Simultaneous EEG and functional MRI

van Houdt, P.J.

2013

document version
Publisher's PDF, also known as Version of record

citation for published version (APA)
van Houdt, P. J. (2013). *Simultaneous EEG and functional MRI: A noninvasive tool in the presurgical evaluation of focal epilepsy*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

CHAPTER 8

General Discussion

The general aim of this thesis was to improve and evaluate the potential of EEG-fMRI as a noninvasive tool in the preoperative planning of patients who are candidates for epilepsy surgery. In the next sections methodological considerations and clinical implications will be discussed. This chapter will end with future perspectives and suggestions for the use of EEG-fMRI in clinical practice.

8.1 Methodological Considerations

In this thesis, methodological improvements for the analysis of the fMRI data are presented (chapter 2 and 3). A model-driven fMRI approach was used to reveal those brain regions that were significantly associated with IEDs present in the EEG. Also a data-driven technique was used to explore whether epilepsy-related changes were also present in fMRI data without visible IEDs in scalp EEG (chapter 7).

8.1.1 Model-driven fMRI analysis

The model-driven fMRI approach is based on a GLM framework. This is by far the most common approach for fMRI analysis. The outcome of this method depends on the underlying model, i.e. the way predictors and confounders are defined. Therefore, a priori knowledge is needed about all effects that explain variations in the fMRI signals of a particular experiment. We have shown that the fMRI signals can be corrected by creating a regressor from the variation in pulse height of the pulse oximeter signal at the subject's finger (chapter 3). Moreover, it has already been demonstrated that fMRI analysis can be improved by adding realignment parameters of the fMRI preprocessing step (Friston et al. 1996; Lemieux et al. 2007), RETROICOR parameters (Glover et al. 2000; Lund et al. 2006), heart beat intervals (de Munck et al. 2008; Shmueli et al. 2007), and respiratory depth (Birn et al. 2008). Note that correction for these effects is especially important for event-related fMRI designs, because blocked design experiments usually have a better signal-to-noise ratio as a result of averaging. Some studies specifically focused on the improvement of the sensitivity of EEG-fMRI studies in epilepsy. For example, the sensitivity increases when the fMRI data are corrected for sleep phenomena (Moehring et al. 2011), other physiological EEG rhythms like alpha rhythm (Tyvaert et al. 2008b), or eye blinks and swallowing events (Chaudhary et al. 2012). However, the number of confounders cannot be increased without consequences, because this will cause a reduction in the degrees of freedom resulting in a decrease of statistical power. Furthermore, multicollinearity between regressors should be avoided to prevent overfitting of the model. For a perfect fMRI model, a better understanding of the underlying relation between fMRI and physiological functioning is required. This can be achieved by dedicated experiments in which oxygen saturation is measured more directly. For example, using a sensor based on high sensitive multispectral imaging of oxygen saturation in skin tissue (Arimoto 2006).

The yield of the GLM approach is further determined by the HRF model that is used. The first EEG-fMRI studies in epilepsy patients adopted the analytical strategy from other fMRI studies in which the HRF was modeled with a canonical shape and a maximal response at 5 s (see Figure 1.4). However, in EEG-fMRI studies of epilepsy the HRF was found to deviate from this model: HRFs with different peak times, negative responses as well as noncanonical BOLD responses have been found. These differences are not specific for epilepsy, because in healthy volunteers the shape of the HRF related to visual stimuli or motor tasks also varies between subjects, brain regions, and stimuli (e.g. Handwerker et al. 2004; Aguirre et al. 1998; Conner et al. 2011; Siero et al. 2011). Therefore, some researchers argued that no assumptions about the shape of the HRF should be made (Grouiller et al. 2010; Lu et al. 2006; Lu et al. 2007; Lemieux et al. 2008; van Houdt et al. 2010a). In the same line of thought, we used a finite impulse response (FIR) model in our studies. The first reason for such a flexible approach is to increase the yield of EEG-fMRI, because the FIR model is sensitive to any temporal pattern associated with the appearance of IEDs, not just canonical shapes. Some authors argue that this is not necessary, because they claim that only canonical HRFs are related to the epileptic focus (e.g. Lemieux et al. 2008). Our data, however, did not confirm this conclusion (chapter 2 and 6).

