephalographic (EEG) recordings. A non-invasive localization of epileptic zones at high spatial resolution promises to contribute to our understanding of the pathophysiology of seizures and the successful outcome of surgical treatments in pharmaco-resistant epilepsy.

Previous work has identified a variety of problems when performing EEG recordings in a high-field magnet and during scanning (for example, for early fMRI studies of epileptic seizures without EEG monitoring see Jackson et al., 1994; Detre et al., 1996; for EEG-triggered image acquisitions of interictal spikes see Seeck et al., 1998; Symms et al., 1999; Patel et al., 1999; Krakow et al., 1999). Unfortunately, triggering to an abnormal EEG pattern does not fully reveal the physiologic BOLD MRI responses due to a delayed image acquisition and the lack of pre-activity baseline images. Moreover, triggered images are prone to intensity changes of successive acquisitions which become increasingly saturated unless the experimental parameters ensure pure spin-density contrast without any T1 weighting. On the other hand, simultaneous EEG and MRI recordings are affected by induced electric currents in the EEG electrodes and cables which originate from the application of magnetic field gradients during imaging. More recent modifications promise to improve distorted EEG signals with the use of sophisticated post-acquisition algorithms but still require extensive computational efforts (Goldman et al., 2000; Hoffmann et al., 2000; Allen and Josephs, 2000; Sijbers et al., 2000).

Here we present an easy-to-use approach for combined EEG/fMRI recordings and an application to a patient with a symptomatic, generalized epilepsy syndrome. In particular, we have developed a strategy for continuous EEG recording during ongoing MRI and addressed the control of subject motion, the evolution of the BOLD MRI signal in response

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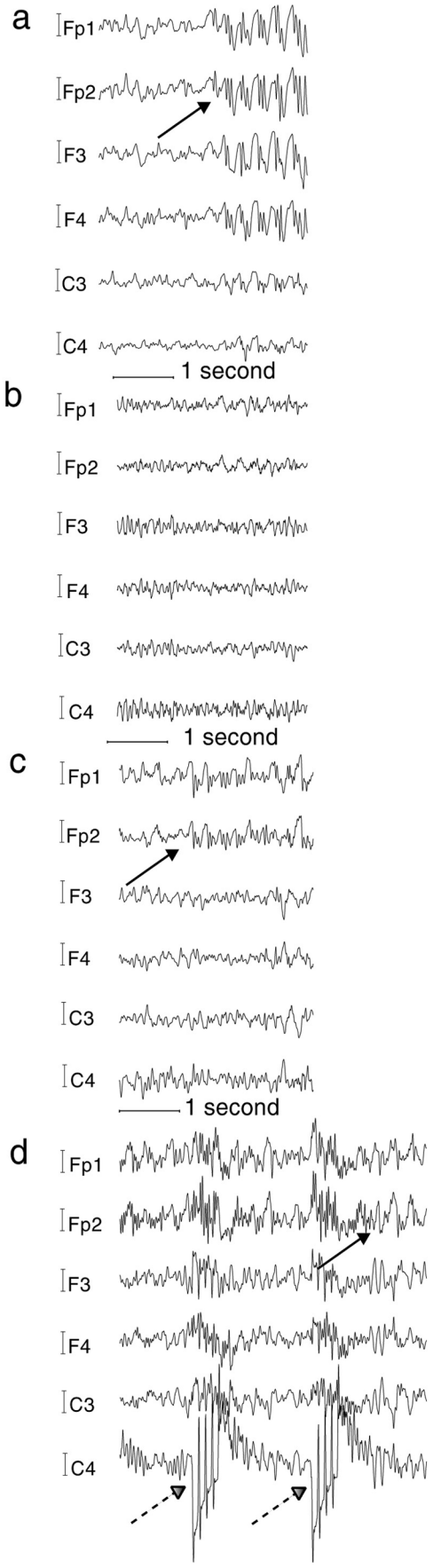

to EEG abnormalities, and the interpretation of derived maps of epilepsy-related activity.

