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EEG-triggered functional MRI of interictal epileptiform activity in patients with partial seizures

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Summary

EEG-triggered functional MRI (fMRI) offers the potential to localize the generators of scalp EEG events, such as interictal epileptiform discharges, using a biological measurement as opposed to relying solely on modelling techniques. Although recent studies have demonstrated these possibilities in a small number of patients, wider application has been limited by concerns about patient safety, severe problems due to pulse-related artefact obscuring the EEG trace, and lack of reproducibility data. We have systematically studied and resolved the issues of patient safety and pulse artefact and now report the application of the technique in 24 experiments in 10 consecutive patients with localization-related epilepsy and frequent interictal epileptiform discharges (spikes or spike wave). At least two experiments were performed for each patient. In each experiment, 10- or 20-slice snapshot gradient-echo planar images were acquired ~3.5 s after a single typical epileptiform discharge (activation image) and in the absence of discharges (control image). Between 21 and 50 epileptiform discharges were sampled in each experiment. The significance of functional activation was tested using the *t* test at 95% confidence on a pixel-by-pixel basis. Six of the 10 patients showed reproducible focal changes of the blood oxygen level-dependent (BOLD) signal, which occurred in close spatial relationship to the maximum of the epileptiform discharges in the concurrent EEG. No reproducible focal BOLD signal changes were observed in the remaining four patients. In conclusion, EEG-triggered fMRI is now a sufficiently developed technique to be more widely used in clinical studies, demonstrating that it can reproducibly localize the brain areas involved in the generation of spikes and spike wave in epilepsy patients with frequent interictal discharges.

Keywords: functional MRI; EEG; epilepsy; interictal epileptiform discharges; epilepsy surgery

Abbreviations: BOLD = blood oxygen level-dependent; EPI = echo planar imaging; fMRI = functional MRI; SPECT = single photon emission computed tomography

Introduction

Interictal epileptiform discharges recorded by scalp EEG are the mainstay for classifying types of epilepsy, and their localization has an important role in the presurgical evaluation of drug-resistant patients (Gilliam *et al*., 1997). Knowledge of the underlying generators of these EEG events, however, is still limited. Due to their restricted spatial sampling and the 'inverse problem' (working back from distant scalp potentials to hypothesize about the likely sites of their generators), neither EEG nor magnetoencephalography can directly identify these generators (Ebersole, 1998). On the other hand, the low temporal resolution of PET and single photon emission computed tomography (SPECT) prevents the investigation of brain activation linked to brief epileptiform discharges.

In contrast, case reports of patients with localization-related epilepsy have shown recently that functional MRI (fMRI) may allow the detection of local changes in blood oxygenation associated with subclinical epileptic seizures (Jackson *et al*., 1994) and interictal epileptiform discharges (Warach *et al*., 1996; Seeck *et al*., 1998; Symms *et al*., 1998). The acquisition of MRI linked to brief subclinical events requires the recording of the EEG during the MR scanning

procedure. It has been shown that the EEG can be recorded inside an MR scanner with sufficient quality to detect high-amplitude discharges and to trigger fMRI acquisitions after these events (Ives *et al*., 1993; Huang-Hellinger *et al*., 1995). However, safety issues and EEG artefacts due to magnetic fields in the MR scanner which may obscure the EEG trace have limited the method so far and precluded its wider application (Ives *et al*., 1993; Huang-Hellinger *et al*., 1995). We have established a protocol to ensure patient safety during EEG recording (Lemieux *et al*., 1997) and developed a method for the on-line subtraction of pulse artefact (Allen *et al*., 1999), which has been regarded as the most significant EEG artefact inside the MR scanner (Ives *et al*., 1993; Huang-Hellinger *et al*., 1995; Allen *et al*., 1999).

We used this new recording technique to monitor the EEG of patients with partial seizures undergoing MRI and triggered ultra-fast snapshot multislice echo planar imaging (EPI) blood oxygen level-dependent (BOLD) fMRI acquisitions after single epileptiform discharges (spike or spike wave) were identified in the on-line EEG. The site of the fMRI activation was compared with the focus of previous interictal scalp EEG recordings and, if available, invasive and ictal EEG recordings. All patients were studied at least twice on different occasions in order to investigate the reproducibility of the fMRI results.

Methods

Patients

Ten consecutive patients (seven male, three female, median age 28.5 years, range 22–48 years) with a confirmed diagnosis of medically intractable localization-related epilepsy were studied. The clinical data of the patients are summarized in Table 1. The study was approved by the ethics committee of the National Hospital for Neurology and Neurosurgery and all patients gave informed consent. The patients showed frequent stereotyped focal epileptiform discharges in previous routine 20-channel scalp EEG recordings with an average of at least one epileptiform discharge per minute. Patients with less frequent, generalized or multifocal interictal discharges were excluded from the study. Five patients underwent presurgical evaluation prior to the study, including ictal video-EEG recording ($n = 5$) and electrocorticography ($n = 1$).