The estimation of the shape of the HRF is important from a fundamental point of view as well: to obtain more insight in the coupling between electrophysiology and hemodynamics. So far, the interpretation of the shape of the HRF remains difficult, because it presents a complex interplay between $CMRO_2$, CBF, and CBV that can be affected by many external factors. Since variations in the HRF are also found in healthy volunteers, it is difficult to determine which effects are specific for epilepsy (Rosa et al. 2010). Our data did not show a consistent relation between the shape of the HRF and the type of IEDs, type of lesions, or the role of an area (i.e. onset or propagation of IEDs), possibly due to the heterogeneity of our patient population (chapter 6). Nevertheless, the shape of the HRF may reveal interesting information. For example, variations in time-to-peak can be used for interpretation of the timing of activations (Lindquist et al. 2007), such as the dynamics of seizures (Tyvaert et al. 2009). The HRF sometimes has a negative peak time, meaning that the BOLD response appeared before epileptic activity was visible in the EEG (Hawco et al. 2007; Jacobs et al. 2009; Pittau et al. 2011). The early BOLD activity is in some cases the result of synchronized neuronal activity invisible for scalp EEG, and in other cases reflects a metabolic change that is not caused by neuronal activity (Pittau et al. 2011). Noncanonical HRFs may also have a clinically relevant explanation, but more likely they have a methodological explanation: the model for the fMRI data is not complete yet. If not all confounding effects are included in the GLM or if not all IEDs are included in the IED density function, this might result in HRFs with irregular shapes.

8.1.2 Data-driven fMRI analysis

In contrast to the GLM approach, spatial ICA does not use a priori information about the confounding effects in the fMRI data or the underlying HRF model. Instead the technique estimates the sources of the fMRI signals without any assumptions about the shape of the HRF. The reason to chose spatial ICA over other data-driven techniques, such as correlation analysis, was that ICA does not require a priori knowledge about the selection of regions or voxels of interest. Several studies have shown that ICA is a useful approach for the analysis of fMRI data in patients with epilepsy, because it reveals components that are related to the epileptic activity (Rodionov et al. 2007; Thornton et al. 2010b; LeVan et al. 2009; LeVan et al. 2010a). In our study, we showed that the added value of ICA might be even more promising than argued by these authors, because ICA appears able to reveal epileptic networks also in parts of the data without the presence of visible IEDs in scalp EEG.

The difficulty with ICA, and with any data-drive technique, is the interpretation of the results. ICA yields a large number of components, and currently it is, to our knowledge, not possible to select the relevant components without a priori information about the epilepsy of the patient. Therefore, ICA alone cannot be used as an independent analytical technique yet. A few classifiers are presented in the literature that are aimed to characterize ICs automatically (Thomas et al. 2002; Tohka et al. 2008; De Martino et al. 2007). These classifiers look for certain characteristics that can separate artificial components from possible BOLD components. For such purposes, a training data set is required in which the components are divided based on visual inspection. The classifier of De Martino et al. (2007) divides the components in several groups: BOLD, motion artifacts, EPI artifacts, susceptibility artifacts, physiological noise, noise with a high spatial frequency, and noise with a high temporal frequency. This approach could assist the interpretation of the components; the epileptic component should be classified in the group of BOLD components (Thornton et al. 2010b). Ultimately, we would like to build a classifier that automatically separates the epileptic component from all other components. For that purpose, fMRI data of a large number of patients with different types of epilepsy are required and it should be examined whether these components have common characteristics that can separate them from the rest. An important point to consider in such approach is that standard resting-state networks may be part of the epileptic network (Laufs 2012).

The ICA and GLM approaches are not competing methods per se; they may be complementary to each other. For example, ICA could be used as a preprocessing step prior to the GLM approach. Since the GLM set-up might not be optimal when not all sources of artifacts are known, ICA may help to remove these artifacts (Thomas et al. 2002). First all independent components are estimated with spatial ICA. Then the artificial components are identified, either visually or automatically. A new fMRI data set is created from the non-artificial components, which is subsequently used in the GLM analysis. This approach may help to understand whether "strange" noncanonical HRFs are the result of an incomplete GLM set-up; when all artificial components are removed from the data with ICA and the shape of the HRF is still noncanonical, this effect can probably not be explained by an incomplete GLM (see section 8.1.1). Another approach, based on the ideas of Heller et al. (2005) could be to perform the GLM analysis on the time courses of the separate components under the assumption that all voxels of one component behave similarly. This will decrease the number of statistical tests and increase the signal-to-noise ratio of each statistical comparison (Heller et al. 2005).