2. Materials and methods

The patient was a 30-year-old male suffering from symptomatic, generalized epilepsy syndrome with atypical absence seizures and generalized tonic-clonic seizures since the age of 6 years after a head injury. When we examined the patient, he had up to 10 atypical absence seizures and a maximum of one generalized tonic-clonic seizure per day. Infantile history was marked by slow developmental maturation and mental retardation. Despite several attempts to control the seizures, including the use of high-dose carbamazepine and valproat acid, the patient did not become seizure-free. At the time of this study, the patient was on only one medication, lamotrigine. Interictal EEG showed a diffusely slow background, a bi-frontotemporal theta-delta-slowing and generalized interictal poly-spike and slow-wave complexes. A video EEG was not done. All MRI scans were normal.

MRI studies were conducted at 2.0 T (Siemens Vision, Erlangen, Germany) using the standard imaging headcoil. Dynamic 'functional' deoxyhemoglobin-sensitive MRI recordings were based on a blipped gradient-echo echo-planar imaging sequence (TR = 2000 ms, mean TE = 53 ms, flip angle 70°, frequency-selective fat suppression) at 2×2 mm^2 resolution and 4 mm section thickness. A multi-slice acquisition of 4 sections resulted in a total measuring time of 500 ms leaving a 1500 ms delay before image repetition. During this latter period, the continuous EEG recording remained sufficiently undisturbed to allow an unambiguous retrospective evaluation. The examination comprised a total of 4 scans with 6 min of measuring time each. To improve the volume coverage, two complementary scans were arranged in such a way as to cover a contiguous volume of 32 mm thickness by 8 sections. The locations studied in this patient covered the upper frontal cortex as well as the fronto-dorsal and occipital cortex along the AC-PC line in respective oblique transverse-to-coronal orientations.

EEG recordings employed a commercially available MR-compatible EEG system and 10 Ag/AgCl scalp electrodes with shielded leads (EMR, Schwarzer GmbH, München,

Fig. 1. EEG of the patient using a common reference ('Goldman'). Solid arrows indicate poly-spike and slow-wave complexes. (a) Interictal EEG activity with poly-spike and slow-wave complexes recorded outside the magnet. (b) Normal EEG pattern recorded inside the magnet but without scanning. (c) Interictal EEG activity with poly-spike and slow-wave complexes inside the magnet but without scanning. (d) Interictal EEG activity with poly-spike and slow-wave complexes during MRI (500 ms image acquisitions followed by 1500 ms pauses). During scanning the EEG is distorted by induced currents from the imaging gradients (broken arrows). The repetition of the artifacts provides a 2 s horizontal time scale. Vertical scales correspond to 70 μV in (a) and 100 μV in (b–d).

Germany). The system's main component is a non-ferrous headbox which could be placed inside the magnet bore about 50 cm from the patient's head. The function of the headbox is to digitize the recorded EEG and to encode it into an optic signal which then is transmitted by a fiber optic cable to a personal computer outside the magnet room. The EEG was displayed using a common reference of several electrodes which were placed on the scalp according to the 10–20 standard positions (FP2, FP1, C4, C3, F3, F4, P3, P4) using conventional adhesive electrode gel (Nihon Kohden, Japan). Skin-electrode impedance was under 5 kΩ.

