Published in final edited form as:

Epilepsia. 2011 July ; 52(0 4): 38–42. doi:10.1111/j.1528-1167.2011.03151.x.

Combining EEG and fMRI in the study of epileptic discharges

Jean Gotman and **Francesca Pittau**

Montreal Neurological Institute, McGill University, Montreal, QC, Canada

SUMMARY

The combining of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) is a unique noninvasive method for investigating the brain regions involved at the time of epileptic discharges. The neuronal discharges taking place during an interictal spike or spike-wave burst result in an increase in metabolism and blood flow, which is reflected in the blood oxygen–level dependent (BOLD) signal measured by fMRI. This increase is most intense in the region generating the discharge but is also present in regions affected by the discharge. On occasion, epileptic discharges result in decreased metabolism, the origin of which is only partially understood. EEG-fMRI applied to focal epilepsy results in maxima of the BOLD signal most often concordant with other methods of localization and has been shown to help in localizing epileptic foci in nonlesional frontal lobe epilepsy. It has also demonstrated the involvement of the thalamus in generalized epileptic discharges. In patients with new-onset epilepsy it could be used to evaluate the source and extent of the brain structures involved during discharges and their evolution as the disease progresses.

Keywords

fMRI; Blood oxygenation level dependent effect; Spikes; New onset epilepsy

Scalp electroencephalography (EEG) is the simplest and probably most effective method for observing epileptic discharges. It is noninvasive and can easily be recorded over long periods, allowing the documentation of the different types of epileptic discharges that can be present in a patient: clinical seizures, interictal spikes and sharp waves, background abnormalities, and so-called electrographic seizures. The weakness of the scalp EEG is that it reflects mostly what happens in the parts of the brain that are close to the skull and it does not have a high spatial resolution. Some of these weaknesses can be remedied by combining EEG with functional magnetic resonance imaging (fMRI), allowing measurement of the blood oxygenation level dependent (BOLD) signal. It becomes then possible to see anywhere in the brain and with high spatial resolution the metabolic changes related to the scalp EEG discharges. Because MR scanning is used, the recording is necessarily limited in time and it is obviously not likely that seizures are recorded. In this article, we review the main aspects of the EEG-fMRI technique and review some of its important findings. Although EEG-fMRI has until now been used primarily in patients with long-standing epilepsy, there is no reason that it could not be used when patients are newly diagnosed. This method is noninvasive and it may be that it will be helpful in assessing the impact of

Address correspondence to Jean Gotman, Montreal Neurological Institute, 3801 University Street, Montréal, QC, Canada H3A 2B4. jean.gotman@mcgill.ca.

Disclosure

The authors have nothing to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

epileptic discharges on the brain by determining the extent of brain tissue involved at the time of a discharge.

Recording EEG and fMRI in Combination

Details of the methodology have been described in several publications (Gotman et al., 2006; Ullsperger & Debener, 2010). It consists of the following steps:

1. Obtain electrodes and an amplifier/recorder system that is MR compatible. Silver or gold electrodes can be used and optical transmission of the amplified EEG outside the scanner room is recommended.
2. Ensure that the patient is comfortable and remains as immobile as possible during the necessarily long scanning session; the session is long to ensure that the patient has a sufficient number of epileptic events.
3. fMRI scanning while recording the EEG results in large artifacts in the EEG. These can be removed by software after the scan to recover a “clean” EEG and allow one to mark the time of epileptic events.
4. Build a mathematical model of what the BOLD signal should be at the voxels involved in the epileptic event. If a voxel is involved in the event, its time course should change as a result of each event in a predictable fashion (in accordance with the hemodynamic response function, or HRF).
5. Analyze the time course of every voxel and find those having a time course significantly correlated with the model. Such voxels are related to the marked epileptic events in the EEG. Either they take part in its generation or they are a consequence of the event.

Figure 1 shows an example of the EEG event recorded in the scanner and the voxels activated by this event superimposed on an anatomic MRI. The most uncertain part of the analysis of EEG-fMRI data relates to the choice of the HRF in creating the model. A so-called canonic HRF, peaking at around 5 s after neuronal activation, has been used commonly in cognitive studies and in epilepsy. It was shown, however, that the HRF can have different shapes and latencies and that it may be important to use different HRFs to ensure the optimal uncovering of BOLD responses (Benar et al., 2002; Bagshaw et al., 2004; Grouiller et al., 2010).