8.2 Clinical Implications

8.2.1 Interpretation of EEG-fMRI results

The second aim of this thesis was the evaluation of EEG-fMRI in the presurgical work-up. Most studies so far, used a noninvasive gold standard based on scalp EEG to validate the EEG-fMRI results, like we did in chapter 2 (Salek-Haddadi et al. 2006; Hawco et al. 2007; Kobayashi et al. 2006c; Zijlmans et al. 2007; Bagshaw et al. 2006). These comparisons suggest a good general concordance level for EEG-fMRI (Walker et al. 2010; Laufs et al. 2010). However, the currently best gold standards available are invasive EEG recordings (Lazeyras et al. 2000; Bénar et al. 2006; Al-Asmi et al. 2003). Our study is the first study that investigates the concordance between EEG-fMRI and the spatiotemporal patterns of IEDs in the ECoG data for a large patient population (see chapter 6). In our view, this comparison is the first step in the validation of

EEG-fMRI. Our general observation was that when EEG-fMRI shows a small focal BOLD region, also the interictal invasive EEG patterns are focal. Conversely, when EEG-fMRI shows a widespread correlation pattern in which HRF clustering does not provide clear distinction in spatially adjacent regions, the invasive EEG data also show a widespread interictal pattern of different types of IEDs. These findings suggest that the sensitivity of EEG-fMRI is high with regard to the areas that are active during interictal epileptiform activity.

Another finding of chapter 6, consistent with for example Salek-Haddadi et al. (2006) and Vulliemoz et al. (2009), is that the EEG-fMRI correlation pattern consists of more than just one significantly activated area. Most EEG-fMRI studies focus on the maximal positive BOLD response as important for interpretation, whereas negative BOLD responses were considered to be less important. Although these negative HRFs are not completely understood yet, in the last few years more evidence is gained that they are also relevant (e.g. chapter 6 and Bénar et al. 2006; Kobayashi et al. 2006a; Vulliemoz et al. 2009; Rathakrishnan et al. 2010). Furthermore, it are not the largest significant BOLD regions per se that are related to the epileptic focus, but also small clusters of significant BOLD can be relevant (Vulliemoz et al. 2009, chapter 6).

EEG-fMRI correlation analysis of IEDs usually yields multiple activated brain regions, and as argued, it is not sufficient to focus on the maximal positive correlations and ignore the rest. Therefore, the question arises how the EEG-fMRI correlation pattern should be interpreted. Some authors hypothesize that the correlation pattern represents a pattern of onset and propagation of epileptic activity, suggesting that EEG-fMRI reflects an epileptic network underlying the IEDs (e.g. Salek-Haddadi et al. 2006). In chapter 6 we made an attempt to verify that assumption by investigating which BOLD regions are related to onset and propagation of activity using ECoG. A similar attempt was made by Vulliemoz et al. (2009) who used EEG source imaging of the IEDs measured during scanning. Our study confirmed the hypothesis that both onset and propagation areas were present in the EEG-fMRI correlation pattern. The idea of an epileptic network fits within the current development of epilepsy from single zone concept to a network concept (Lemieux et al. 2011; Laufs 2012; Richardson 2010). This theory assumes that for each patient a typical set of interacting networks specifies the epilepsy characteristics of the patient (Laufs 2012). These networks can either be local or more distributed over the brain (Laufs 2012). EEG-fMRI can be used to get insight in the distribution of such a network. An interesting idea is to investigate these networks further with diffusion imaging techniques to find out if structural pathways between activated regions exist (Hamandi et al. 2008; Diehl et al. 2010).

In our study, we could, however, not directly relate all EEG-fMRI areas to onset or propagation of activity due to the limited sampling of invasive EEG electrodes. Prospective studies, in which EEG-fMRI results are used to plan invasive EEG electrodes, are necessary to determine exact values of sensitivity and specificity of EEG-fMRI.