EEG recording

The EEG was recorded in the MR scanner using the following procedure. Standard Ag/AgCl disk electrodes were applied on the scalp using collodion; these had 15 kΩ current-limiting carbon resistors fitted adjacent to each electrode (Lemieux *et al*., 1997). The electrodes were connected to a non-ferrous headbox (developed in-house) placed at the entrance to the bore of the magnet. The headbox was connected to a Neurolink Patient Module (Physiometrix, N.Billerica, Mass., USA), which digitizes and transmits the EEG signal out of the scanner room via a fibre optic cable to the Neurolink Monitor Module, which reconstructs the analogue EEG signals. These were then recorded using a digital EEG recording system (sample rate 200 Hz, bandwidth 0.12–50 Hz).

For each experiment, 12 electrodes were applied to scalp positions FP1/FP2, F7/F8, T3/T4, T5/T6, O1/O2, Fz and Pz according to the 10/20 system. In addition, two precordial ECG channels were recorded to facilitate pulse artefact subtraction (75 kΩ current-limiting resistors were fitted to each ECG electrode) (Allen *et al*., 1999). The EEG data were digitally remontaged and displayed to show bitemporal chains. In eight patients, on-line pulse artefact subtraction software was used to aid visual detection of the epileptiform discharges (Fig. 1). This method subtracts an averaged pulse artefact waveform calculated for each electrode during the previous 10 s. Technical details have been described elsewhere (Allen *et al*., 1999).

fMRI acquisition and processing

fMRI was performed on a 1.5 Tesla Horizon EchoSpeed MRI scanner (General Electric, Milwaukee, Wis., USA) using snapshot gradient-echo EPI [TE (echo time) = 40 ms, 24 cm field of view]. In the first studies of patients 1 and 2, 10 contiguous 5 mm slices were acquired with a 128 × 128 matrix. Patient 1 was studied in axial and coronal orientations. Patient 3 (with a proposed epileptogenic zone in the mesial temporal lobe) was studied in coronal orientation to better visualize mesial temporal lobe structures and with a reduced matrix size (64 × 64) to reduce the susceptibility artefacts due to the presence of air in nearby sinuses. For all other experiments, axial acquisition with 20 contiguous 5 mm slices with a 64 × 64 matrix was performed (Table 2). The acquisition time was 3.5 s for 10 slices and 4.5 s for 20 slices. For all studies based on a 64 × 64 matrix, additional high-resolution multi-shot EPI images [matrix 256 × 256, 16 shots, repetition time = 3 s, all other parameters as fMRI data] were acquired. These images have geometric distortions similar to the fMRI data and were used as anatomical references for the fMRI data.

Images were acquired after ‘activation’ and ‘control’ states, defined by visual inspection of the on-line EEG. The activation state was defined as a single stereotyped epileptiform discharge (spike or spike wave). As the peak blood oxygenation level change detected by fMRI occurs ~4–7 s after the onset of brain activity (Hennig *et al*., 1995; Rosen *et al*., 1998), a delay of ~3.5 s between observation of the discharge and image acquisition was applied. Acquisitions started <3 or >4 s after the EEG event and acquisitions following equivocal activation or control states were excluded from the statistical analysis ($<7\%$ of acquisitions in all studies). Control images were acquired after periods of at least 10 s of background EEG activity without epileptiform activity. Image acquisition was performed non-periodically with activation and control images interleaved, depending on

Table 1 *Clinical, EEG and MRI data for the patients*

Patient	Age, duration (years), sex	Aetiology; seizure type	Interictal EEG	Ictal EEG (onset)	Structural MRI
1	48, 7 F	Chronic encephalitis, left hemisphere; SPS, CPS, SGTCS	SW, left mid-temporal	Widespread over left hemisphere	Mild outer left hemicerebral atrophy
2	22, 22 M	Cortical dysgenesis; CPS, SGTCS	Sp, right temporal and parasagittal	–	Nodular heterotopia of right central region and medial parietal
3	26, 10 F	Hippocampal sclerosis; CPS, SGTCS	SW, left anterior-temporal	Left sphenoidal electrode (preoperative)	Left temporal lobectomy. Sclerosis of residual hippocampus
4	29, 14 M	Low-grade astrocytoma (surgical treatment 11 years ago and radiotherapy 3 years ago); SPS, CPS	SW, left frontal	Widespread over left hemisphere	Focal scarring of left middle frontal gyrus
5	33, 19 M	Infantile febrile seizure/ hippocampal sclerosis; CPS	Sp, ShW, left mid-temporal	No lateralization	Left-sided hippocampal sclerosis
6	29, 18 F	Dysplastic neuroepithelial tumour; CPS	Sp, right anterior, mid-temporal	No lateralization	Lesion of right inferior temporal gyrus
7	25, 18 M	Head trauma; SPC, CPS	SW left temporo-central	–	Ischaemic brain damage of left post. MCA area
8	43, 27 M	Cryptogenetic; CPS	Sp, ShW right mid-temporal	–	Without finding
9	24, 24 M	Cortical dysgenesis; CPS, SGTCS	Sp, left anterior, mid-temporal	–	Bilateral malformation of cortical development
10	28, 22 M	Cryptogenic; CPS, SGTCS	SW, bilateral occipital, left > right	–	Without finding

CPS = complex partial seizure; SGTCS = secondary generalized tonic clonic seizure; Sp = spike; SPS = simple partial seizure; ShW = sharp wave; SW = spike and slow wave.

the sequence of the EEG events. An interval of at least 15 s was established between successive acquisitions to ensure the same T_1 weighting for each acquisition.

