



Imaging of Interictal Epileptiform Discharges Using Spike-triggered fMRI

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Abstract. 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. We have addressed and resolved the issues of patient safety and EEG quality inside the MR scanner and report here the application of this technique in 29 experiments in 14 patients with localization-related epilepsy and frequent interictal epileptiform discharges (spikes or spike wave). In each experiment, 20-slice snapshot gradient echo echo-planar images (EPI) were acquired approximately 3.5 seconds after single epileptiform discharges (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 on a pixel-by-pixel basis using statistical parametric mapping. Eight of the 14 patients showed focal changes of the blood oxygen level dependent (BOLD) signal, which occurred in close spatial relation to the maximum of the epileptiform discharges in the concurrent EEG. Six of the eight patient showing a fMRI activation were studied at least twice and had reproducible results. We conclude that EEG-triggered fMRI is now a sufficiently developed technique to be more widely used in clinical studies, demonstrating that it can reproducibly localize brain areas involved in the generation of spikes and spike wave in epilepsy patients with frequent interictal discharges which is not possible with other non-invasive techniques.

1. Introduction

For more than 50 years interictal epileptiform discharges (IED) recorded by scalp EEG are the mainstay for diagnosing and classifying the type of epilepsy. The knowledge of the underlying generators of these EEG events, however, is still limited. Due to their restricted spatial sampling and the "inverse problem", neither EEG or MEG (magnetoencephalography) can directly identify these generators. On the other hand, the low temporal resolution of PET and SPECT prevents the investigation of brain activation linked to brief IED.

In contrast it has been shown recently that functional MRI (fMRI) allows the detection of local changes in blood oxygenation associated not only with epileptic seizures [1] but also IED [2,3,4]. The acquisition of MR images linked to brief subclinical events like IED

requires the recording of EEG during the MR scanning procedure [5,6]. We have previously reported on a fMRI-compatible EEG acquisition system that ensures patient safety (mainly through current-limiting resistors) [7], excellent EEG quality (using on-line pulse artifact suppression) [8] and functional images with minimum artifacts (by using appropriate materials for electrode assemblies and shielding of electromagnetic noise) [9]. We have used this optimized recording technique to monitor the EEG of epilepsy patients undergoing MRI and triggered ultra-fast snapshot multi-slice EPI blood oxygen level dependent (BOLD) fMRI acquisitions after single IED (spike or spike wave) were identified in the on-line EEG [4]. The purpose of this study was to identify the generators of the IED and correlate their site to the focus of previous interictal scalp EEG recordings, invasive and ictal EEG recordings and, if present, structural lesions in the anatomical MRI.

2. Methods

2.1 Patients

Fourteen patients (10 male, 4 female, median age 27 years, range: 17 - 48) with a confirmed diagnosis of medically intractable localization-related epilepsy were studied. The study was approved by the ethics committee of the National Hospital for Neurology and Neurosurgery and all patients gave informed consent. Ten patients had lesions in the structural MRI (5 x cortical dysgenesis, 2 x hippocampal sclerosis, low grade astrocytoma, posttraumatic brain damage), the remaining 4 patients had a normal structural MRI. All 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 or generalized IED were not included in the study.

2.2 EEG recording

EEG was recorded in the MR scanner using the following system: Standard Ag/AgCl disk electrodes were applied on the scalp using collodium; these had 12 kOhm current limiting resistors fitted adjacent to each electrode [7]. 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, MA, 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 analog 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 the 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 artifact subtraction (75 kOhm current limiting resistors were fitted to each ECG-electrode) [8]. EEG data was digitally remounted and displayed to show bitemporal chains. In 12 patients, on-line pulse artifact subtraction software was used to aid visual detection of the epileptiform discharges. This method subtracts an averaged pulse artifact waveform calculated for each electrode during the previous 10 seconds. Technical details have been described elsewhere [8].

2.3 fMRI acquisition and processing

fMRI was performed on a 1.5 T Horizon EchoSpeed MRI scanner (General Electric, Milwaukee, USA) using snapshot gradient-echo EPI (TE = 40 ms, 24 cm field-of-view). Acquisitions of 20 contiguous 5 mm slices with a 64x64 matrix were performed at each time-point. The acquisition time was 4.5 seconds. Additional high resolution multi-shot EPI images (matrix 256x256, 16 shots, TR = 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 IED (spike or spike wave). As the peak blood oxygenation level change detected by fMRI occurs approximately 4 to 7 seconds after the onset of the brain activity [10,11], a delay of approximately 3.5 seconds between the observation of the discharge and the image acquisition was applied. Control images were acquired after periods of at least 10 seconds of background EEG activity without epileptiform activity. Image acquisition was performed non-periodically with activation and control images interleaved, depending on the sequence of the EEG events. An interval of at least 15 seconds was established between successive acquisitions to ensure the same T1-weighting for each acquisition.