EEG-fMRI in Focal Epilepsy

During the last 10 years, multiple studies have demonstrated that the BOLD signal usually increases in regions tightly coupled with the region presumably generating focal interictal spikes (Benar et al., 2002). The same studies have shown that changes are also present in the BOLD signal at a distance from the presumed focus, in regions with no apparent EEG change (Kobayashi et al., 2006a). These remote changes are most often increases in BOLD signals but sometimes are a decrease in BOLD. Such changes imply that the BOLD signal is able to reveal distant effects of epileptic spikes. In cases where data from intracerebral electrode studies were available, the regions of BOLD changes were confirmed (Benar et al., 2006).

In the context of the localization of epileptic foci in the presurgical evaluation of patients with medically intractable epilepsy, EEG-fMRI has demonstrated its ability to contribute complementary information (Zijlmans et al., 2007). In patients with nonlesional frontal lobe epilepsy, it was possible to localize epileptic foci subsequently confirmed by pathologic analysis or other imaging modalities (Moeller et al., 2009). In patients with malformations

of cortical development it was possible to identify deep generators (Kobayashi et al., 2006b). It has also been shown that when the surgical removal included the region of BOLD activation, there was a good postsurgical outcome (Thornton et al., 2010).

A few studies have reported BOLD changes in relation to brief seizures with absent or minimal clinical manifestations. Such seizures generate BOLD signal changes much larger than spikes. Their dynamics can be analyzed and they can be informative with respect to the region of onset and the region of propagation (Tyvaert et al., 2009). Studies have also demonstrated that in some pathology there is a tendency for ictal and interictal responses to correspond, whereas in other pathologies they differ (Tyvaert et al., 2008). The dynamic analysis of seizures is a unique approach to investigating the region of onset and the regions of propagation in the whole brain noninvasively.

It was shown recently that scanning with a 3T (3 Tesla) magnet was more sensitive than scanning with 1.5T, a finding that is not surprising but was confirmed (Gholipour et al., 2011). In the same study, the reproducibility of EEG-fMRI studies was demonstrated, making one more confident in clinical applicability (Fig. 2). Although safety issues are complex, it was also demonstrated recently that it is possible to perform EEG-fMRI studies in patients with intracerebral electrodes (Vulliemoz et al., 2011). The studies have reported BOLD signal increase near the regions showing spikes.

A paradoxical response has been observed in a few studies, and is not explained: Instead of the usual increase in BOLD signals, some spikes or sharp waves are followed by a decrease in BOLD signal (Kobayashi et al., 2006c; Jacobs et al., 2009; Rathakrishnan et al., 2010). This decrease is located in the presumed region of spike generation and appears to have the same localization value.

EEG-fMRI in Generalized Epilepsy

The first studies of patients with generalized spike and wave discharges revealed some expected and some surprising results (Salek-Haddadi et al., 2003; Aghakhani et al., 2004): Most patients showed a bilateral symmetrical activation of the thalamus, a region that had been implicated in experimental animal models but that could not be investigated directly in humans. Whereas one could have expected a widespread cortical activation, with frontal predominance in accordance with the common EEG distribution, a variety of cortical activation and deactivation patterns were observed, sometimes frontal but other times central and parietal. These patterns were largely bilateral and symmetrical.

Unlike patients with focal epilepsy, patients with idiopathic generalized epilepsy and frontally predominant spike and wave discharges constitute a homogeneous group and they were subjected to a group analysis, as is often done in fMRI studies of cognitive function in normal individuals. This group study (Gotman et al., 2005) clearly demonstrates the following pattern: activation of the thalamus and of mesial frontal regions as well as insulae bilaterally and the cerebellum. There were also prominent bilateral frontal, parietal, and posterior cingulate deactivations. These deactivations were in close correspondence with the *default mode network* (Raichle et al., 2001), a network that is active when normal subjects are at rest and deactivated when they engage in a task. In the context of spike and wave discharges, this lifting of the default mode network was interpreted as possibly causing the decrease in awareness experienced by most patients during the generalized EEG bursts.

The preceding findings were confirmed in subsequent studies (Moeller et al., 2008), which also revealed that the caudate nucleus was most often deactivated as well. It was also found that the cortical activation was, as originally observed, variable from patient to patient but consistent across the different bursts of a single patient (Moeller et al., 2010). That study and

that of Bai et al. (2010) also demonstrated that hemodynamic changes could occur prior to the EEG discharge and often lasted much longer, leading to a difficulty in interpreting the neurovascular coupling in this situation.

Is There a Role for EEG-fMRI in New-Onset Epilepsy?