Because of hardware restrictions, the number of time-points was limited to 98 per study. This led to a maximum acquisition of 49 activation and 49 control states, as equal numbers of activation and control states were used for the statistical analysis. The typical total scanning time was 60–90 min depending on the frequency of EEG events.

The images were registered (Bullmore *et al*., 1996) and then the Stimulate software (Strupp, 1996) was used to perform a two-tailed *t* test at the 95% confidence level between the activation and control images on a pixel-by-pixel basis to determine significantly activated regions. In-plane clustering of three pixels was used to remove small and scattered activated regions that were unlikely to represent genuine brain activity. In addition, regions of activation that were not evident in adjacent locations on at least two contiguous slices were rejected.

Results

In all 24 experiments the EEG quality was sufficient to detect activation and control periods reliably throughout the study, although in 19 experiments (eight of the patients) pulse artefact subtraction was necessary to achieve good EEG quality (Fig. 1). Epileptiform discharges recorded inside the scanner had a localization, amplitude and configuration similar to those in previous recordings under routine conditions. Image acquisition for the activation states was started on average 3.53 s (SD 0.24) after the epileptiform discharges were observed in the EEG. No clinical or electroencephalographic manifestations of ictal events occurred during the scanning procedure in any experiment. None of the patients reported discomfort or other adverse events due to the EEG recording procedure during the experiments.

In six out of 10 patients, a significant focal activation was seen in the fMRI data. Significant activations were defined as being contiguous over at least two slices and reproducible in repeated studies. Reproducibility of activations was defined as activated voxels that were located in the same cerebral lobe and at least partly overlapped between studies. As repeated studies were acquired and registered independently without spatial normalization, co-registration of these studies could not be performed and the interstudy anatomical correlation between activated areas was assessed quantitatively by visual inspection. In all six patients, these reproducibility criteria were met only by a single activated area, which showed co-localization with the EEG spike/spike wave focus in all cases (defined by concordant lateralization of the activated cortical area and the maximum of the