The specificity of EEG-fMRI seems relatively low, and will not help the surgeon to optimize the surgical decisions. Unfortunately, we were not able to increase the specificity, because there was not an apparent relation between HRF characteristics and the role of an area within the network (onset or propagation of IEDs). On the other hand, EEG-fMRI patterns almost always include the seizure onset zone (chapter 6). Therefore, EEG-fMRI might be suitable as a tool to guide the planning of invasive electrodes. It should be kept in mind that not all EEG-fMRI regions can possibly be sampled with invasive EEG and in cases of bilateral or very widespread activations. For this reason, the results of EEG-fMRI should be interpreted together with other noninvasive presurgical techniques.

8.2.2 Contribution of EEG-fMRI in presurgical evaluation

EEG-fMRI will not yield additional or new information for all patients compared to other techniques in the presurgical evaluation. Situations where EEG-fMRI could specifically contribute to the presurgical evaluation are:

- when activations in deeply situated cortex such as mesial structures are expected. Therefore, EEG-fMRI may assist in the decision which type of invasive electrodes should be used: depth electrodes, grids, or a combination of those.
- for patients in whom multifocal sources are expected.
- for patients with multiple electroclinical hypotheses. EEG-fMRI could reveal additional evidence for one of them.
- for a more precise localization or delineation of the focus (Pittau et al. 2012). For example, with EEG-fMRI it is possible to make a distinction between basal frontal and anterior temporal activations, which is much more difficult with EEG or MEG source localization techniques.
- to create hypotheses for the presence of subtle lesions that were not seen at the MRI before (Moeller et al. 2009).

However, systematic comparisons with other presurgical techniques, such as MEG, PET, and SPECT, are necessary to exactly establish the added value of EEG-fMRI. When new techniques are introduced for the presurgical evaluation they are usually compared to one other technique, such as EEG-fMRI to IED dipole localization (Bagshaw et al. 2006), MEG to ECoG (Agirre-Arrizubieta et al. 2009), or MEG to EEG (Ossenblok et al. 2007; Colon et al. 2009). To understand the contribution of each technique, they should be compared systematically and simultaneously. Such a comparison should result in guidelines for the use of a certain technique in clinical practice.

8.2.3 Limitations of EEG-fMRI

When applying EEG-fMRI in clinical practice, it is important to keep its limitations in mind. First, a shown in chapter 2, the sensitivity of EEG-fMRI depends on the number of IEDs in the EEG. Currently EEG-fMRI is only useful in patients with a sufficient number of IEDs during the recording. As already discussed, ICA may provide insight in this matter, but further investigations are required before ICA can be used in clinical practice. In addition, scalp EEG cannot detect all types of IEDs, which also limits the analysis.

fMRI also has limitations by itself. Since fMRI correlation analysis is based on differences between a control and an active state, it is not possible with fMRI to detect physiological processes that continuously require energy. In addition, fMRI contains very little temporal information, thus, it is not possible to disentangle time differences of fast occurring events (< TR).

Similar to other techniques based on interictal discharges, the relevance of the results for the localization of the epileptogenic zone is limited. Brain regions active in the interictal state are usually a good indicator for the areas involved in the generation of seizures, but the results are usually more extensive and therefore not synonymous to the epileptogenic zone. However, since EEG-fMRI includes the seizure onset zone and resection area in most cases (chapter 5 and 6, Thornton et al. 2010b; Grouiller et al. 2011; Pittau et al. 2012), EEG-fMRI seems very suitable to guide the implantation of invasive electrodes.

8.3 Future Perspectives

8.3.1 Towards clinical practice

EEG-fMRI is gradually moving from a research tool towards a clinical application (de Munck et al. 2009b). Although most research centers follow a similar general analysis pipeline (Figure 8.1), the individual steps are not standardized yet. For example, the specification of the HRF model varies over centers, which can influence the yield of the GLM, as was shown in this thesis (chapter 2). Also the confounders that are added to the model are not standardized. In our opinion, confounders that correct for physiological functions should always be included in the model. Another issue is the statistical threshold used for the detection of significant correlation patterns. For example, should FDR or family wise error values be used, or, as proposed by Hauf et al. (2012), a fixed number of activated voxels? It will be important to set-up guidelines for analysis and interpretation of the data in clinical practice. Although difficult, a large retrospective multicenter study, in which different analytical approaches are compared systematically, would be helpful to reach such standards.

