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RAPID COMMUNICATION

Event-Related fMRI with Simultaneous and Continuous EEG: Description of the Method and Initial Case Report

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We report on the initial imaging findings with a new technique for the simultaneous and continuous acquisition of functional MRI data and EEG recording. Thirty-seven stereotyped interictal epileptiform discharges (spikes) were identified on EEG recorded continuously during the fMRI acquisition on a patient with epilepsy. Localization of the BOLD activation associated with the EEG events was consistent with previous findings and EEG source modeling. The time course of activation was comparable with the physiological hemodynamic response function (HRF). The new methodology could lead to novel and important applications in many areas of neuroscience.

INTRODUCTION

Electroencephalography (EEG) is the method of choice for the monitoring of certain aspects of the brain's normal activity, such as sleep stages and levels of consciousness, and for the assessment of a number of neurological conditions (Emerson and Pedley, 2000). EEG is characterized by an excellent temporal resolution but a limited spatial resolution.

Functional magnetic resonance imaging (fMRI) has proven to be a powerful tool for the localization of brain activity on a millimeter scale (Turner *et al.*, 1998). In fMRI, knowledge of the brain's state throughout data acquisition is essential as the method relies on contrasts between images acquired in different brain states. In the standard so-called block design fMRI experiments this is accomplished by imposing a succession of stimulation and rest periods of fixed duration. More recently, the advent of event-related fMRI has allowed the analysis of events with variable or random presentation sequences (Josephs *et al.*, 1997).

In epilepsy, the localization of the generators of interictal epileptiform discharges (IEDs, spike or sharp wave) is important for clinical and basic science purposes. Although increasingly sophisticated electrophysiological measurement methods have been developed, e.g., EEG with up to 256 channels, the lack of an independent means of measuring the abnormal brain activity has limited the validation of source localization methods. The recent advent of safe and high-quality EEG recording inside the MRI scanner has given us the tools necessary to compare blood-oxygenation level dependent (BOLD) image contrast and EEG-derived localization information (Ives *et al.*, 1993; Lemieux *et al.*, 1997; Allen *et al.*, 1998). EEG-triggered fMRI, where the fMRI data is acquired at a fixed interval following events of interest (e.g., spikes) and "rest" periods, has already demonstrated the usefulness of EEG/fMRI in the investigation of epilepsy (Warach *et al.*, 1996; Krakow *et al.*, 1999). However, it suffers from two main limitations, both linked to the obliteration of the EEG during the image acquisition. First, there are constraints on the scanning rate and the duration of each scan: the minimum time gap between successive image acquisitions must be of the order of 15 s (for 1.5T scanners) in order to avoid signal variations due to T1 signal decay and the maximum duration of each image acquisition must be less than the expected duration of the BOLD response in order to ensure proper separation of the responses from events which may occur during image acquisition, and therefore be undetected. These limits on the scan acquisition parameters can also be expressed in terms of the spontaneous event ("spiking") rate, which highlights the implications for patient selection. The event rate must be low enough

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such that the mean separation between events is at least as large as the minimum scanning interval (~15 s) to avoid the effects of undetected events (due to EEG obliteration) but also high enough to allow acquisition of sufficient image data in a 45-min period.[1] Second, the spike-triggered approach relies on assumptions about the BOLD response peak time and duration; in our experimental design we assumed that the BOLD response to spikes peaks around 5 s and has returned to baseline 15 s postevent for all spikes and in all subjects. Given the difficulty of measuring the temporal characteristics of the hemodynamic response function (HRF) associated with spikes using the triggered approach, there is uncertainty about the optimality of this model. Given these limitations, we have found BOLD activations associated with interictal spikes in approximately 50% of the patients studied (Krakow *et al.*, 1999).

We have recently described a new system capable of recording good quality EEG throughout the fMRI acquisition through removal of a well-characterized image acquisition artifact (see Methods section for a brief description) (Allen *et al.*, 2000). This new method should enable the identification of all EEG events and the use of a more sophisticated event-related fMRI approach by allowing the acquisition of images at random time-lags in relation to the EEG events of interest (Josephs *et al.*, 1997). As discussed by Aguirre *et al.* (1998), precise knowledge of the HRF in individual subjects and experimental conditions is an important factor in the optimal acquisition and analysis of event-related fMRI. Therefore, our initial aim was to illustrate how shape of the HRF associated with epileptiform discharges can be characterized.