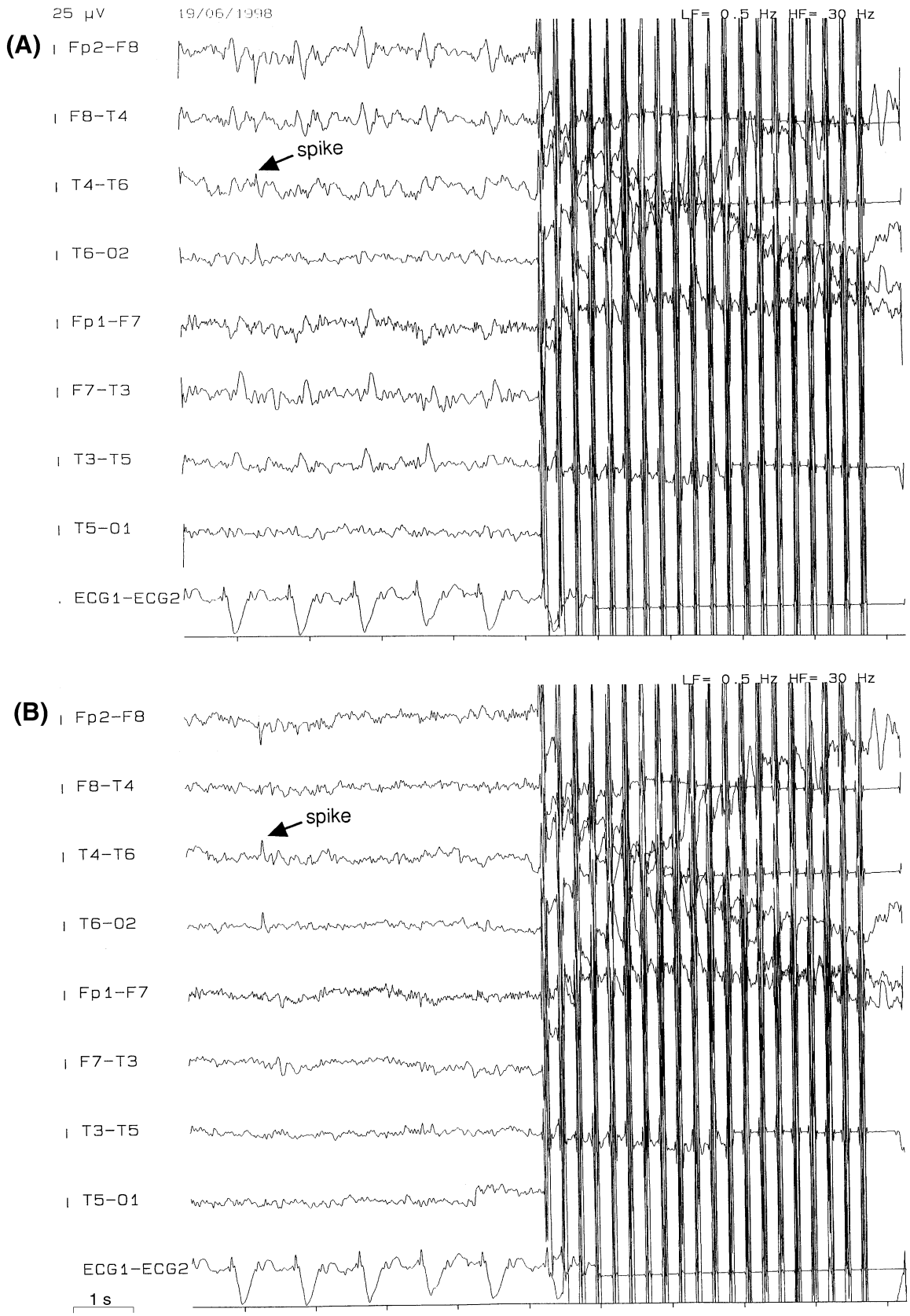

Fig. 1 Patient 2. EEG recording inside the MR scanner. The same EEG sequence with a low-amplitude spike over the right hemisphere without (**A**) and with (**B**) pulse artefact subtraction. The spike is clearly detectable only with applied pulse artefact subtraction. 3.5 s after the spike, the image acquisition artefact of a 20 slice EPI acquisition occurs.

Table 2 *Results of EEG recordings inside the MR scanner and fMRI activations*

Patient	Study no.	Orientation	No. of slices	Matrix size	No. of spikes	EEG results*	fMRI results Localization	No. of slices
1	1.1	Axial	10	128 × 128	49	SW; T3	Left superior	3
	1.2	Axial	10	128 × 128	45	184.2 (SD 33.1) μV	temporal lobe	3
	1.3	Coronal	10	128 × 128	45			5
	1.4	Axial	20	64 × 64	46			5
2	2.1	Axial	10	128 × 128	47	Sp; T4, T6	Right parietal	6
	2.2	Axial	10	128 × 128	42	84.2 (SD 15.4) μV	lobe, within	2
	2.3	Axial	20	64 × 64	47		lesion	3
3	3.1	Coronal	10	64 × 64	47	SW; T3	Left mesial	2
	3.2	Coronal	10	64 × 64	46	168.1 (SD 26.3) μV	temporal lobe	3
4	4.1	Axial	20	64 × 64	37	SW; F7, T3	Left posterior	5
	4.2	Axial	20	64 × 64	21	187.8 (SD 26.3) μV	frontal lobe and	–
	4.3	Axial	20	64 × 64	40		superior temporal lobe, adjacent to postsurgical damage	3
5	5.1	Axial	20	64 × 64	39	Sp, ShW; T3	No activation	–
	5.2	Axial	20	64 × 64	45	68.7 (SD 14.2) μV		–
6	6.1	Axial	20	64 × 64	34	Sp; T4, T6	Right perisylvian region,	3
	6.2	Axial	20	64 × 64	48	118.3 (SD 13.8) μV	adjacent to lesion	3
7	7.1	Axial	20	64 × 64	26	SW; T5, O1	No activation	–
	7.2	Axial	20	64 × 64	47	92.9 (SD 6.9) μV		–
8	8.1	Axial	20	64 × 64	49	S, Shw; T4	No activation	–
	8.2	Axial	20	64 × 64	49	48.2 (SD 4.4) μV		–
9	9.1	Axial	20	64 × 64	49	Sp; T3	Left temporal	4
	9.2	Axial	20	64 × 64	46	67.8 (SD 16.9) μV	(first experiment only)	–
10	10.1	Axial	20	64 × 64	49	SW; O1, T5, O2	Left occipital lobe	4
	10.2	Axial	20	64 × 64	48	127.2 (SD 15.4) μV		8

*EEG recording inside the scanner: morphology of epileptiform discharge; electrode(s) showing maximum amplitude (Sp = spike; SW = spike and slow wave; ShW = sharp wave); mean amplitude of all epileptiform discharges used to trigger fMRI acquisitions.

epileptiform discharge). Details of the localization and extent of the significant activations for all studies are given in Table 2. Figures 2–4 present typical examples of activation maps of individual fMRI studies, overlaid on high-resolution EPI images. Areas of significant signal increase during the activation state are overlaid in red, representing a percentage signal increase of 1–2%. Figure 3 gives an example of the through-slice contiguity of activations, and Fig. 4 presents corresponding slices of repeated studies to provide a typical example of the reproducibility of activations.