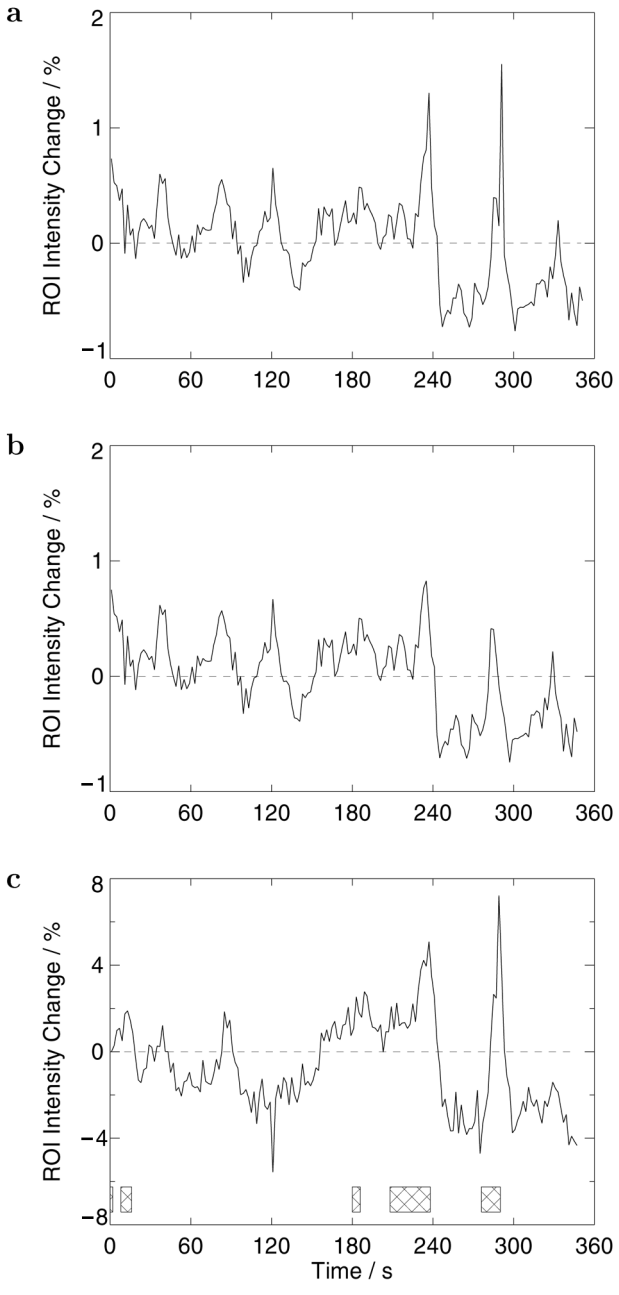

Fig. 2. BOLD MRI signal intensity time courses of the patient (selected 6 min period). (a) Global time course of all brain pixels including images affected by gross subject motions. (b) Same as (a) but after removal of two motion-affected images identified by visual inspection of a cine display (time points 238 and 292 s, respectively). (c) Focal time course of brain pixels identified as 'activated' in response to interictal EEG abnormalities with use of a reference function (boxes) shifted by 6 s relative to the onset of abnormal EEG patterns. The data correspond to the 'activation' map shown in Fig. 3d.

The rating of the EEG was performed off-line by an experienced epileptologist (H.J.B.) who identified normal episodes as well as segments of epileptic activity. The assignment of these events to specific image numbers was facilitated by the regular occurrence of EEG artifacts caused by gradient switching. Gross motion artifacts were identified by visual inspection of the dynamic image series using a cine display mode, as well as by extracting global signal intensity time courses of all brain pixels. In all scans, these independent methods revealed the same motion-affected images which were subsequently removed from the image series. The EEG evaluation yielded a reference function consisting of 0 for normal periods and 1 during seizures. It was employed for a pixelwise correlation with the corresponding BOLD MRI signal intensity time course. Time shifts of 0, 2, 4 and 6 s with respect to the onset of epileptic activity were tested to account for hemodynamic latencies. The resulting maps of correlation coefficients were thresholded and color-coded using an automated statistical treatment following methods previously described for functional mapping (Kleinschmidt et al., 1995).

3. Results

Fig. 1 shows interictal EEG recordings of the patient outside and inside the magnet. In comparison with periods of normal and abnormal EEG activity either outside the magnet (Fig. 1a) or in the absence of scanning (Fig. 1b,c), combined EEG/fMRI (Fig. 1d) allowed a similar identification of epileptic activity, i.e. poly-spike and slow-wave complexes, during the 1500 ms scanning pauses. The distortion of the EEG traces was largely confined to the actual switching of magnetic field gradients during the respective 500 ms imaging periods. Although a closer inspection revealed a pronounced baseline drift after MRI scanning, the quality of the EEG during these periods was sufficient for a proper evaluation of a reference function which identified time frames of epileptic activity for subsequent MRI analysis.

