EEG-Correlated Functional MRI: Recent Methodologic Progress and Current Issues

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Electroencephalography is a long-established technique and remains a crucial diagnostic tool in epilepsy. The high temporal resolution of EEG allows the detection of transient events, such as spikes, which are often an important feature in patients with epilepsy. However, it has low spatial resolution. Functional magnetic resonance imaging (fMRI), first demonstrated in 1990, with its high spatial resolution and noninvasiveness, has had a substantial impact on functional imaging. Combined EEG and fMRI promises to be a tool with all the desirable features of both individual techniques.

EEG recording in the MR environment (per-MRI EEG) was first demonstrated in 1993 (1). EEG-correlated fMRI studies were first performed during interictal (2–5) and normal brain activity (6). An interleaved approach to data acquisition, called spike-triggered EEG-fMRI (see later), demonstrated the ability of fMRI to detect significant blood oxygen level–dependent (BOLD) signal changes associated with interictal spikes (3,7). However, the MRI scanner is a hostile environment that has imposed substantial limitations on EEG recording. Combined EEG and fMRI promises to be a tool with all the desirable features of both individual techniques.

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EEG QUALITY

The most crucial practical difficulty that must be overcome before useful functional data can be acquired is the pulse artifact (or cardioballistogram) that appears in the EEG when the patient is positioned in the scanner because of the presence of the strong static field (1). A second, also very important problem, is the obliteration of the EEG during image acquisition, which significantly limits applicability, sensitivity, and the capacity to measure the time-course of BOLD signal change (11).

Better understanding of the effects of the MR environment on EEG recording over the last 5 years has led to significant improvements in per-MRI EEG quality. There are three possible sources of interference in the MR imager: the radio frequency (RF) pulses, the switching magnetic gradient fields, and movement of the EEG electrodes in the strong permanent magnetic field. These changes in magnetic flux give rise to undesired induced voltages in the EEG.

Cardioballistic and other movement-related artifacts

These arise from the cardioballistic movements of the body and EEG leads, and also can be caused by vibrations from the scanner coolant pump. The former has been found to be highly variable between subjects and electrode positions (12). It can be reduced by minimizing the area of the EEG wire loops and lead fixation (13). A bipolar montage of the EEG can further reduce the amplitude of these artifacts (13,14). Any remaining artifacts can be removed by averaging and subtraction of the artifacts synchronized to the ECG, either online (12) or offline (9,14,15). These algorithms are based on running averages and subtraction, and rely on the fact that the artifact is correlated to the ECG only. They can provide a degree of EEG quality sufficient for the accurate identification of interictal discharges or sleep stages necessary for EEG-triggered fMRI or other interleaved designs (14,16).

Interference during MR imaging: the image-acquisition artifact

EEG is obscured by interference during scanning because of induced voltages in the leads subjected to the
rapidly changing gradient fields (9). Given that the BOLD response is expected to peak 2–7 s after each event and last $\leq 12$ s, it is thus advisable to restrict scanning to a period of latency and duration corresponding roughly to the response peak. For longer scan times, the EEG and MR data cannot be correlated because of the obliteration of the EEG and possible presence of undetected significant EEG events. Therefore, extended data acquisition after a single event or continuous scanning with EEG correlation is possible only if the image-acquisition artifact can be removed from the EEG. The time course of the artifact will depend on the gradient-switching sequence (timing, amplitude, rate of change), the position, and effective area of the circuits formed by the EEG leads and subject’s head. Furthermore, switching of the magnetic gradients causes vibrations of the MR scanner, which can result in small movements in the EEG leads and subject, and thus induced voltages.

Two solutions to the problem of EEG-imaging artifact removal have been proposed (9,10). Both rely on amplification with sufficient dynamic range to avoid saturation due to the large artifact and limiting EEG leadloop area. The method by Allen et al. (10) uses 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; this is followed by pulse artifact suppression. Validation was based on comparative spectral analysis and accuracy of the identification of separately recorded spike–wave complexes (median amplitude, 74 $\mu$V) added to EEGs recorded in five subjects.

Conversely, Hoffmann et al. (9) emphasized the need for mechanical means of restricting lead movement. They proposed a postprocessing filtering method based on the Fast Fourier transform (FFT); segments of EEG without MR activity are compared with the FFT of the EEG recorded during imaging. Frequencies with amplitudes over a threshold determined based on the FFT of the normal EEG are then discarded. The inverted FFT gives the corrected EEG. It has been shown that this processing does not affect the EEG quality significantly for the detection of interictal spikes, even if $>40\%$ of the frequencies of an EEG have been removed. This method requires no special interface between the EEG and MR scanner. The temporal resolution of the processing is limited by the duration of EEG segments used for the FFT.