In some experiments several small areas appeared activated in addition to the presumed epileptic focus. These areas could be distinguished from the activation concordant to the EEG focus by (i) showing no through-slice contiguity and (ii) not being reproducible between studies. These signal changes were typically localized at CSF/brain tissue boundaries, mainly at the brainstem, the interhemispheric fissure, the lateral ventricles and the frontal and occipital poles of the brain.

The scalp EEG electrodes caused small signal dropouts in the echo planar images, affecting mainly the scalp and skull signal. Occasionally, the artefact also intruded into parts of the cortex, but not to an extent that would compromise the areas showing fMRI activation.

In three patients (patients 5, 7 and 8), no significant activation was found in either of the repeated experiments. In these patients the amplitude of the interictal epileptiform activity was lower [mean amplitude 69.9 μV (SD 18.3)] compared with the patients who were studied successfully [mean amplitude 144.9 μV (SD 37.9)]. In addition, in two of these patients (patients 5 and 8) the morphology of the epileptiform activity was more variable than in the other patients, and not only spikes but also sharp waves were used to trigger fMRI acquisitions. Patient 7, however, had stereotyped spike-wave discharges with a mean amplitude of 92.9 μV (SD 6.9) throughout the experiment, which were nevertheless not associated with an fMRI activation. Patient 9 showed a clear fMRI activation in the first experiment, which was not reproducible in the repeated experiment. Patient 4 was studied three times, and showed a significant fMRI activation in the first and third experiments only, in which 37 and 40 epileptiform discharges, respectively, were

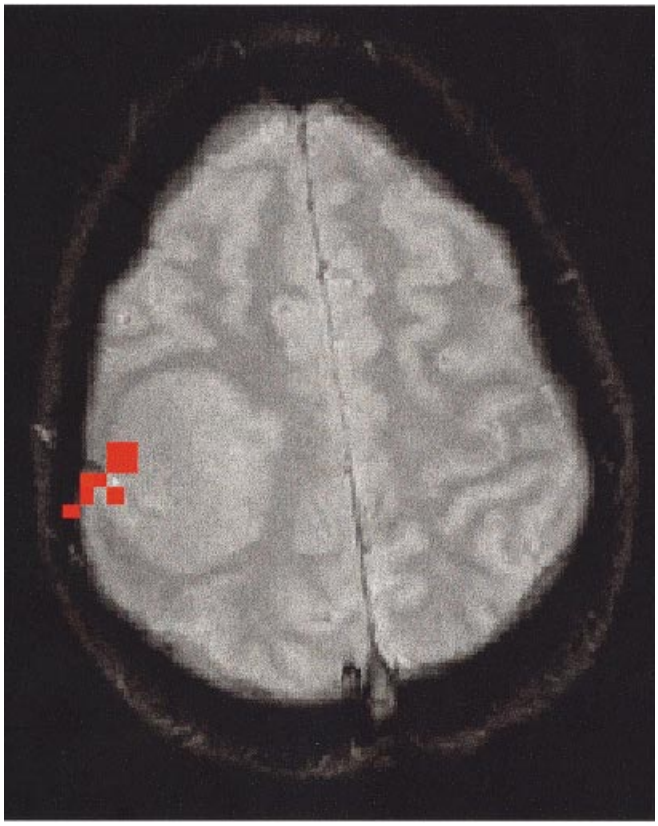

Fig. 2 Activation map of an individual fMRI experiment overlaid on a high-resolution echo planar image of patient 2 (the corresponding EEG is displayed in Fig. 1). The activation is adjacent to the cleft in the lateral part of the nodular heterotopia. This result was shown in all three experiments.

included in the statistical analysis as activation states. In contrast, the second experiment, comprising only 21 epileptiform discharges, did not show any activation. In our study, the smallest number of activations leading to a significant fMRI activation was 34. In most of the experiments showing a positive result, 45–49 activations were sampled (Table 2).

Discussion

We found EEG-triggered EPI BOLD fMRI to be a practicable and robust method in the evaluation of epilepsy patients with focal epileptiform discharges. In all 24 experiments, we were able to obtain a good-quality EEG, detect spontaneous interictal epileptiform discharges on-line and to trigger EPI BOLD acquisitions after these events.

