A framework to integrate EEG-fMRI with intracerebral recordings


5.1 Introduction

Patients with drug-resistant localization-related epilepsy are potential candidates for surgical resection of the cortical area responsible for the generation of epileptic seizures. Prior to surgery, standard clinical procedures (video-EEG, MRI) and additional noninvasive techniques (magnetoencephalography (MEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT)) are performed to create hypotheses about the areas that are most likely involved in the generation of seizures. In complex cases in which noninvasive results are inconsistent, the standard procedures are followed by intracranial EEG recordings. This technique allows the recording of electrical activity from electrodes on grids or strips at the surface of the brain (ECoG) or from implanted depth electrodes (SEEG). With these invasive techniques only a small part of the brain can be covered and, therefore, a careful selection of the electrode sampling area is crucial for a successful outcome of intracranial investigations.
Recently, EEG-fMRI has been evaluated as a new noninvasive technique for the preoperative work-up (Thornton et al. 2010; Zijlmans et al. 2007). This technique investigates the correlation between IEDs and BOLD changes. The relation between both modalities is described with the HRF, representing the time course of the BOLD effect in response to an increase of electrical brain activity associated with IEDs. Most studies have analyzed the EEG-fMRI data within a GLM framework by extracting an IED density function from the EEG (i.e. representing the occurrence of IEDs) and used it as a regressor of interest after convolution with a standard HRF (e.g. Friston et al. 1998) or estimating the HRF from the data itself (e.g. de Munck et al. 2007; Glover 1999; Lu et al. 2006). As a result, a spatial pattern is obtained indicating the brain areas that are significantly involved during the epileptiform discharges. Compared to high resolution EEG and MEG source localization, EEG-fMRI has the advantage that it enables the visualization of activity from multifocal and deeply situated cortical areas without the use of complicated source reconstruction models. The primary goal of our study is to obtain additional evidence for the relevance of EEG-fMRI to guide the implantation of depth electrodes.

Before EEG-fMRI can be used as an additional diagnostic tool in the preoperative work-up, the added value of the technique should be assessed in relation to invasive EEG as a gold standard. In previous studies, EEG-fMRI has been compared to the clinical interpretation of interictal spikes or to the seizure onset zone determined from ECoG or SEEG recordings (Bénar et al. 2006; Grova et al. 2008; Lazeyras et al. 2000; Thornton et al. 2010b; Tyvaert et al. 2008a; Vulliemoz et al. 2010; Zijlmans et al. 2007; Grouiller et al. 2011; Pittau et al. 2011). These previous results were promising, because they showed good concordance between EEG-fMRI and invasive EEG recordings in most cases. To obtain more evidence for the usefulness of EEG-fMRI to guide the implantation of depth electrodes, the present study attempts to relate EEG-fMRI to the SEEG recordings in a more quantitative and automated way. For that purpose, we assume that the appearance of IEDs in SEEG are associated with increased activity of the epileptic network, resulting in significantly increased mutual correlations of the SEEG signals (Bettus et al. 2008). By formulating this assumption in a GLM framework, standard regression analysis reveals the electrodes that are activated during IEDs. With this proposed method, the only input from the clinician is the timing of the IEDs in the SEEG data, from which the IED density function is constructed that is used as predictor in the GLM. Similar to standard fMRI analysis, results can be visualized by plotting the color-coded correlation coefficients of each SEEG electrode contact onto the structural MRI of the individual patient, once the SEEG electrode positions are known in MRI coordinates.

Previous studies have indicated that the level of concordance is increased between the EEG-fMRI results and the clinical profile of the patient when the EEG-fMRI data are analyzed with a flexible approach in which the HRF is estimated from the data (Lu et al. 2006; van Houdt et al. 2010a). This method also provides information about the
shape of the HRF, which might contain additional information about the activated areas (Lemieux et al. 2008; Lindquist et al. 2007), though the precise interpretation of HRF shapes in relation to epilepsy remains unexplained. For the preoperative work-up, it would be very useful if the HRF shape could be used as an additional indicator for the role of an activated area in the epileptic network.

To explore the validity of this quantitative approach, we use a sample of five patients for whom both EEG-fMRI and SEEG data were available. The EEG-fMRI and SEEG results are projected on the same structural MRI to facilitate a systematic comparison of the results. For clinical validation of EEG-fMRI and SEEG analyses, the results were related to the visual review of the IEDs in the SEEG data and to the identified seizure onset zone, resected area and postoperative outcome.