The temporal evolution of the hemodynamically driven BOLD MRI signal in response to abnormal electric activity is demonstrated in Fig. 2 which depicts signal intensity time courses at various stages of data analysis. As a first step, a global time course of all brain pixels and raw images (Fig. 2a) served to confirm the identification of motion-affected images independently obtained by visual inspection of a cine display. Removal of two images in this example (Fig. 2b) reduced the peak percentage intensity changes typically generated by movements across image contrast borders. Finally, Fig. 2c exhibits a focal time course of 'activated'

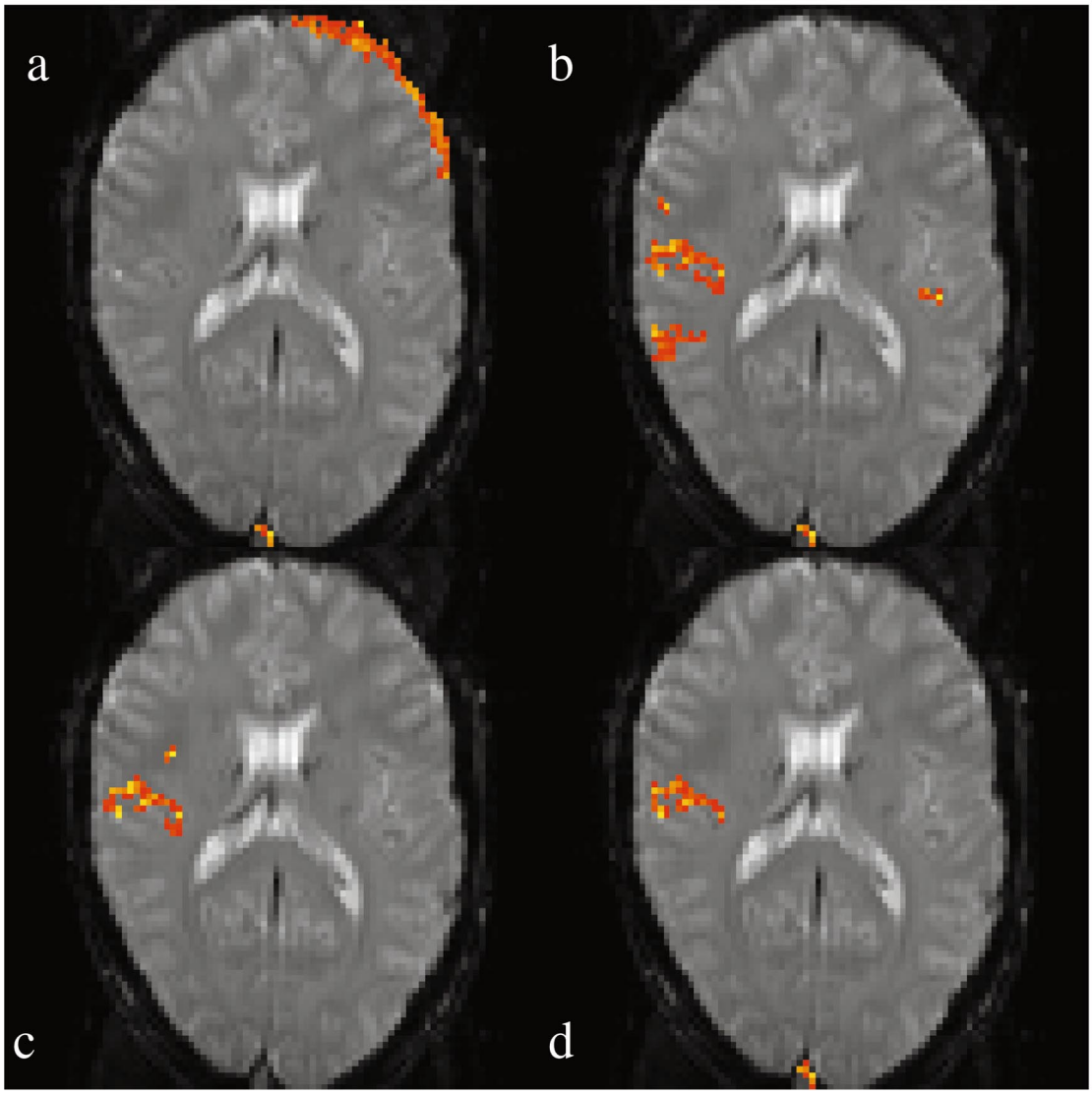

Fig. 3. BOLD MRI maps of the patient. The maps reveal focal areas of high correlation between BOLD MRI responses and interictal EEG activity with polyspike and slow-wave complexes. The respective EEG reference function was shifted by (a) 0 s, (b) 2 s, (c) 4 s, and (d) 6 s with respect to the onset of epileptic activity to account for hemodynamic latencies. Longer delay times reduce motion artifacts at contrast borders as, for example, visible in left frontal areas in (a).

brain pixels which represent areas of reduced deoxyhemoglobin concentration in temporal correlation with EEG abnormalities. It is noteworthy that pertinent activations were only observed in the lower volume along the AC-PC orientation, whereas no correlated BOLD MRI responses were detected in the upper frontal cortex.

The reference function used in Fig. 2c (shaded boxes) was shifted by 6 s relative to the onset of EEG spikes to account for the flow-mediated response characteristics of the BOLD MRI signal. The strategy also helps to eliminate artifactual 'activations' due to subject motions. The underlying rationale is the assumption that – if present – correlated motions occur as immediate movements during the first few seconds after the onset of spike and slow-wave complexes. In contrast, BOLD MRI responses exhibit a hemodynamic latency and rise time that typically causes a time-to-maximum effect for short cortical events of about 4–6 s (Fransson et al., 1998). The validity of this principle is well demonstrated by a comparison of the correlation coefficient maps shown in Fig. 3. Whereas the absence of any delay yields motion-induced 'pseudo-activation' at contrast borders along the left frontal cortex (Fig. 3a), the use of a 2 s (Fig. 3b), 4 s (Fig. 3c), or 6 s delay (Fig. 3d) avoids such artifacts and focuses the EEG-related activation to a zone in the right-hemispheric insular area.