The MR image quality was not significantly compromised by the EEG recording and in seven out of 10 patients we found focal MR signal increases associated with the focal epileptiform discharges seen in the concurrent EEG. These activations showed co-localization with the focus seen in routine scalp EEG and in the EEG recording during the experiment, and were reproducible in six cases. Additional electrocorticography was performed in one patient (patient 1), and it confirmed the co-localization between interictal epileptiform activity and fMRI activation. In the three patients with fMRI activation and previous lateralizing ictal EEG recordings (patients 1, 3 and 4; Table 1), the findings were concordant. Activation was seen in patients with different underlying pathologies (chronic encephalitis, hippocampal sclerosis, cortical dysgenesis, tumour). In patients with focal lesions, the activation overlapped or was adjacent to the lesion (patients 2, 4 and 6; Fig. 2). Patient 3 had undergone previous epilepsy surgery with an anterior lobectomy of the left temporal lobe without improving the frequency of seizures. In this case, the fMRI revealed an activation in the remaining mesial temporal lobe, in keeping with an epileptogenic zone beyond the previous resection (Fig. 3). The activation of deep temporal structures is remarkable as it is correlated with epileptiform discharges recorded by scalp EEG. This requires propagation of the epileptiform activity to a larger superficial cortical area. An activation solely in deep structures might suggest that fMRI more readily identified the site of primary spike generation. This hypothesis would be in keeping with the result for patient 10 (Fig. 4). In this case the scalp EEG showed bilateral occipital discharges, while the activation map revealed unilateral occipital activation on the side of EEG predominance. The possibility that the site of the primary generator of epileptic activity is associated with different metabolic and haemodynamic changes compared with brain areas involved in the propagation of this activity requires further study, given its potential clinical relevance.

Investigations of epileptic foci in humans have been limited hitherto by the low spatial or temporal resolution of the diagnostic tools available. Due to their restricted spatial sampling and the insoluble inverse problem, neither EEG nor magnetoencephalography can directly localize the source of epileptic activity. PET and SPECT studies have shown increased blood flow and metabolism in the region of the seizure focus during ictal events (Engel *et al*., 1983; Lee *et al*., 1986) and, in contrast, decreased blood flow and metabolism during the interictal state (Engel *et al*., 1982). Because of their low temporal resolution, however, these methods sample activity continuously over a prolonged period of time, and hence cannot investigate the changes in blood flow and oxygenation related to single epileptiform discharges. By time-locking the fMRI acquisition to single EEG events, our study confirms the results of previous case reports (Warach *et al*., 1996; Seeck *et al*., 1998; Symms *et al*., 1998) that EEG-triggered fMRI can identify brain activation associated with subclinical discharges with a high spatial resolution and completely non-invasively.

Methodological considerations

Methodological limitations of spike-triggered fMRI are caused by genuine BOLD imaging characteristics. Firstly, after a brief neuronal activation, the BOLD contrast signal changes start to increase ~2 s after the stimulus, peak after

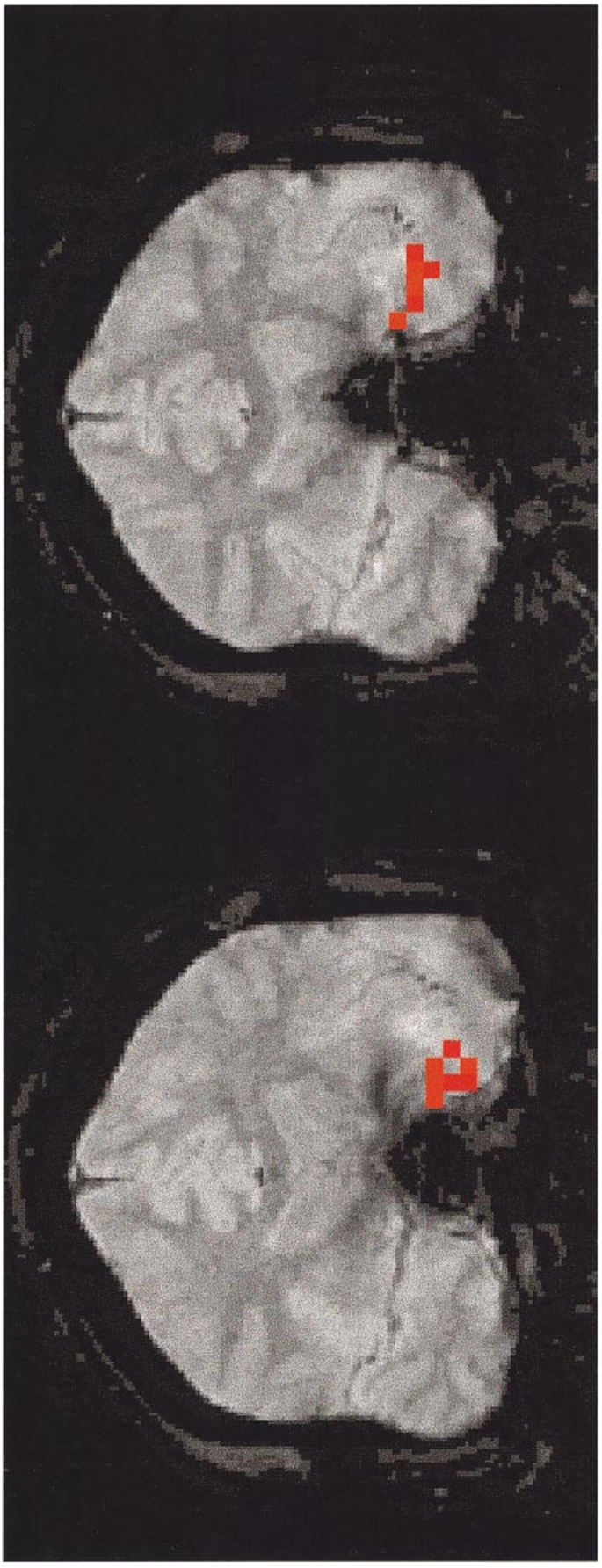

Fig. 3 Patient 3. Activation map of an individual study. The two contiguous slices showing activation of the left mesial temporal lobe are displayed.