All of the studies described herein have been carried out in patients with long-standing epilepsy, sometimes medically refractory. Could they be performed in newly diagnosed patients and what would be their interest? All the studies are dependent on the ability to record epileptic EEG abnormalities during the 30–90 min scanning period. For patients showing sufficiently frequent discharges (a few per hour) an EEG-fMRI study can be performed with a high likelihood of positive findings. This technique is noninvasive as it only implies EEG recording and MR scanning. EEG-fMRI studies could document the likely source of the discharge and allow a subsequent assessment of change when epilepsy evolves. It is also possible to assess the extent of other regions involved; they may be related to cognitive or learning difficulties experienced by patients.

Part of the complexity of the method relates to the need to record the EEG in the scanner. New approaches are currently being developed that may allow the analysis of BOLD changes related to epileptic discharges, even in the absence of EEG recordings. This may make the investigation very simple and more widely applicable as part of an imaging protocol.

Acknowledgments

This work was supported by grant MOP-38079 of the Canadian Institutes of Health Research.

References

Aghakhani Y, Bagshaw AP, Benar CG, Hawco C, Andermann F, Dubeau F, Gotman J. fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. Brain. 2004; 127:1127–1144. [PubMed: 15033899]

Bagshaw AP, Aghakhani Y, Benar CG, Kobayashi E, Hawco C, Dubeau F, Pike GB, Gotman J. EEG-fMRI of focal epileptic spikes: analysis with multiple haemodynamic functions and comparison with gadolinium-enhanced MR angiograms. Hum Brain Mapp. 2004; 22:179–192. [PubMed: 15195285]

Bai X, Vestal M, Berman R, Negishi M, Spann M, Vega C, Desalvo M, Novotny EJ, Constable RT, Blumenfeld H. Dynamic time course of typical childhood absence seizures: EEG, behavior, and functional magnetic resonance imaging. J Neurosci. 2010; 30:5884–5893. [PubMed: 20427649]

Benar CG, Gross DW, Wang Y, Petre V, Pike B, Dubeau F, Gotman J. The BOLD response to interictal epileptiform discharges. Neuroimage. 2002; 17:1182–1192. [PubMed: 12414258]

Benar CG, Grova C, Kobayashi E, Bagshaw AP, Aghakhani Y, Dubeau F, Gotman J. EEG-fMRI of epileptic spikes: concordance with EEG source localization and intracranial EEG. Neuroimage. 2006; 30:1161–1170. [PubMed: 16413798]

Gholipour T, Moeller F, Pittau F, Dubeau F, Gotman J. Reproducibility of interictal EEG-fMRI results in patients with epilepsy. Epilepsia. 2011; 52:433–442. [PubMed: 21054351]

Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. Proc Natl Acad Sci U S A. 2005; 102:15236–15240. [PubMed: 16217042]

Gotman J, Kobayashi E, Bagshaw AP, Benar CG, Dubeau F. Combining EEG and fMRI: a multimodal tool for epilepsy research. J Magn Reson Imaging. 2006; 23:906–920. [PubMed: 16649203]

Grouiller F, Vercueil L, Krainik A, Segebarth C, Kahane P, David O. Characterization of the hemodynamic modes associated with interictal epileptic activity using a deformable model-based

analysis of combined EEG and functional MRI recordings. Hum Brain Mapp. 2010; 31:1157–1173. [PubMed: 20063350]

Jacobs J, Levan P, Moeller F, Boor R, Stephani U, Gotman J, Siniatchkin M. Hemodynamic changes preceding the interictal EEG spike in patients with focal epilepsy investigated using simultaneous EEG-fMRI. Neuroimage. 2009; 45:1220–1231. [PubMed: 19349236]

Kobayashi E, Bagshaw AP, Benar CG, Aghakhani Y, Andermann F, Dubeau F, Gotman J. Temporal and extratemporal BOLD responses to temporal lobe interictal spikes. Epilepsia. 2006a; 47:343–354. [PubMed: 16499759]

Kobayashi E, Bagshaw AP, Grova C, Gotman J, Dubeau F. Grey matter heterotopia: what EEG-fMRI can tell us about epileptogenicity of neuronal migration disorders. Brain. 2006b; 129:366–374. [PubMed: 16339793]

Kobayashi E, Bagshaw AP, Grova C, Dubeau F, Gotman J. Negative BOLD responses to epileptic spikes. Hum Brain Mapp. 2006c; 27:488–497. [PubMed: 16180210]

Moeller F, Siebner HR, Wolff S, Muhle H, Boor R, Granert O, Jansen O, Stephani U, Siniatchkin M. Changes in activity of striato–thalamo–cortical network precede generalized spike wave discharges. Neuroimage. 2008; 39:1839–1849. [PubMed: 18082429]

