EEG–fMRI validation studies in comparison with icEEG: A review

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ABSTRACT

Simultaneous EEG–fMRI is a non-invasive investigation technique developed to localize the generators of interictal epileptiform discharges (IED) in patients with epilepsy. Although the value of EEG–fMRI in epilepsy presurgical evaluation is being assessed clinically, its utility is still controversial. In this review, we considered EEG–fMRI applications in epilepsy presurgical evaluation with a focus on validation studies that compared the results of EEG–fMRI with those of the current “gold standard” intracranial EEG (icEEG) in order to assess its utility of seizure focus localization and the possibility for EEG–fMRI to reduce the need for invasive techniques such as icEEG. Since the advances of EEG–fMRI partially rely on the maturation of its data analysis, we also reviewed the methodological developments in EEG–fMRI analysis. It is possible that combining with other neuroimaging modalities such as MEG/MSI and ESI, EEG–fMRI may play a greater role in epilepsy presurgical evaluation.

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1. Introduction

The development of electroencephalogram (EEG) recording during functional MRI (fMRI) was motivated by the clinical interest in mapping changes in neural activity associated with epileptic discharges in EEG onto images of brain anatomy (Ives et al., 1993). Simultaneous recording of electrophysiology and functional magnetic resonance imaging (fMRI) bridges the gap between neurophysiology and functional neuroimaging. Scalp EEG provides information regarding neuronal activity at high temporal resolution and low spatial localization, while fMRI measures neuronal activity indirectly through blood flow changes with high spatial resolution. Combining EEG recording with fMRI scanning opens the opportunity to uncover the brain regions showing changes in the fMRI signal in response to epileptic spikes in EEG (Gotman et al., 2006).

EEG–fMRI measures the hemodynamic correlates of interictal epileptiform discharges (IEDs) in EEG and can be likened to source localization using high-density EEG/ESI (EEG Source Imaging) and magneto-encephalography (MEG) in terms of limited recording time and emphasis on IED (Rosenkranz and Lemieux, 2010). Mapping IEDs in epilepsy has several advantages: frequent IEDs are common in patients with partial seizures; IEDs are not associated with stimulus-correlated motion; fMRI activations associated with single IEDs are less likely (yet still possible) to be confounded with propagation effects in comparison to ongoing ictal activity (Krakow et al., 1999).

Precise localization of the epileptic focus is a prerequisite for good surgical outcome in patients with drug-resistant focal epilepsy. The epileptic focus, i.e., the epileptogenic zone (EZ), is the brain region where the seizure originates and the minimum brain volume whose resection is necessary and sufficient for seizure ablation (Luders et al., 1993). Since IED-related blood oxygenation level-dependent (BOLD) increases tend to be located near the irritative zone (IZ) (Salek-Haddadi et al., 2006; Kobayashi et al., 2006d) which is often wider than the ictal onset or EZ, EEG–fMRI often identifies distributed brain areas of interictal spiking in epileptic patients who have frequent IEDs (Zijlmans et al., 2007). Thus, EEG–fMRI helps to reveal the epileptogenic network and provides additional information about the epileptic source in the presurgical work-up (Zijlmans et al., 2007; Moeller et al., 2009; Rosenkranz and Lemieux, 2010).

IEDs recorded by scalp EEG are the mainstay for classifying types of epilepsy, and their localization is an important role in the presurgical evaluation of drug-resistant epileptic patients (Gilliam et al., 1997). For patients with drug-resistant focal seizures undergoing epilepsy surgery who need invasive intracranial EEG (iEEG) analysis (e.g., EEG with intracranial grids) to localize the epileptic focus, EEG–fMRI may contribute to decisions on iEEG implantation strategies. The EEG–fMRI approach has been used for the exploration of interictal as well as ictal epileptic activity to localize the epileptogenic zone and thus gradually recognized by some epilepsy surgery centers (Al Asmi et al., 2003; Lemieux et al., 2001; Gotman et al., 2004, 2005; Kobayashi et al., 2005, 2006a,b,c,d; Laufs et al., 2006d; Salek-Haddadi et al., 2006; Bénar et al., 2006; Zijlmans et al., 2007; Marques et al., 2009; LeVan et al., 2010; Moeller et al., 2009; Thornton et al., 2010; Grouiller et al., 2011). As a non-invasive technique, EEG–fMRI is
useful in mapping regional changes in the cerebral BOLD changes that are time-locked to IEDs (Rosenkranz and Lemieux, 2010). Apart from EEG–fMRI, other non-invasive neuroimaging modalities such as MEG/MSI (Magnetic Source Imaging), PET and SPECT are also valuable in epilepsy source localization. Each of them has strengths and limitations. For example, MEG/MSI is sensitive to the magnetic fields induced by IEDs, but is very expensive; MEG and EEG cannot detect deep spikes in the brain; PET and SPECT can detect deep epileptic lesion, but their spatial resolutions are relatively low and they do not measure epileptic activity directly. In addition, SPECT only works with some seizures. Thus, each imaging modality may provide concordant or complementary information and it is necessary to assess and validate the clinical value of each of the non-invasive localization techniques in epilepsy. For details of these non-invasive imaging modalities (including their assessment and comparisons), see review of Whiting et al., 2006.