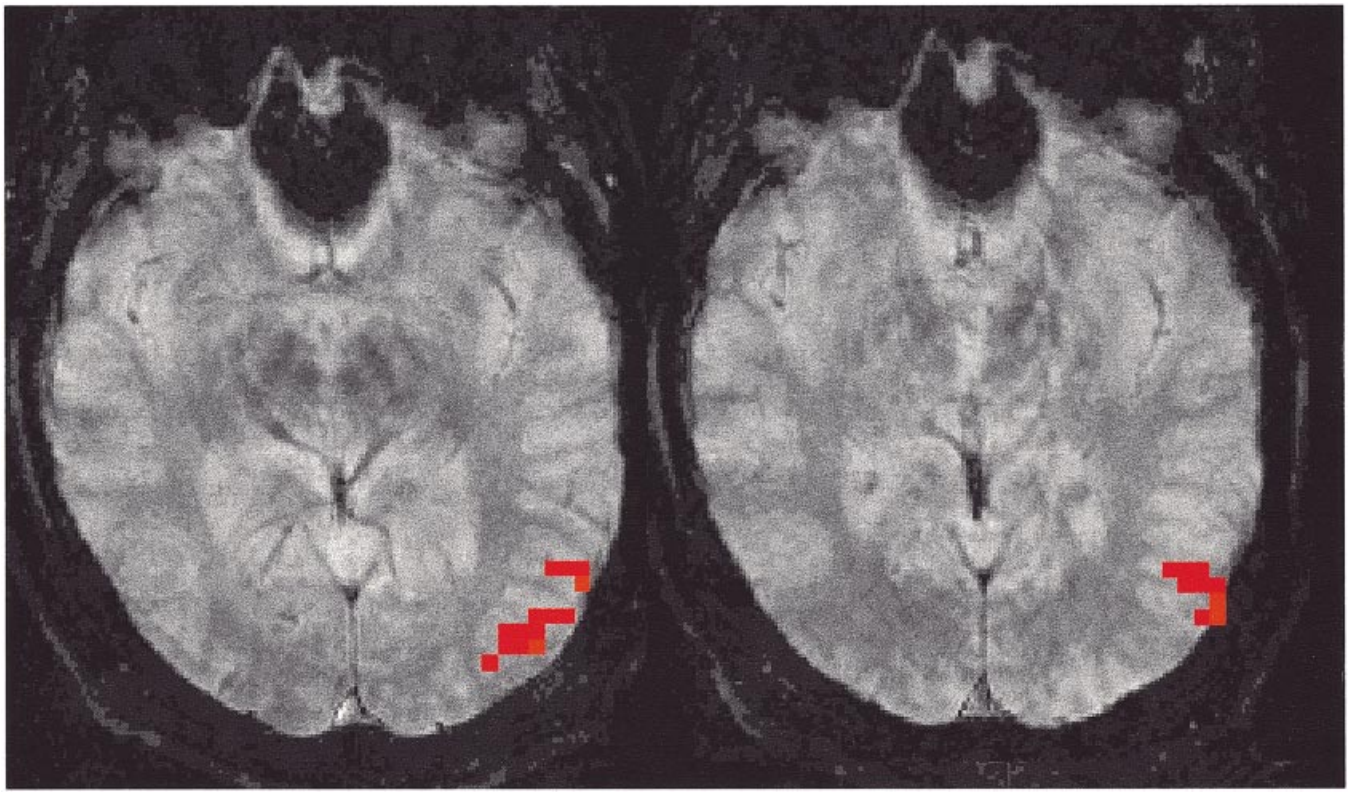

Fig. 4 Patient 10. Corresponding slices of the activation maps of the first (left) and second (right) study are displayed to give a typical example of the reproducibility of the results. The same area in the left occipital lobe was activated in both studies.

4–7 s and last ~10 s with high variability (Hennig *et al*., 1995; Rosen *et al*., 1998). These dynamics prevent the distinction between regions that are sequentially activated within a few seconds or even fractions of a second. Hence, in widespread (e.g. patient 4) or multifocal activation the primary source of the discharge cannot be determined. Secondly, the low signal-to-noise ratio of BOLD imaging requires sampling of activation and control states. Using a 1.5 Tesla scanner, we found that at least 30 epileptiform discharges had to be sampled to obtain an activation clearly distinguishable from noise, even when low-resolution images (64×64 matrix) with a relatively high signal-to-noise ratio (~100) were used. This limits the applicability of this method to patients with a high frequency of interictal epileptiform discharges, and the duration of the study is highly dependent on the frequency of appropriate EEG events. There is a trade-off whereby increasing the number of events sampled improves signal-to-noise ratio but requires a prohibitive scanning time and may increase misregistration problems caused by patient movement.