We report on our initial imaging findings from the first experiment with continuous EEG/fMRI and event-related analysis of epileptic events. Specifically, we demonstrate the potential ability of the method to provide spatiotemporal information on the brain activity underlying the generation of spontaneous EEG events.

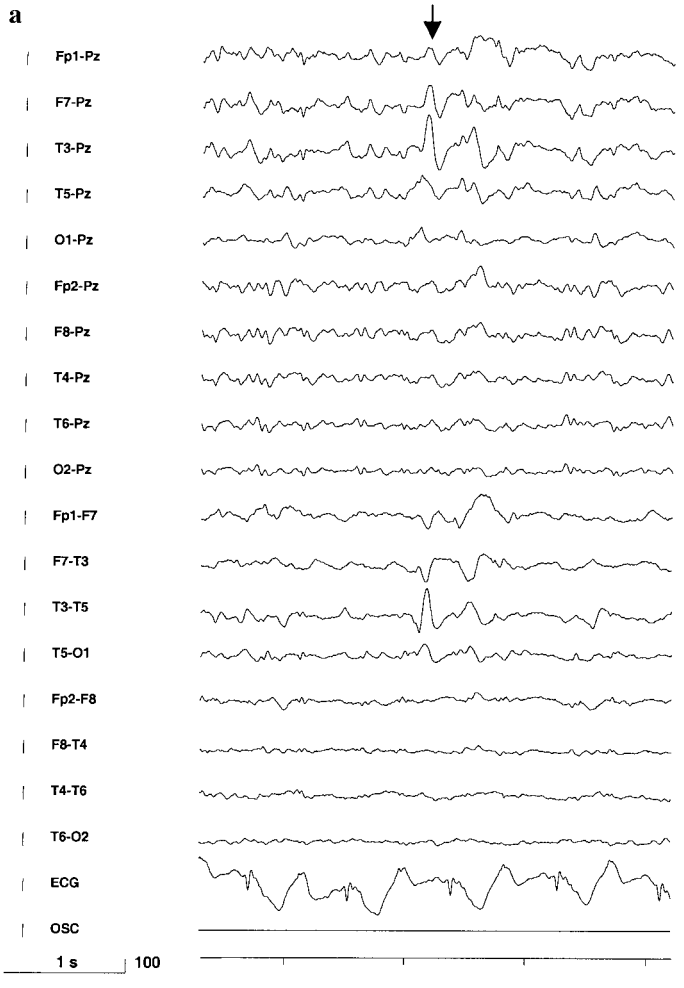

FIG. 1. EEG recorded inside the MRI scanner, showing a typical event of interest. The 10 upper traces show a referential montage, followed by bitemporal chains, the ECG (used for pulse artifact suppression; distorted due to the presence of the strong magnetic field), and the slice acquisition pulses (used for image acquisition artifact suppression and EEG/fMRI synchronization). Same filter settings in both cases. (a) Recorded before the start of the fMRI acquisition, with pulse artifact suppression; (b) Recorded during the fMRI acquisition, with pulse and image acquisition artifact suppression. Both show a typical epileptiform discharges at F7/T3 (indicated by the arrow; peak-to-peak amplitude ~200 μV). There is an asymmetry of the background activity, with irregular slow activity on the left.

METHODS

Patient and Data

The study was performed on a 50-year-old patient with chronic encephalitis of the left hemisphere and intractable partial and secondary generalised seizures. The study was approved by the ethics committee of the National Hospital for Neurology and Neurosurgery and the patient gave informed consent. The standard 20-channel scalp EEG showed frequent spikes with a maximum over the left temporal region. Previous intraoperative electrocorticography had revealed spiking cortex in the pars opercularis of the left superior temporal gyrus and the adjacent perisylvian region. This patient was studied because previous spike-triggered fMRI studies had revealed consistent BOLD activations, in agreement with previous electroclinical findings [(Krakow *et al.*, 1999) patient 1] and 30% of the individual spikes resulted in a significant activation (Krakow *et al.*, 2001).