Moeller F, Tyvaert L, Nguyen DK, LeVan P, Bouthillier A, Kobayashi E, Tampieri D, Dubeau F, Gotman J. EEG-fMRI: adding to standard evaluations of patients with nonlesional frontal lobe epilepsy. Neurology. 2009; 73:2023–2030. [PubMed: 19996077]

Moeller F, LeVan P, Muhle H, Stephani U, Dubeau F, Siniatchkin M, Gotman J. Absence seizures: individual patterns revealed by EEG-fMRI. Epilepsia. 2010; 51:2000–2010. [PubMed: 20726875]

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A. 2001; 98:676–682. [PubMed: 11209064]

Rathakrishnan R, Moeller F, Levan P, Dubeau F, Gotman J. BOLD signal changes preceding negative responses in EEG-fMRI in patients with focal epilepsy. Epilepsia. 2010; 51:1837–1845. [PubMed: 20550554]

Salek-Haddadi A, Lemieux L, Merschhemke M, Friston KJ, Duncan JS, Fish DR. Functional magnetic resonance imaging of human absence seizures. Ann Neurol. 2003; 53:663–667. [PubMed: 12731002]

Thornton R, Laufs H, Rodionov R, Cannadathu S, Carmichael DW, Vulliemoz S, Salek-Haddadi A, McEvoy AW, Smith SM, Lhatoo S, Elwes RD, Guye M, Walker MC, Lemieux L, Duncan JS. EEG correlated functional MRI and postoperative outcome in focal epilepsy. J Neurol Neurosurg Psychiatry. 2010; 81:922–927. [PubMed: 20547617]

Tyvaert L, Hawco C, Kobayashi E, LeVan P, Dubeau F, Gotman J. Different structures involved during ictal and interictal epileptic activity in malformations of cortical development: an EEG-fMRI study. Brain. 2008; 131:2042–2060. [PubMed: 18669486]

Tyvaert L, LeVan P, Dubeau F, Gotman J. Noninvasive dynamic imaging of seizures in epileptic patients. Hum Brain Mapp. 2009; 30:3993–4011. [PubMed: 19507156]

Ullsperger, M.; Debener, S. Simultaneous EEG–fMRI: recording, analysis and application. Oxford University Press; New York: 2011.

Vulliemoz S, Carmichael DW, Rosenkranz K, Diehl B, Rodionov R, Walker MC, McEvoy AW, Lemieux L. Simultaneous intracranial EEG and fMRI of interictal epileptic discharges in humans. Neuroimage. 2011; 54:182–190. [PubMed: 20708083]

Zijlmans M, Huiskamp G, Hersevoort M, Seppenwoolde JH, van Huffelen AC, Leijten FS. EEG-fMRI in the preoperative work-up for epilepsy surgery. Brain. 2007; 130:2343–2353. [PubMed: 17586868]