Although there are a number of literature reviews on EEG–fMRI (Gotman et al., 2006; Krakow, 2008; Laufs et al., 2008; Rosenkranz and Lemieux, 2010), few focused on EEG–fMRI validation studies (in comparison with iEEG) in presurgical evaluation. In addition, few previous reviews on EEG–fMRI addressed the question whether it is possible for EEG–fMRI and/or in combination with other non-invasive neuroimaging modalities to reduce the need of invasive techniques such as iEEG in presurgical evaluation. This review will investigate the utility of EEG–fMRI in epileptic surgical planning with an emphasis on EEG–fMRI validation studies and the role of EEG–fMRI as well as its potential in presurgical evaluation.

2. EEG–fMRI validation studies and results

Since invasive techniques such as iEEG are usually lengthy, sampling-limited and costly with risk of complications, the role of EEG–fMRI as a non-invasive tool for presurgical evaluation is of particular interest. Several studies using fMRI during simple partial seizures reported BOLD effects concordant with the brain regions harboring the epileptic focus (Warach et al., 1994; Detre et al., 1995; Jackson et al., 1994; Connelly, 1995). The performance of EEG–fMRI is usually assessed by validation studies using iEEG, the current gold standard for localizing the epileptogenic zone (Luders et al., 1993).

In general, the EEG–fMRI validation studies are few and the study designs are relatively simple (most of them are retrospective studies where the majority of patients selected were with focal epilepsy. In addition, most patients underwent EEG–fMRI and fewer patients underwent iEEG). Based on certain evidence (Seeck et al., 1998; Lazeyras et al., 2001; Bagshaw et al., 2004; Kobayashi et al., 2005; Laufs et al., 2006d; De Tiègue et al., 2007), Laufs and Duncan (2007) pointed out that EEG–fMRI cannot supersede any of the current methods because validation studies are lacking and informative results are only obtained in some patients, etc. However, there is growing evidence that EEG–fMRI studies with iEEG comparison in general confirmed the co-localization between the source of IEDs and fMRI activation (Zijlmans et al., 2007; Grova et al., 2008; Tyaert et al., 2008; Moeller et al., 2009; Thornton et al., 2010; Grouiller et al., 2011), which opened the possibility that the non-invasive EEG–fMRI may play a greater role in epilepsy presurgical evaluation.