Continuous EEG/fMRI

Ten channels of common reference EEG and two ECG channels were recorded inside the MR scanner using a nonferrous EEG head-box and a digital EEG

[1] Patient discomfort and movement can become significant factors after 45–60 min.

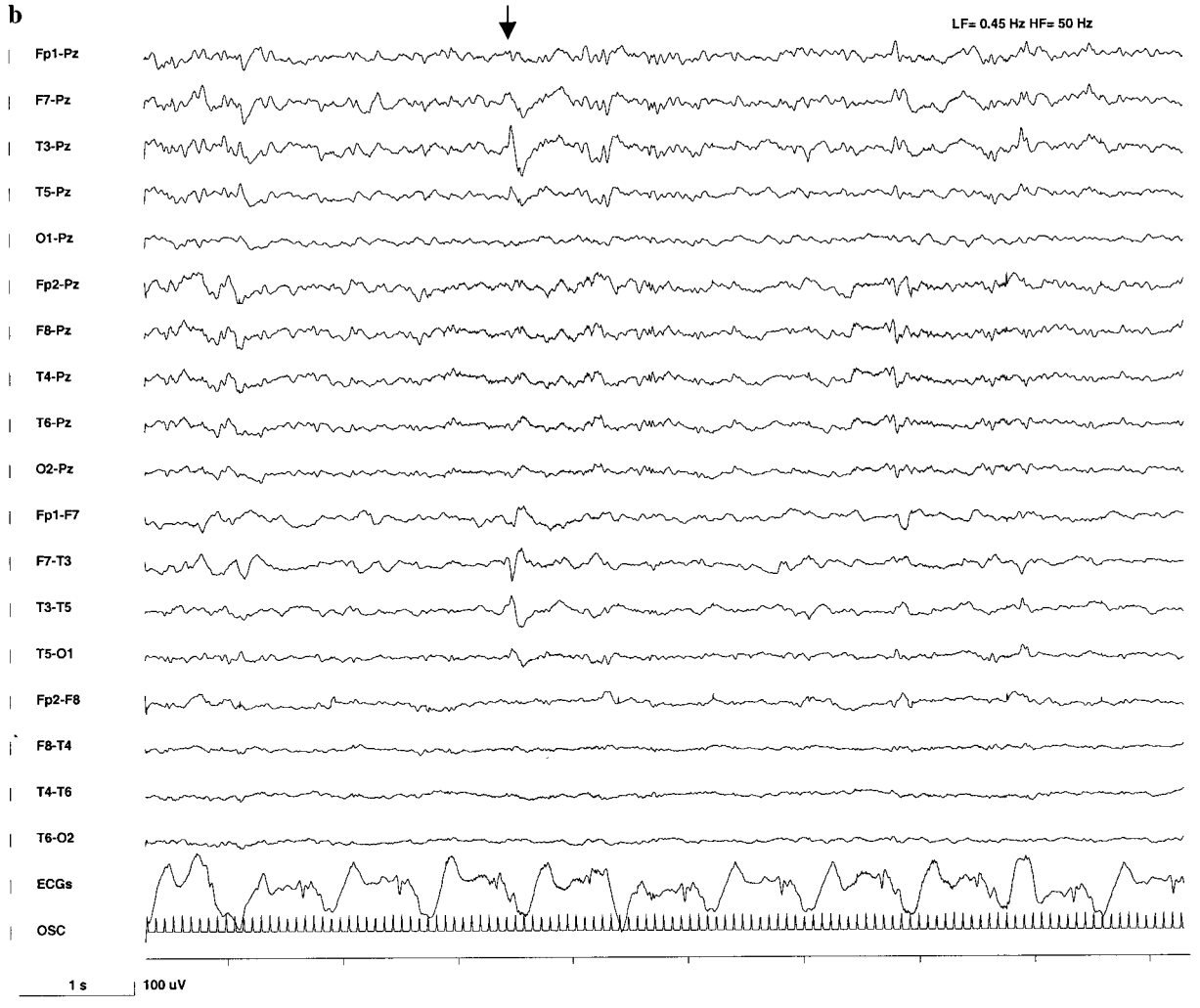

FIG. 1—*Continued*

recording system (sampling rate: 5000 Hz), developed in-house. Gold EEG electrodes fitted with 10 kOhm, 1 Watt current-limiting safety resistors were applied to Fp1, F7, T3, T5, O1 and the contralateral homologous channels; reference: Pz (Lemieux *et al.*, 1997, 1998; Krakow *et al.*, 2000). On-line pulse and imaging artefact removal was used to monitor the EEG during the experiment (Allen *et al.*, 1998, 2000). The imaging artefact removal method has been described in detail previously (Allen *et al.*, 2000). In summary, the new EEG acquisition system uses careful design of filtering and gain sections of the EEG amplifier to avoid saturation during imaging artifact, digitization at 5000 Hz of EEG data and a scanner generated slice-timing pulse. For each channel, online subtraction of a running time-averaged waveform (synchronized with the slice-timing pulse) is followed by adaptive noise cancellation and a running time-averaged EEG signal synchronized to the ECG is subtracted to remove the pulse induced artifact (Allen *et al.*, 1998). Validation was based on comparative spectral analysis and accuracy of the identification of separately recorded spike-wave complexes (median amplitude: 74 μV) added to EEGs recorded in five subjects (Allen *et al.*, 2000).

The experiment was conducted on a 2T MRI scanner (Siemens Magnetom Vision; Siemens, Erlangen, Germany). Then 1200 volumes each consisting of 20 axial slices (1.8 mm thick, 1.2 mm gap; TE: 40 ms; TR/slice: 76 ms; FOV: 192 mm; 64 × 64 image matrix) were acquired continuously over a period of 30 min, 24 s.

EEG Source Analysis

In a separate session, approximately 30 min of 64-channel EEG was recorded (reference: AFZ) in a routine setting outside the MR scanner using the Neuroscan QuickCap (Neuroscan, Sterling, VA). Twenty 2-s epochs each containing a typical spike were extracted from the recording and averaged. Source analysis was performed for the averaged waveform using the CURRY 3.0 software (Neuroscan). A realistically shaped boundary-element conduction model was de-