Especially the visual review of the EEG is currently labor-intensive due to residuals of the pulse artifacts and subtle movements that may resemble IEDs (Flanagan et al.

2009). The large number of pulse artifact removal algorithms presented in the literature already suggests that this artifact is very difficult to remove. The problem with these artifacts is the beat to beat variation in terms of shape and magnitude (chapter 4). Therefore, we would currently advise to verify the marked IEDs also in the uncorrected EEG. Another solution would be to have multiple observers and only include the overlapping IEDs as proposed by Zijlmans et al. (2007), but this also complicates the use of EEG-fMRI in clinical practice.

The visual review of the EEG would be facilitated by actually measuring motion artifacts independent of the EEG. For example, by recording motion with wired loops fixed to the EEG cap (Masterton et al. 2007). These loops measure motion of the wires in general, thus small head movements and pulse artifacts. These additional recordings could be helpful to interpret the EEG, in particular with the distinction between true IEDs and motion or residuals of the pulse artifact (Flanagan et al. 2009). Furthermore, these signals can be used to correct the EEG for pulse artifacts (Masterton et al. 2007). Another way is to simultaneously record video inside the scanner (Chaudhary et al. 2010) combined with a new technique that can automatically estimate subtle movements from a video, *Eulerian Video Magnification* (Wu et al. 2012). This method can also be used to estimate blood pulse based on changes in skin color (Wu et al. 2012).

Even better would be to automatically detect IEDs or another valid epileptic characteristic from the EEG data such that visual review can be omitted (Vulliemoz et al. 2010). A promising approach recently presented by Grouiller et al. (2011) is the use of topographic maps created from IEDs outside the scanner. These maps are spatially correlated with the topographic maps of the EEG inside the scanner. Large correlations would indicate the presence of IEDs and thus provides a way to automatically create an IED-related regressor.

8.3.2 From a research point of view

Besides the topics for further research mentioned in the previous sections, some recent technical advances open new interesting avenues. First, the co-registration of invasive EEG and fMRI is safe under strict conditions (Carmichael et al. 2008; Carmichael et al. 2010). This raises great opportunities from a clinical point of view as well as from a fundamental interest, because it provides more insight in the coupling between electrophysiology and hemodynamics. The first case studies look promising (Vulliemoz et al. 2011; Carmichael et al. 2012): for the two patients that were scanned, no adverse health effects were reported, the pulse artifacts are small compared to epileptic activity, and most importantly significant BOLD regions were obtained in proximity of the active electrode contacts, but also in distant brain regions. Therefore, we expect that this technique will become important in future research.