4. Discussion

In comparison with triggering, continuous EEG recordings with partially overlapping MRI periods provides a more constant, less disruptive auditory environment of the

subject. In our experience this strategy significantly improves the comfort and cooperativity of the patient whose only task is to passively undergo a regular MRI acquisition scheme. Technically, a further reduction of the gradient artifact in the EEG is still warranted. Possible solutions may include an on-line subtraction of the reproducible gradient-induced distortions and a removal of the post-MRI baseline drift. Further improvements may be obtained by using twisted EEG cables which should result in less electric noise and a quicker recovery of induced currents (Goldman et al., 2000).

The motion problem has been dealt with by consecutive steps involving (1) the identification of motion-corrupted images by visual inspection of raw image series, (2) a quantitative analysis of whole brain BOLD MRI signal intensity time courses, and (3) the elimination of residual motion effects by shifting the EEG-derived reference function by about 4–6 s relative to the onset of abnormal activity. This strategy resulted in robust BOLD MRI responses to epileptic activity that resemble the same characteristics as are commonly observed for functional challenges. It may therefore be concluded that the hemodynamic alterations observed during interictal epileptiform activity are based on similar mechanisms as in sensory stimulation or cognitive processing. Accordingly, the increased MRI signal reflects a net decrease of the absolute concentration of deoxyhemoglobin.

An unresolved problem is the degree to which the EEG-correlated activations in the insular area correspond to the patient's primary epileptic zone. Although similar arguments also hold true for the generation of the underlying EEG abnormalities, it remains an open question whether pertinent maps indicate true foci of epileptic activity or related processing of induced activity or both? In fact, because epileptic activity tends to rapidly propagate to other cortical regions, it cannot be excluded that BOLD MRI responses occur not only in the primary epileptic zone but also in cortical projections of such regions as well as in other brain systems 'processing' various aspects of the actual event. Nevertheless, the present developments of combined EEG/fMRI recordings open the way to study these questions in much greater detail and in a large number of patients.

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