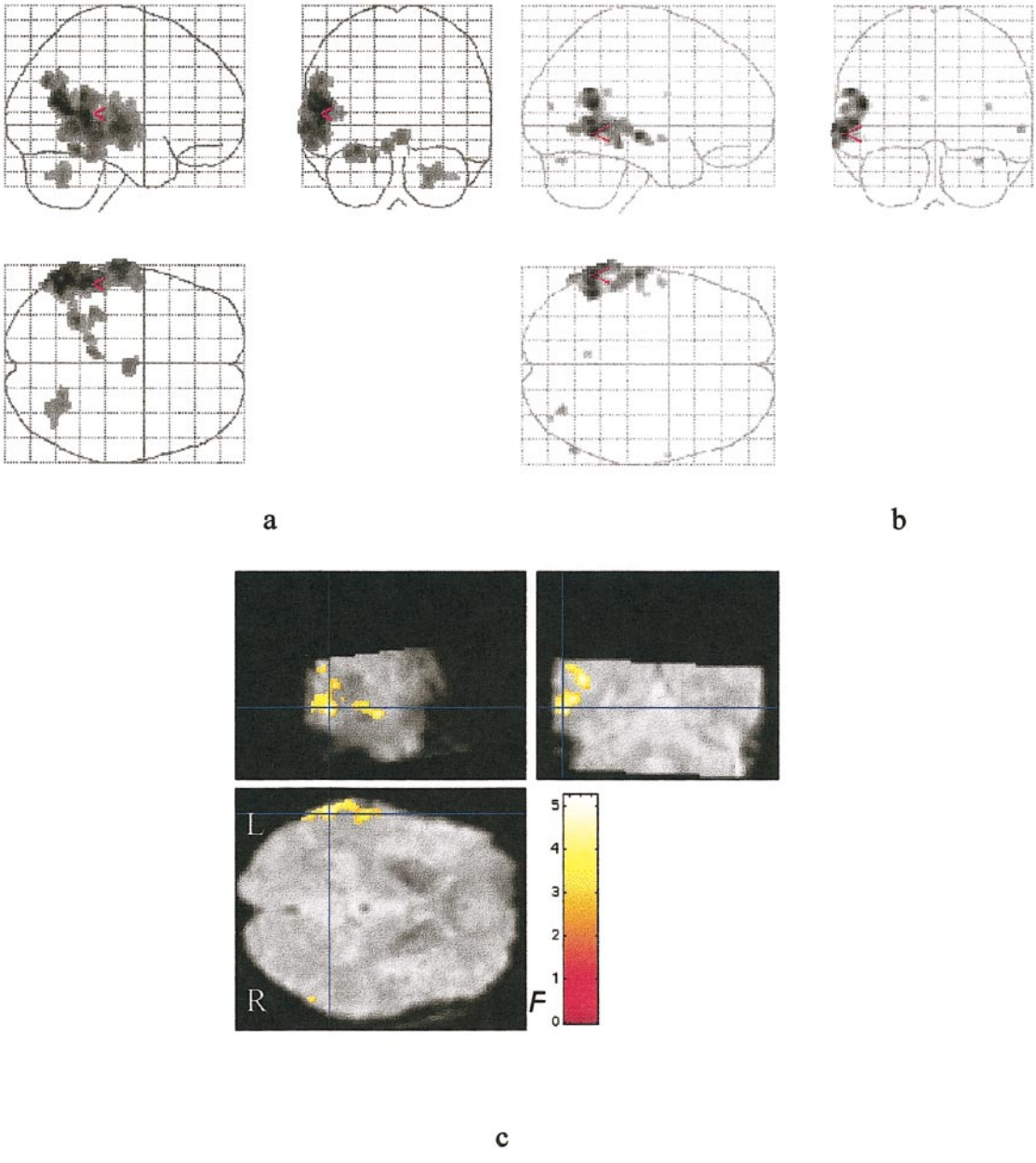

FIG. 2. (a) SPM{*t*} obtained in previous spike-triggered experiment represented on a graphical representation of the spatially normalized brain (so-called "glass brain"). (b) SPM{*F*} of the spike-related events in the continuous EEG-fMRI experiment. Height threshold: $P < 0.001$ (uncorrected). (c) Highlighted cluster projected onto orthogonal slices of the mean EPI, showing activation localization in the left temporal region.

rived from T1-weigthed volume scans by automatic segmentation (Wagner *et al.*, 1995). The T1-weighted volume data had the following characteristics, devised to obtain high-resolution and full coverage of the head: fast IR-prepared SPGR (TI/TR/TE: 450/17.4/4.2 ms, flip angle: 20°), 280 × 210 mm field of view, 256 × 192 matrix, 124 1.8 mm slices. A signal-to-noise ratio normalization was performed, followed by a principal components analysis (PCA) to obtain dominating spatio-temporal field patterns (Fuchs *et al.*, 1999). This allowed us to determine the probable number of generators needed to model the data with two PCA loading values significantly greater than unity (expressed as a factor of the signal-to-noise ratio) and a third component with a loading value near unity. A model with three moving dipoles was thus used.

The BOLD echoplanar images were registered to the T1 volume using SPM99 for visualization purposes (Ashburner *et al.*, 1997).

EEG and fMRI Analysis

The EEG recording was examined retrospectively to identify spike and sharp wave complexes and record