In the early years, Krakow et al. studied 10 consecutive patients with focal epilepsy (1 underwent ECoG or iEEG) and found that EEG–fMRI could reproducibly localize the brain areas generating IEDs which indicated that EEG–fMRI could assist presurgical evaluation (Krakow et al., 1999). Details of the study are listed in Table 1. Later, Lazeyras et al. (2000) studied 11 epilepsy patients retrospectively (iEEG was performed on 6 of them) using the EEG–triggered fMRI which was an early technique that image acquisition was manually triggered by an experienced EEG reader in the activated condition. They reported that the accuracy of EEG–triggered fMRI reached 83.3% (5/6) and concluded that EEG–fMRI is a safe and powerful non-invasive tool that improves the MRI diagnostic value by precisely localizing the epileptic focus (Lazeyras et al., 2000). Al-Asmi et al. found that iEEG largely (50%, 4/8) confirmed that the EEG–fMRI activation regions represent epileptogenic areas (Al Asmi et al., 2003). Bagshaw et al. reported that in 3 out of 4 (75%) patients, EEG–fMRI results were consistent with those of iEEG results (Bagshaw et al., 2004). Bénar et al. further found the concordance between EEG–fMRI and iEEG—when there is an intracranial electrode near an EEG or fMRI peak, it usually includes one active contact (Bénar et al., 2006). While in the absence of IEDs, Laufs et al. demonstrated that EEG–fMRI with EEG frequency analyses was useful in detecting the epileptogenic area in focal epilepsy which was supported by iEEG (Laufs et al., 2006d). In recent years, Zijlmans et al. (2007) investigated the utility of EEG–fMRI on 29 patients who were rejected for epilepsy surgery due to non-localized seizure focus. They reported that in the presurgical work-up, EEG–fMRI improved localization in four out of six unclear focal foci, and contributed to the localization of multifocality. Further, they found that in four patients, EEG–fMRI opened new prospects for surgery and in two of these patients iEEG supported the EEG–fMRI results (Zijlmans et al., 2007). In children with drug-resistant epilepsy, De Tiègue et al. found that EEG–fMRI activations co-localized with the presumed location of the epileptic focus in four children and one of which was confirmed by iEEG indicating that EEG–fMRI is a promising tool to non-invasively localize epileptogenic regions in epileptic children (De Tiègue et al., 2007). In patients with malformations of cortical development (MCDS), Tyaert et al. recorded interictal and ictal events and found that during seizures, the BOLD signal changes were always in the overlying cortex and never in the heterotopia which was confirmed by the iEEG findings in 2 patients (Tyaert et al., 2008). Grova et al. demonstrated that the hemodynamic response to epileptic spikes was concordant with iEEG results in 3 patients (Grova et al., 2008), Moeller et al. (2009) compared EEG–fMRI results with that of iEEG in two cases and reported that in one patient, the resected cortex corresponded with fMRI results and in another, EEG–fMRI activation was adjacent to the resected area. Further, Thornton et al. (2010) captured ictal EEG–fMRI to visualize plausible seizure related hemodynamic changes. They found that when scalp EEG reflects seizure onset, GLM reveals localized BOLD changes concordant with the ictal onset zone; and when scalp EEG does not accurately reflect seizures, ICA provides additional information and iEEG confirmed ICA identified cases in 8 out of 9 patients (Thornton et al., 2010). Moreover, Grouiller et al. (2011) improved the yield of EEG–fMRI with a novel approach that integrated the information of long-term clinical EEG (Fig. 1) and found EEG–fMRI concordant or moderately concordant with iEEG and/or surgical site in 14 out of 18 patients (Grouiller et al., 2011). Therefore, simultaneous EEG and fMRI recording provide valuable information to localize the brain regions generating interictal epileptiform activity and identify the epileptogenic zone. Details of the main methods and results of the above EEG–fMRI studies compared with iEEG (and/or surgical site) are given in Table 1.

3. Discussion

There are several previous reports in which the reliability of EEG–fMRI has been determined against iEEG recordings (Seeck et al., 1998; Bénar et al., 2002; Bagshaw et al., 2004; Thornton et al., 2007). The discordance between EEG–fMRI and iEEG results might be due to the different timing and environments of EEG–fMRI and iEEG recordings. In addition, EEG and iEEG recordings and fMRI assess different phenomena (electric activity vs. hemodynamic response) at different locations related to the spikes. Moreover, there are limitations in EEG recordings, and limitations in iEEG as
the gold standard for source localization. On the one hand, EEG has relatively low sensitivity in epilepsy ranging between 25 and 56% and better specificity ranging between 78 and 98% (Smith, 2005). Nayak et al. (2004) have shown that only 9% of the total number of discharges identified using intracranial electrodes were detectable by inspection of the scalp EEG alone. On the other hand, due to restricted sampling, it is not rare to observe nonlocalized icEEG obtained from patients with drug-resistant epilepsy (Knowlton et al., 2008a). Although a subset of IED-related fMRI activations partly overlap with IED sources (Bénar et al., 2006), fMRI signal changes restricted sampling, it is not rare to observe nonlocalized icEEG obtained from patients with drug-resistant epilepsy (Knowlton et al., 2008a). Although a subset of IED-related fMRI activations partly overlap with IED sources (Bénar et al., 2006), fMRI signal changes restricted sampling, it is not rare to observe nonlocalized icEEG obtained from patients with drug-resistant epilepsy (Knowlton et al., 2008a). Although a subset of IED-related fMRI activations partly overlap with IED sources (Bénar et al., 2006), fMRI signal changes

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are generally in good agreement providing information on epileptic activity (EA) that overlaps, and both methods can evaluate the epileptic network and neuronal connectivity involved during epileptic discharges. They also pointed out that BOLD changes are frequently observed at distant areas, suggesting that EEG−fMRI may provide additional information on the generators and structures during EA, and their impact on brain function (Dubeau and Tyvaert, 2010). More validation studies with larger sample sizes are needed to reveal the true utility of EEG−fMRI in presurgical evaluation.