Due to hardware restrictions, the number of time-points was limited to 98 per study. This led to a maximum acquisition of 49 activation- and control- states, respectively, as equal numbers of activation and control states were used for the statistical analysis. The typical total scanning time was 60 to 90 minutes, depending the frequency of EEG events. The SPM96 package was used to perform spatial realignment and statistical analysis [12]. The significance threshold was set to $p < 0.001$ and the extent threshold to $p < 0.05$.

3. Results

In all 29 experiments the EEG-quality was sufficient to detect activation and control periods reliably throughout the study, though in 24 experiments (twelve of the patients) on-line pulse artifact subtraction was necessary to achieve good EEG quality. IED recorded inside the scanner had a similar localisation, amplitude and configuration as in previous recordings under routine conditions. None of the patients reported discomfort or other adverse events due to the EEG recording during the experiments. Between 21 and 49 fMRI acquisitions triggered after IED were sampled in each study, the smallest number of IED leading to a significant fMRI activation was 34. In most of the experiments sing a positive result, 45 to 49 activation timepoints were sampled.

In 8 out of 14 patients, a focal activation was seen in the fMRI data. In all cases this was a single cortical area. Four of the fMRI positive patients had a cortical dysgenesis, one a hippocampal sclerosis and one a low grade astrocytoma; two patients had a normal structural MRI. Figure 1 presents the SPM96 activation map of a patient with hippocampal sclerosis, showing an activation in the mesial temporal lobe. In all patients, the fMRI activation showed co-localization with the EEG spike-focus; in all patients with lesional epilepsy, the fMRI was overlapping or adjacent to the lesion. Six of the 8 patients underwent repeated (2 to 5) experiments, in all of these cases the activation was reproducible.

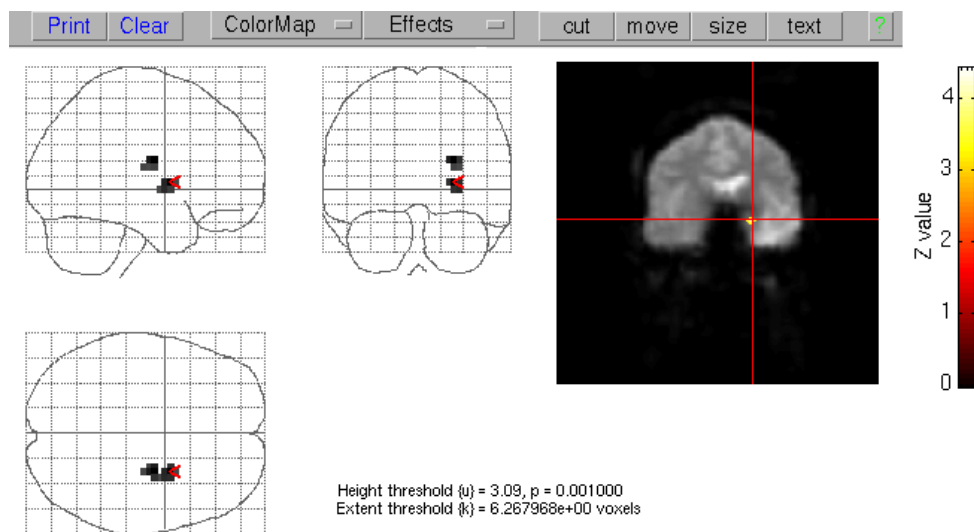


Figure 1. SPM activation map showing activation of the left mesial temporal lobe.

Discussion

In this study we were able to obtain a good quality EEG in the MR scanner in all experiments, detect spontaneous IED on-line and trigger EPI BOLD acquisitions after these events. The MR image quality was not significantly compromised by the EEG recording and in 8 out of 14 patients we found focal MR signal increases associated with the focal IED seen in the concurrent EEG. These activations showed co-localisation with the focus seen in previous routine scalp EEG and the EEG recording during the experiment. Additional electrocorticography was performed in one patient and confirmed the co-localization between interictal epileptiform activity and fMRI activation. In the four patients with fMRI activation who had previous lateralizing ictal EEG recordings, the lateralization was concordant. Activation was seen in patients with different underlying pathologies (chronic encephalitis, hippocampal sclerosis, cortical dysgenesis, and tumour). Figure 1 shows the activation map of a patient with refractory left mesial temporal lobe seizures who underwent previous epilepsy surgery with a left anterior temporal lobectomy without improving the seizure frequency. The fMRI revealed an activation in the remaining (sclerotic) mesial temporal lobe, in keeping with an epileptogenic zone beyond the previous resection. The activation of deep temporal structures is remarkable as it is correlated with epileptiform discharges recorded with 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 of a patient with bilateral occipital discharges, who showed a unilateral occipital fMRI activation on the side of the EEG predominance. The possibility that the site of the primary generator of epileptic activity could be associated with different metabolic and hemodynamic changes compared to brain areas involved in the propagation of this activity requires further studies given its potential clinical relevance.