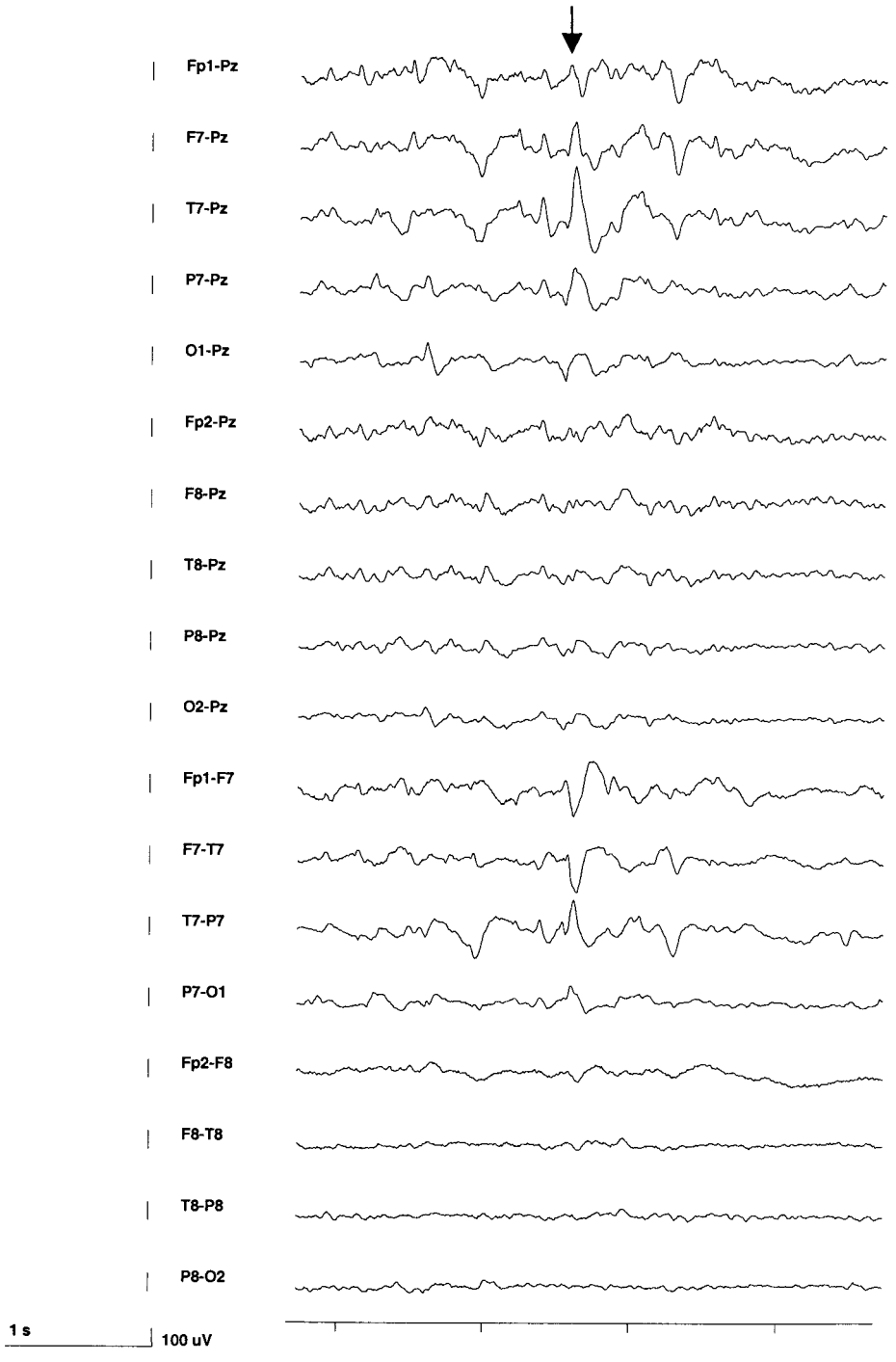

FIG. 3. Segment of 64-channel EEG recorded outside the MR scanner, displayed using a montage similar to the one used in Fig. 1 for intra-MRI EEG to facilitate comparison. The segment contains a typical spike used for source reconstruction, indicated by the arrow. Note that electrode labelling differs between two EEG systems, with the following equivalents: T7 (64-channel) = T3; P7 (64-channel) = T5.

the corresponding fMRI slice number (from the slice pulse channel; range: 1 to 24,000[2]).

The fMRI data were realigned, spatially normalized, and smoothed (Gaussian kernel; full width at half-maximum: 6 mm) using SPM99 (Friston, 1995; Ashburner and Friston, 1999). The fMRI event slice number was then used as input for an event-related analysis of the time course of BOLD activation using a windowed Fourier expansion (8 sines, 8 cosines, plus constant term; window width = 64 s) and the resulting SPM{F} was thresholded at $P < 0.001$ (uncorrected) (Josephs *et al.*, 1997).