The yield of EEG–fMRI studies (i.e., the significant BOLD signal change in response to IED) varies from study to study, especially in relatively large-sample-size EEG–fMRI studies. For example, in an EEG–fMRI study of 38 patients, the total number of patients with response was 14 of 31 (45%) Al Asmi et al. (2003); while in a study of 63 patients with focal epilepsy, 34 patients showed IEDs during a 40-minute EEG–fMRI acquisition session and the correlation analysis revealed significant IED-related BOLD changes in 67% of cases (Salek-Haddadi et al., 2006). In another EEG–fMRI research,
29 of 35 (83%) showed BOLD responses (Kobayashi et al., 2006d). These studies indicate that in order to make an EEG–fMRI study more efficient, the patients selected should have frequent IEDs. On the other hand, the application of data-driven fMRI analysis techniques (i.e. not relying on the occurrence of pathological discharges on EEG) may help to increase the yield of fMRI...
(Hamandi et al., 2005; Rosenkranz and Lemieux, 2010). For example, Laufs et al. demonstrated that in the absence of IEDs that are normally used to model fMRI data, automated EEG frequency analyses in EEG–fMRI may prove to be useful for planning the placement of intracranial electrodes to map epileptogenic areas (Laufs et al., 2006d). In addition, provocative measures such as sleep deprivation or medication that influences the number of IEDs (Halasz et al., 2002; Mäkiranta et al., 2005) may be relevant to increase the diagnostic yield of EEG–fMRI (Zijlmans et al., 2007). Alternatively, new techniques such as using epilepsy-specific EEG voltage maps (based on long-term EEG, correlated with hemodynamic changes) to help localize the epileptic focus increase the yield of EEG–fMRI, allowing better targeting for surgical resection or implantation of intracranial electrodes (Grouiller et al., 2011).

Since EEG–fMRI provides valuable information about the epileptic source in the presurgical work-up, it influences clinical decision-making by strengthening or refining the source localization hypothesis (Zijlmans et al., 2007). In addition, the reproducibility of EEG–fMRI has been demonstrated recently (Gholipour et al., 2011). In some epilepsy centers, EEG–fMRI has been gradually recognized as a non-invasive investigation technique. However, to make EEG–fMRI a more useful investigation tool, there is much room for improvement.

Although EEG continues to play a central role in the diagnosis and management of patients with epilepsy, a fundamental problem in EEG–fMRI is the limited sensitivity of scalp EEG (Kobayashi et al., 2001; Merlet et al., 1998). For example, a recent study indicated that current noninvasive EEG and MEG source localization studies could not accurately identify true mesial temporal spikes (Wennberg et al., 2011). Therefore, it is crucial to develop more sensitive EEG to better detect IEDs while suppressing noise in the magnetic environment. The location of spike generator, the distance between an EEG electrode to the spike generator and the density of EEG electrodes may be the key factors to EEG sensitivity. In MEG, Stefan et al. (1990, 2000, 2003) found that the diagnostic yield increases with the number of sensors in a study comparing the diagnostic yield of 37- and 74-channel MEG systems, suggesting that the use of whole-head systems with densely spaced arrays of sensors will contribute more to the presurgical evaluation. Similarly in EEG, an EEG/ESI (EEG source imaging) study on a group of 14 patients (with refractory focal epilepsy and Engel class 1 surgical outcomes) showed that ESI accuracy (indexed by the distance from the nearest surgical margin to the location of a single fit inverse model) improved by around 2 cm from a 31 to a 63 electrode set-up, with little change from a 63 to a 123 electrode set-up (Lantz et al., 2003). The diagnostic yield of EEG/ESI increased with high-resolution (128- or 256-channel) EEG/ESI and the localization accuracy is 74%-90% for lesional and non-lesional epilepsy (Brodbeck et al., 2009; Brodbeck et al., 2010).