As epileptiform discharges are generated unpredictably, the MRI data were acquired in a non-periodic manner, with interleaved sampling of activation and control states. Compared with continuous image acquisition, this approach requires on-line analysis of the EEG, but has the advantage of allowing activation and control periods to be individually sampled to maintain the desired ratio of activation to control image, which substantially reduces the number of acquisition periods required.

We used the Stimulate software package because it allows non-periodically acquired data to be processed conveniently. As other software packages suitable for non-periodic paradigms (e.g. SPM99) become available, more sophisticated processing of event-related fMRI will be possible.

In contrast to the mapping of ictal activity with fMRI, which, due to formidable clinical and technical problems, is restricted to exceptional cases (e.g. focal status epilepticus or serial seizures without gross movement) (Jackson *et al*., 1994; Detre *et al*., 1995), the mapping of interictal activity has several advantages: (i) frequent interictal discharges are a common phenomenon in patients with partial seizures; (ii) interictal discharges are not associated with stimulus-correlated motion; and (iii) fMRI activations associated with single discharges are less likely to be confounded with propagation effects compared with ongoing ictal activity.

By using a method for the on-line subtraction of pulse artefact, we were able to apply our method to patients with low-amplitude epileptiform discharges. Pulse artefact is the most significant EEG artefact caused by the magnetic fields of the MR scanner, persists throughout the recording and can obscure EEG events with a smaller amplitude (Ives *et al*., 1993; Huang-Hellinger *et al*., 1995; Allen *et al*., 1999). It has large inter-individual variability and its occurrence is unpredictable. Frontal and central EEG channels are

predominantly affected, with a mean artefact amplitude of >50 μV in the majority of subjects (Allen *et al*., 1999). In this study, on-line pulse artefact subtraction was essential in eight of 10 patients to reliably detect epileptiform discharges (Fig. 1).

Our results suggest that high-amplitude discharges are more likely to be associated with a larger focal fMRI activation (e.g. patients 1 and 4). Corresponding to this, two of the three patients without fMRI activation had particular low-amplitude discharges with variable morphology (both spikes and sharp waves). It is not clear, however, why patient 7, who had stereotyped discharges with a relatively high amplitude, did not show an fMRI activation and why the activation in patient 9 was not reproducible. While our method of combining EEG and fMRI offers the possibility of the highly specific detection of local changes in blood oxygenation associated with interictal epileptiform discharges, it might not be sensitive enough to detect all activated areas. Further improvements of the signal-to-noise ratio are therefore required. In particular, the thresholding applied may also account for the relatively small size of the fMRI activation compared with the cortical areas involved in generating epileptiform discharges found by electrocorticography.

Clinical relevance

The main diagnostic question in patients with localization-related epilepsy, particularly in presurgical evaluation, is to localize the area of brain necessary to generate seizures, the 'epileptogenic zone'. fMRI triggered after interictal epileptiform discharges localizes the brain areas involved in generating these particular EEG events. The area of cortex that generates interictal spikes is labelled the 'irritative zone'. This is not necessarily identical with the cortical area that initiates seizures, the 'ictal onset zone', but typically has a close spatial relationship to it (Ebersole and Wade, 1991; Lüders *et al*., 1996). In studies with patients undergoing epilepsy surgery, the distribution of interictal spikes has been shown to be a good predictor of surgical outcome (Gilliam *et al*., 1997). Hence, the localization of brain areas contributing to the irritative zone by fMRI has the potential to become a useful additional non-invasive method in the presurgical evaluation of patients with intractable epilepsy. To determine the significance of our fMRI findings, further work is needed to study the results in relation to the anatomical extent of the spiking cortex identified by electrocorticography and to the surgical outcome with respect to the extent of removal of the activated area in those patients who subsequently undergo epilepsy surgery. Furthermore, the distribution of fMRI-derived cortical activation could be used to constrain generator modelling of the scalp-recorded epileptiform discharges, and thereby may be helpful in addressing the inverse problem, which limits the interpretation of scalp EEG. A recent case report revealed co-localization of fMRI signal changes triggered by interictal epileptiform activity and three-dimensional EEG source localization in a patient with multifocal localization-related epilepsy (Seeck *et al*., 1998). These results, however, have to be confirmed in larger groups of patients with stereotyped focal discharges as presented in our study.

In conclusion, EEG-triggered fMRI can reproducibly visualize the brain areas involved in generating interictal epileptiform discharges with high spatial resolution. This non-invasive method therefore has the potential to improve our understanding of the pathophysiology of epilepsy and the interpretation of scalp EEG findings, and to assist in the presurgical evaluation of patients with intractable partial seizures.

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