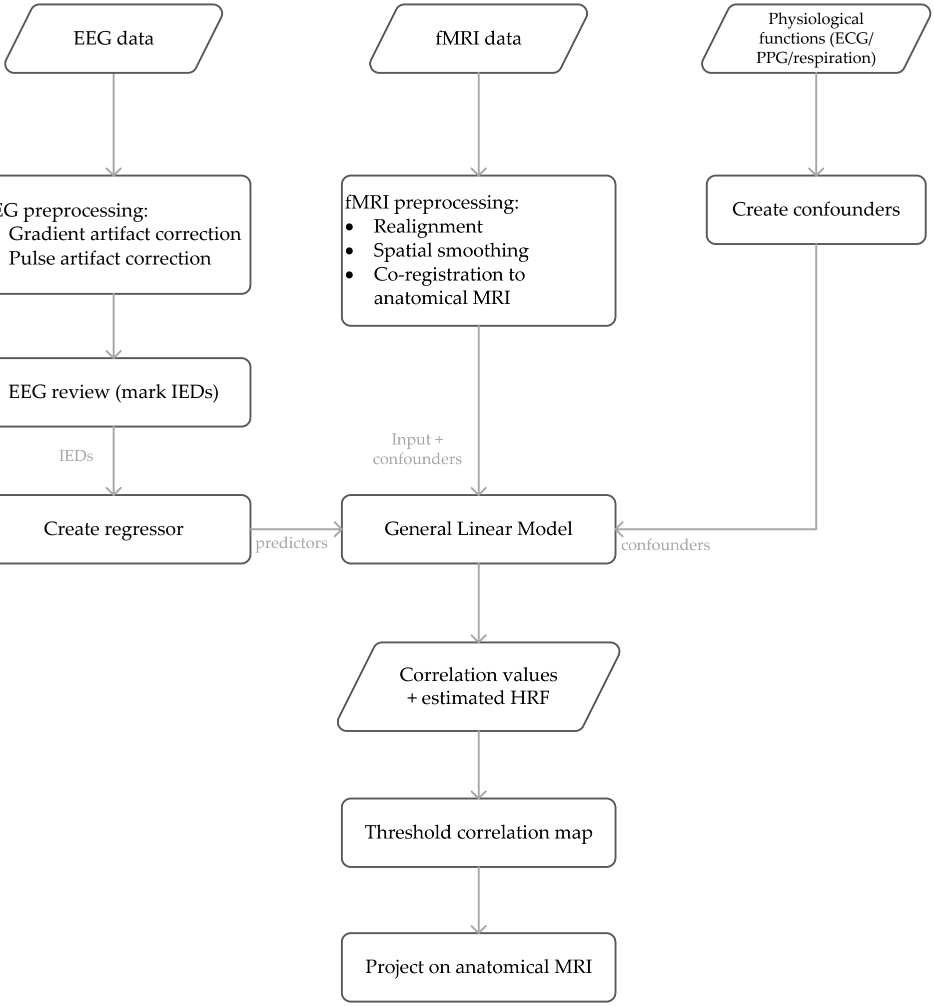

Figure 8.1: General analysis pipeline of the EEG-fMRI data. The first steps are the preprocessing of the EEG and fMRI data. The EEG is reviewed by an EEG technician to determine the moments that IEDs occur. These moments are translated into an IED density function that is used as a predictor in the GLM. The preprocessed fMRI data is used as input for the GLM. From the physiological signals several confounders are extracted such as RETROICOR, heart beat intervals, and VIPH. The GLM yields a correlation value and optionally also an estimation of the HRF for each voxel in the brain. The correlation values are thresholded such that only statistically significantly activated voxels are visible. For visualization, these thresholded maps are projected on an anatomical MRI.

Freyer et al. (2009) have shown that it is possible to record ultrahigh frequencies (up to 1 kHz) with EEG-fMRI by improved scanning strategies and gradient artifact correction algorithms. In principle, the recording of high frequency oscillations (HFO) in epilepsy patients should then also be possible with EEG-fMRI. HFO are a different type of epileptic marker that seem accurate predictors of the seizure onset zone (e.g. Zijlmans et al. 2012; Jacobs et al. 2012; Andrade-Valenca et al. 2011). The advantage of HFO is that their frequency range does not interfere with the frequency of pulse artifacts in the EEG and therefore, no correction is necessary. However, it will be a challenge to separate HFO from muscle and other non cerebral artifacts (Worrell 2012).

The localization and interpretation of EEG-fMRI data may further benefit from imaging at ultra high magnetic fields (7 T) and ultrafast imaging. The latter gives the opportunity to investigate brain activity with a high temporal resolution ($\approx$ 100 ms) (LeVan et al. 2010b; Zahneisen et al. 2011), such that the timing of the HRF makes more sense. This approach may also provide a better understanding of the neurovascular coupling.

8.4 General Conclusion

The general aim of this thesis was to improve and to evaluate the potential of EEG-fMRI as a noninvasive tool in the presurgical evaluation of patients who are candidates for epilepsy surgery. We have shown that the yield of EEG-fMRI increases with the methodological improvements presented in this thesis. Furthermore, the results of EEG-fMRI appear to be clinically relevant, because EEG-fMRI is usually concordant with IEDs in the invasive EEG data and includes the seizure onset zone and resection area. For this reason, there is an important role for EEG-fMRI in the surgical planning, especially with regard to the determination of the implantation strategy. In comparison to other noninvasive techniques in the presurgical evaluation, EEG-fMRI will have an added value in patients in whom multifocal epilepsy or a focus from deep lying structures is expected. In addition, EEG-fMRI is able to reflect the whole network from onset to propagation, which is hardly possible with EEG alone.