CONTINUOUS AND SIMULTANEOUS EEG-fMRI IN EPILEPSY

Continuous and simultaneous EEG and fMRI acquisition will allow us to exploit the full capacity of EEG and fMRI for the first time. Event-related fMRI is a recent development, based on acquiring images from brief events or activation episodes, in contrast to the conventional block designs (17,18). Event-related fMRI can accommodate periodic or random events. It is therefore ideally suited for continuous EEG and fMRI acquisition, allowing us to map the responses associated with spikes. In terms of experimental efficiency, the fact that a larger amount of data per unit time, and hence per event, is acquired should lead to increased sensitivity. It should also allow an improved characterization of the baseline.

Application

In a typical simultaneous EEG-fMRI event-related experiment at the UCL group’s MRI Unit (London, England), fMRI data are acquired continuously over a period of 35 min, with online visualization of good-quality EEG. The rate of acquisition is one 21-slice volume every 3 s. The EEG recording includes a scanner-generated volume-acquisition pulse used to synchronize the two datasets. Retrospective review of the EEG thus allows the definition event vectors in terms of image numbers and forms the basis of the analysis using the SPM99 (http://www.fil.ion.ucl.ac.uk/SPM) fMRI analysis package. Using an event-related approach, with an unconstrained model of the hemodynamic response time course, a statistical parametric map (SPM) can be obtained that shows areas with significant signal change as well as the associated time course (11). A complete model of the BOLD signal change requires characterization of EEG events, taking into account a range of background and epileptiform abnormalities. In principle, continuous EEG-fMRI should be more sensitive than the triggered approach for the following reasons: a larger amount of data can be acquired per unit time, and the time course of the response in individual subjects can be measured (19). Furthermore, it should allow more flexibility in patient selection than previously possible with the triggered approach.

Figure 1 shows two segments of EEG recorded during a continuous EEG-fMRI experiment, illustrating the effectiveness of the online pulse and image-acquisition artifact-suppression algorithms (10,12). Figure 2 shows a BOLD activation map and the time course of the activation associated with the spike activity at the location of the cross-hair. In this case, the shape of the time course was similar to that derived from experiments with normal brain functions. It is hoped that the spatiotemporal information derived from this new approach will be useful in distinguishing the various types of EEG events and substrates, as well as provide refined hypotheses in cases that are considered for invasive monitoring.

DISCUSSION

Improvements in methods will soon make this method quite accessible. The improvements described indicate
FIG. 1. Two segments of an EEG recording made during a continuous EEG-fMRI experiment using the method by Allen et al. (10). The top 10 channels are referential, followed by a bilateral chain montage, the ECG and OSC, which is the slice-acquisition pulse transmitted by the scanner. The initial segment shows an image-acquisition artifact caused by currents induced in the leads by the switching scanner gradients at the beginning of the experiment and before the suppression algorithm becomes effective, which takes 10 s. The second segment shows a typical spike.
clearly that it is now possible to obtain a good-quality EEG in the MRI machine. Furthermore, the recent experience at the Montreal Neurological Institute has shown that we could minimize the ballistocardiogram artifact sufficiently by fixing the electrodes well and minimizing loops, such that subtraction is not really necessary. Using the method of Hoffmann et al. (9), the epileptic activity can be seen clearly during continuous scanning.

The combination of EEG and fMRI, whether in the form of EEG-triggered fMRI or in the form of continuous fMRI acquisition and event-related fMRI analysis, has the potential of bringing about a new type of information. In the same way as postictal single-photon emission computed tomography (SPECT) is a powerful method of combining EEG and measurement of blood flow to indicate the region of seizure onset, EEG combined with fMRI has the potential to indicate the actual origin of epileptiform spikes recorded on the scalp. Although regions of activation in relation to spikes have been already demonstrated, their relation with the origin of the spike remains to be placed on a solid basis. In some cases, the region of activation is small: does it represent the origin of the spike, or the “tip of the iceberg,” the highest peak of a broad region of activation? It has been demonstrated (20) that scalp spikes correspond to a relatively widespread intracerebral spiking region. How does this region relate to the region of fMRI activation? In other cases, several discrete regions of activation have been reported. Do they correspond to a sequence of spike activity, with one region starting the spike and the others following? Or do they correspond to multiple foci coming together at the time of the spike? Regions of activation also are not always consistent in the same patient.

Finally, continuous EEG-fMRI has the potential for measuring the hemodynamic response of a spike generator (Fig. 2). As noted previously, it will be interesting to investigate whether spikes originating in different pathophysiologic substrates generate different hemodynamic responses, or whether “a spike is a spike,” independent of its origin in a tumor or a dysplastic region. Furthermore, there may also be an effect related to the activity at the primary site of seizure onset or resulting from propagation.

**REFERENCES**