While high-density electrode arrays can improve the spatial resolution of surface EEG signal topography and facilitate source localization, there is a cost of having to measure hundreds of electrodes on the scalp (Plummer et al., 2008). The yield of EEG–fMRI may further increase by developing better EEG processing and source localization software, improving fMRI sequences and improving fMRI analysis methods and software. In addition, questions remain in EEG–fMRI data analysis, especially in IED identification. For example, which approach (manual or automatic) is more accurate and reliable in IED identification? When IEDs are not easily identified by visual inspection, is the automatic approach (e.g., through EEG time-frequency analysis) more reliable? How to standardize EEG–fMRI analysis and make the EEG–fMRI tool easy to use? For convenience and standardization purposes, automatic EEG–fMRI data analysis approaches are preferred, but the accuracy and reliability of such automatic approaches need to be further validated.

Further, it is necessary to conduct more comparison studies between EEG–fMRI and other neuroimaging methods such as MEG/MSI and PET in order to reveal the contribution of EEG–fMRI relative to other modalities in surgical planning and in predicting surgical outcome. In addition, as mentioned previously, more EEG–fMRI validation studies using iEEG are needed to reveal the true utility of EEG–fMRI in the presurgical work-up of patients with epilepsy.

Accurate localization of the epileptogenic foci is the key to successful epilepsy surgery. The problem of localizing the epileptogenic zone in presurgical evaluation may be addressed in two ways.

First, the non-invasive approach. It is concerned about whether it is possible and under what circumstance, to what extent, non-invasive multi-modal neuroimaging (EEG–fMRI with other neuroimaging modalities) might reduce the need and even replace the invasive techniques such as iEEG in localizing the epileptogenic zone or lateralizing the affected hemisphere. Recent studies have explored the development of a non-invasive cortical imaging technique for presurgical planning that may provide information and resolution similar to the invasive iEEG and the work by Ding et al. (2007) is an example. There is an evolving consensus that the combined use of multiple imaging modalities such as MEG, PET, SPECT and MEG improves the accuracy of source localization (Fuchs et al., 1998; Barkley and Baumgartner, 2003; Knowlton et al., 2008a, b; Madan and Grant, 2009). For example, Knowlton et al. (2008a) found that gains in diagnostic yield were seen only with the combination of MSI and PET or MSI and ictal SPECT and thus diagnostic gain may be achieved with addition of either PET or ictal SPECT to MSI. Furthermore, Groening et al. (2009) reported that the combination of EEG–fMRI and ESI improved the interpretation of spike-associated activation network. Although the studies that measure the predictive value of EEG–fMRI in comparison with other modalities are lacking, the trend tends to show that properly combining multi-modal neuroimaging approaches may lead to gains in diagnostic yield. Knowlton et al. pointed out that MEG and additional use of other non-invasive techniques such as FDG-PET and ictal SPECT might bring the possibility of a completely non-invasive epilepsy surgery evaluation into reality in the future (Knowlton et al., 2006).

With the advance of technology, non-invasive multimodal neuroimaging integrating EEG–fMRI, MEG/MSI, PET, SPECT, MRS, etc. may significantly increase diagnostic yield in localizing the epileptogenic zone or lateralizing the affected hemisphere, which possibly will further reduce the need of invasive techniques in the future. Furthermore, the increasing availability of good quality multi-modal data combined with new modeling techniques will allow us to gain deeper insights into the dynamics of epileptic networks (Rosenkranz and Lemieux, 2010).
Second, the invasive approach: for complex epilepsy cases (e.g., MRI-negative focal or multi-foci epilepsy that the epileptic sources are hard to detect), invasive iEEG–fMRI might be the solution since iEEG is more sensitive to IEDs than regular EEG. Simultaneous recordings of fMRI and intracortical neural signals have shown correlations between the BOLD signal changes measured by fMRI and the activity of the main generators of the EEG signals (Logothetis et al., 2001). Safety concerns of iEEG–fMRI have been addressed (Carmichael et al., 2010) and pioneering studies in recent years (e.g., Vulliemoz et al., 2011) have been conducted where the iEEG–fMRI results were either in agreement with iEEG results or concordant with MEG results. More iEEG–fMRI studies with larger sample size might be needed to explore the value, advantages and disadvantages of this invasive approach.

In summary, EEG–fMRI has been proven to be a valuable and promising tool in epilepsy presurgical evaluation. With the advance of technology, this non-invasive approach will become more mature.

Acknowledgments

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References