4.1. Methodological Considerations

Investigations of epileptic foci in humans have been hitherto limited by either the low spatial or temporal resolution of the available diagnostic tools. Due to their restricted spatial sampling and the insolvable "inverse problem" of working back from distant scalp potentials to hypothesise about the likely sites of their generators, neither EEG nor MEG can directly localize the source of epileptic activity. PET and SPECT studies have shown an increased blood flow and metabolism in the region of the seizure focus during ictal events [13,14] and, in contrast, a decreased blood flow and metabolism during the interictal state [15]. Due to 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 brief IED. By time-locking the fMRI acquisition to single EEG events, we could confirm results of previous case reports [2,3,16] that EEG-triggered fMRI is a practicable method to identify brain activation associated with subclinical discharges with a high spatial resolution and completely non-invasively [4].

Methodological limitations of spike-triggered fMRI are caused by genuine BOLD imaging characteristics. Firstly, the BOLD contrast signal changes after a brief neuronal activation start to increase approximately 2 seconds after the stimulus, peak after 4 to 7 seconds and last about 10 seconds with a high variability [10,11]. Thus, these underlying hemodynamics prevent the distinction between sources sequentially activated within a few seconds or even fractions of a second during propagation of IED. 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 IED had to be sampled to obtain an activation clearly distinguishable from noise, even when low resolution images (64x64 matrix), with a relatively high signal to noise ratio (~100), were used. This limits the practicability of this method to patients with frequent IED 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 but requires a prohibitive scanning time and may

increase misregistration problems caused by patient movement.

As IED occur unpredictably, the MRI data were acquired in a non-periodic manner with an interleaved sampling of activation and control states. This type of non-periodic acquisition requires an interval of about 15 seconds between acquisitions to allow the NMR spins to return to equilibrium. Data collection efficiency is thus in the range of only 10%. Furthermore, in contrast to continuous image acquisition EEG-triggered fMRI requires on-line analysis of the EEG. An advantage of spike-triggered fMRI is the possibility to maintain the desired activation to control image ratio which substantially reduces the number of acquisition periods required.

It remains unclear why 6 of the studied epilepsy patients did not show a fMRI activation. While EEG-triggered fMRI offers the possibility of a specific detection of local blood oxygenation changes 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. The applied thresholding in particular may also account for the relatively small size of the fMRI activation compared to the cortical areas involved in generating epileptiform discharges found by electrocorticography.

4.2. Clinical Relevance

Functional (perfusion [17,18], diffusion [19], and BOLD [1,20]) MRI studies can detect focal MR signal changes associated with ictal activity. However, ictal MR scanning is for practical reasons limited to patients with predictable seizure (e.g. reflex epilepsy), seizure series, or continuous seizure activity and is likely to be compromised by seizure-related movement artifacts. Furthermore, functional imaging of ongoing epileptic seizures is likely to be confounded by propagation of the ictal activity. With the possibility of recording EEG inside the MR scanner, IED can be detected during the scanning session and can be used to trigger scan acquisitions [4]. This approach is likely to find a broader application than ictal fMRI, because IED are present in most of epilepsy patients and do not have clinical correlates, in particular motion, which can compromise fMRI quality.

Knowledge of the generators of interictal events identified by EEG-triggered fMRI would provide crucial information for :

1. interpreting the findings of routine EEG studies. The detection of interictal epileptiform discharges in the scalp EEG has been the mainstay for the diagnosis and classification of epilepsy for more than fifty years. However, the EEG interpretation is still limited by the impossibility to identify directly the underlying generators of EEG events. This is due to the restricted spatial sampling and the hitherto insoluble inverse problem of working back from distant scalp potentials to hypothesise about the likely sites of their generators. 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;
2. understanding the underlying pathophysiological mechanisms of epilepsy, e.g. the neuro-vascular coupling of epileptic activity;
3. relating the anatomical site of the underlying structural abnormalities to the sites of functional disturbance;
4. planning the appropriate extent of surgical resection in respect of different lesional pathologies in pharmaco-resistant patients undergoing epilepsy surgery. Experimental work has indicated that there are likely to be different mechanisms of epileptogenesis, and outcome of epilepsy surgery appears to be crucially related to pathology [21].

The main diagnostic question in the presurgical evaluation of epilepsy patients is to localize

the area of brain necessary to generate seizures, the "epileptogenic zone". fMRI triggered after interictal epileptiform discharges localises brain areas being involved in generating these particular EEG events. The area of cortex that generates interictal spikes is labelled as "irritative zone". This is not necessarily identical with the "epileptogenic zone", but has typically a close spatial relationship with it [22,23]. 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 EEG/fMRI findings, further work is needed to compare the results to the anatomical extent of the spiking cortex identified by electrocorticography and to the surgical outcome in relation to the extent of removal of the activated area in those patients subsequently undergoing epilepsy surgery.

5. Conclusion

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

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