[2] 24,000 = 1200 volumes * 20 slices per volume

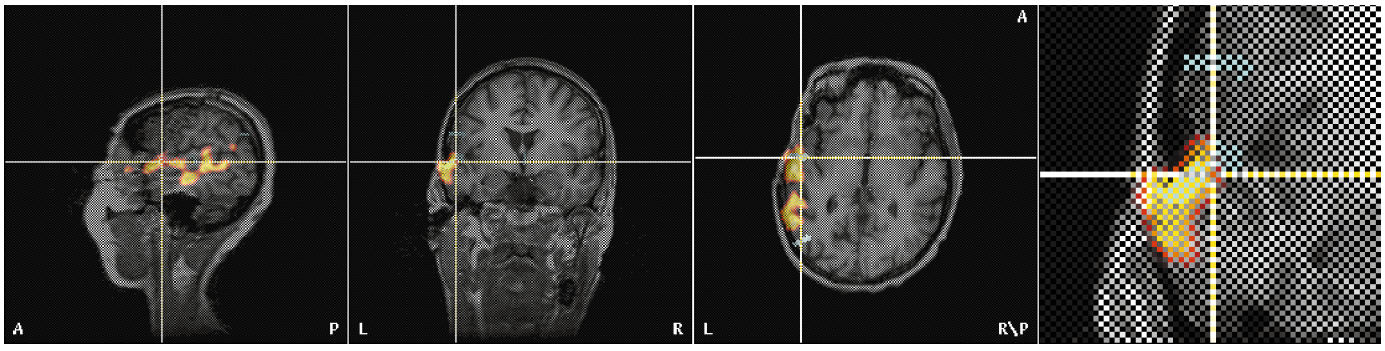

FIG. 4. Model dipoles (light blue) at peak spike amplitude superimposed on T1-weighted anatomical volume scan (grey level) and coregistered BOLD activation ("hot metal" colours). The proportion of variance of the potential distribution explained by this model was 90%.

RESULTS

In the EEG, background activity was observed that was lesser on the left with irregular theta-delta activity (3–6 Hz) and predominant alpha activity (8 Hz) over the right. There were frequent interictal epileptiform discharges maximal over the left temporal region. Of these, high amplitude stereotyped sharp waves (>200 μV) with phase reversal over T3 (left midtemporal) were the most prominent feature. Thirty-seven of these were identified by an expert observer in the entire recording (mean interspike interval was 51 s), labeled, and used for the fMRI analysis. Figure 1 illustrates an EEG segment recorded inside the scanner during fMRI and shows a typical spike and slow wave complex. The thresholded SPM{*F*} revealed an activation located in the left temporal region similar to the activation previously obtained using the spike-triggered method, as shown in Fig. 2. The method used to obtain the spike-triggered result of Fig. 2a was described previously (Krakow *et al.*, 2001); in summary, 43 activation images (i.e., acquired following a spike) were compared to 46 rest images (acquired following a quiet period) using a *t* statistic on a voxel-by-voxel basis; the corresponding *Z* score for the maximum activation was 7.1. For the continuous EEG-fMRI experiment, Fig. 2b, the *F* ratio of the highlighted (maximum) voxel is 5.23 ($P_{\text{corrected}} = 0.001$).

The 64-channel EEG recording showed a similar pattern of abnormal activity (see Fig. 3). Source analysis using the moving dipoles revealed two dominating generators, one located within and the other near the activation area, as shown in Fig. 4.

The time course of the activation at the maximum activation voxel (highlighted in Fig. 2b) peaks at approximately 8–9 s postspike (Fig. 5).

DISCUSSION AND CONCLUSIONS

We have demonstrated for the first time an event-related fMRI analysis of EEG events from continuous and simultaneous EEG/fMRI acquisition to obtain spatiotemporal patterns of activation.

The BOLD activation derived from these data was concordant with previous scalp and intracranial EEG findings, as well as results from previous fMRI studies obtained using spike-triggered EEG/fMRI. This result tends to reinforce our confidence in the method's capacity to provide good quality EEG and our own ability to correctly identify and label IEDs. Regarding the difference in the appearance of the activations derived from the two techniques, these can result from a combination of the following methodological and biological factors: First, variability of the EEG events between the experiments, which is always a possible limitation of repeated studies. We noted that there were no significant changes in the patient's EEG pattern throughout the period spanning the 64-channel EEG, spike-triggered fMRI, and continuous EEG-fMRI ex-