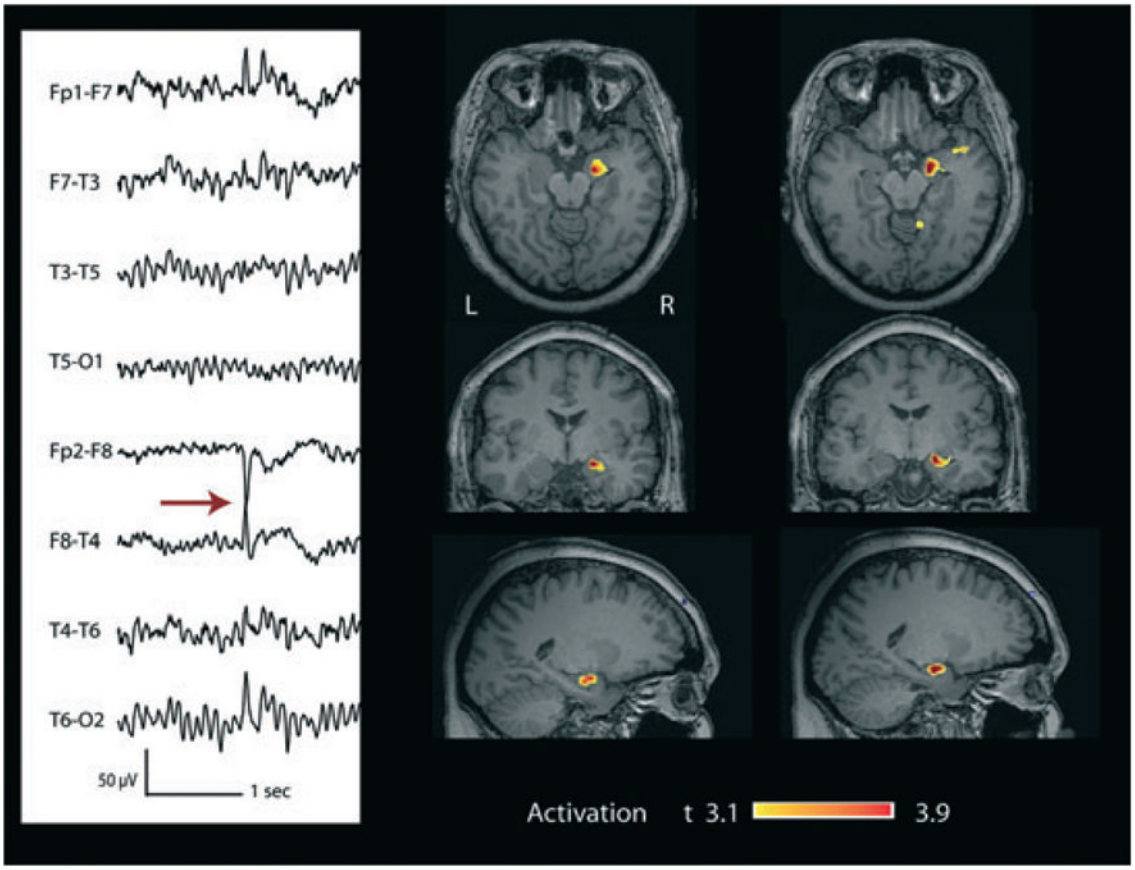

Figure 1.
Thirty-three-year-old woman with mesial temporal lobe epilepsy and right mesial temporal sclerosis. The marked events were spikes with phase reversal at F8 (bipolar montage, EEG on the left). The BOLD response shows an activation area in the right amygdala. *Epilepsia* © ILAE

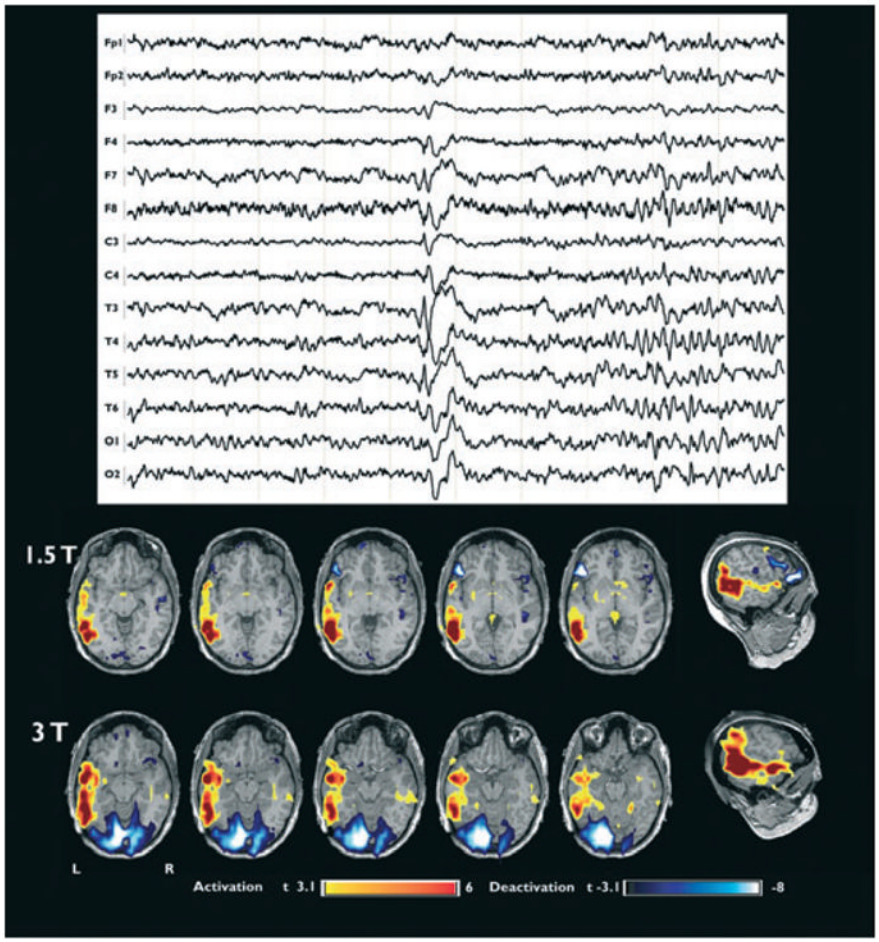

Figure 2.
Left temporal spike and wave in EEG with referential montage (FCz as reference). BOLD response reproducibility shown in 1.5T and 3T studies (from Gholipour et al., 2010). *Epilepsia* © ILAE