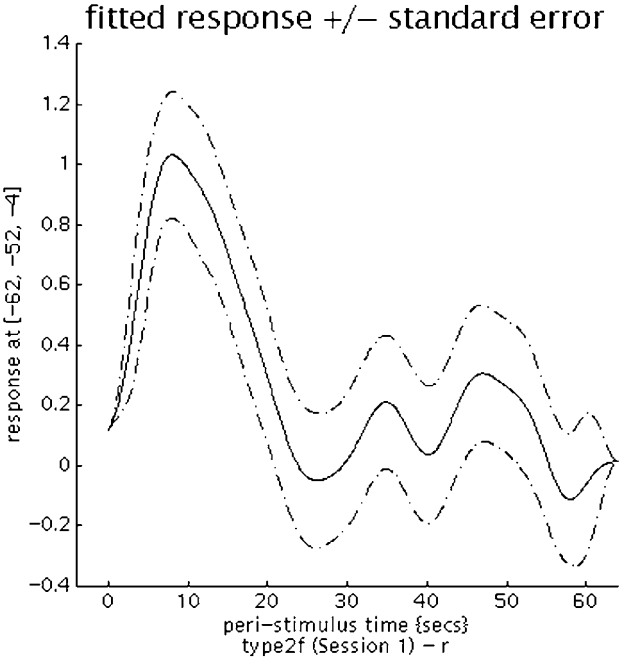

FIG. 5. Time-course of BOLD response at highlighted voxel (red arrow) in Fig. 2b. The response is expressed as a percentage of the mean whole brain signal.

periments, as illustrated in Figs. 1 and 3. Second, and perhaps most importantly, the nature of the questions answered by the analysis is different between the two methods. In the spike-triggered approach, the question is: "which voxels show a significant signal increase between 'rest' and 'activation' images?" and is expressed as a *t* test. This is in contrast to the event-related approach demonstrated here to measure the shape of the HRF, for which our questions are: "which voxels show a pattern of signal change that is consistent across events and that explains a sufficient proportion of the signal variance?," expressed as a *F* ratio, and "what is this pattern?" Therefore, the extent and significance of the derived activations for the two types of data are not directly comparable. Although an event-related approach can also be used to address the first type of question, this would require the assumption of a specific form for the HRF (Aguirre *et al.,* 1998). As noted previously this study is part of our current efforts of characterizing the shape of the HRF for epileptiform discharges in order to derive an optimal experimental strategy.

Our results have also shown good agreement between source localization and the BOLD results. We previously reported that source modelling results from individual events were consistent with the result presented here, with some interevent localization variability (Lemieux *et al.,* 2000). We chose to average a larger number of events in this study for comparison with the fMRI results, which are derived from grouped events. With regards to the number of dipoles used for this study, we did not attempt to derive a separate model based on the smallest number of dipoles that explains a predetermined proportion of the field data. Given the relatively small contribution of the third (in terms of PCA loading) dipole, we expect the results for a two-dipole model to be very similar to those presented here. The problem of source model selection and the comparison of source model-based localization with BOLD and structural imaging are the topic of a more substantial ongoing study. We note that there is currently no model for the relationship between BOLD changes associated with spikes, and the underlying electrical generators. Furthermore, as mentioned previously, the validity of generator models for epileptic spikes remains a debated issue. Therefore, we do not necessarily expect perfect concordance between the BOLD and EEG findings, depending on the location and spread of the underlying activity. Our approach may provide information useful to address this problem. The time-course of the BOLD activation was consistent with the characteristic shape of the expected physiological HRF (Aguirre *et al.,* 1998). In particular, the observed response is consistent with a peak at 5–9 s latency followed by an under-shoot. This knowledge, combined with the fact that the maximum amount of data is acquired in a given total experiment time, should lead to improved sensitivity and efficiency of EEG/fMRI experiments (Dale *et al.,* 1999).

Good quality EEG throughout the fMRI experiment, by recording all events, enables us for the first time to exploit the full power of both modalities. Therefore, the applicability of EEG/fMRI will also be enhanced by expanding the spectrum and frequency of events that can be acquired and analyzed.

The availability of continuous EEG and fMRI data will allow the study of the relationship between the BOLD response on the one hand and the morphology (amplitude, duration, etc.) and relative timing of EEG events on the other (event interaction effects (Friston *et al.,* 1998)). Also, it may be possible to study propagation effects by exploiting the ability of event-related fMRI to provide a superior temporal resolution to scanning repetition time (Josephs *et al.,* 1997).

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