5.2 Methods

5.2.1 Patients

Patients who were candidates for depth recordings in Kempenhaeghe (Heeze, the Netherlands) were asked to participate in the EEG-fMRI study if they met the following criteria: (1) sufficient number of IEDs present in awake EEG recordings. Patients with a very low spike rate (<15 h⁻¹) or very high spike rate (>300 h⁻¹) were excluded from the study; (2) video-EEG monitoring indicated a localized scalp EEG. Of the six patients who agreed to participate in the study, one patient was excluded, because no IEDs were present during EEG-fMRI. The electroclinical and neuroimaging data of the five patients included in the study (3 male, age 39.8 ± 9.5 years) are summarized in Table 5.1. Extensive presurgical assessment was performed in Kempenhaeghe including a structural 3 T MRI confirming anatomical abnormalities (Table 5.1, column 3) and long-term video-EEG monitoring. The hypotheses based on presurgical assessment with regard to the location of the epileptogenic zone (column 4) guided the decision for the placement of the depth electrodes (see for example left upper panel of Figure 5.4).

The EEG-fMRI study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and the local committee of Kempenhaeghe. All patients gave informed consent for the study. Patients were notified that the EEG-fMRI study was not part of the standard presurgical evaluation and that it did not influence any of the clinical decisions, such as the implantation of the electrodes or surgical resection. During the EEG-fMRI study, the patients were on maintenance doses of their habitual AEDs.
Table 5.1: Summary of patient clinical data: age, gender, MRI abnormalities, electroclinical hypotheses prior to implantation of the depth electrodes, location of seizure onset zone based on visual interpretation of the clinical neurophysiologist (A.C.), location of resected area, and postoperative results. The last two columns describe the location of the positive HRF clusters as determined with EEG-fMRI and the location of the most active electrode contacts determined with the automatic interictal SEEG analysis. Abbreviations: MTS = multiple temporal sclerosis; R = right; L = left; T = temporal; F = frontal; O = occipital; P = parietal; m = mesial.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/gender</th>
<th>MRI abnormalities</th>
<th>Electroclinical hypothesis</th>
<th>Seizure onset zone</th>
<th>Resected area</th>
<th>Seizure free (# months)</th>
<th>EEG-fMRI (positive HRF)</th>
<th>Interictal SEEG</th>
</tr>
</thead>
</table>
| Patient 1 | 24/male | MTS L; infarct O-L | • T-L  
• O-L  
• mT-L | mT-L | T-L | Yes (17) | T-L | T-L |
| Patient 2 | 39/male | Heterotopia O-L and O-R; cortical dysplasia T-R | • T-R  
• O-R (heterotopia) | T-R | T-R | Yes (21) | T-R; O-R | T-R |
| Patient 3 | 48/male | Infarction posterior cerebral artery R | • mPO-R  
• T-R  
• Lateral to infarct | mPO-R | mPO-R | Yes (9) | TO-R | PO-R; T-R |
| Patient 4 | 42/female | Porencephalic cyst TP-R; MTS R | • Insula and lateral to cyst  
• mT-R | Insula R; T-R | Insula R; T-R | Yes (7) | T-R; P-R; T-R | T-R; P-R |
| Patient 5 | 46/female | MTS L | • Lateral T-L (Heschl's gyri)  
• Other T-L  
• P-L  
• Insula L | T-L | T-L | Yes (5) | P-L | T-L |
5.2. Methods

5.2.2 Data acquisition

EEG-fMRI recordings

All patients underwent EEG-fMRI in a 3 T Achieva MR scanner (Philips Medical Systems, Best, The Netherlands) while they were asked to lie relaxed with their eyes closed for about 45 min. All patients stayed awake during the recording. Functional images were acquired using a $T_2^*$-weighted EPI sequence (TR 2.5 s, TE 35 ms, flip angle 90°, reconstructed voxel size $3.2 \times 3.2 \times 3$ mm$^3$, 31 or 33 adjacent slices, bottom-to-top slice order). Simultaneously, EEG data were acquired with an MR-compatible EEG amplifier (MicroMed, Treviso, Italy) and a cap providing 64 electrodes positioned according to an extended 10-20 system (sampling rate = 2048 Hz). A bipolar ECG was co-registered. A $T_1$-weighted anatomical scan was made using a spin-echo acquisition (reconstructed voxel size $1 \times 1 \times 1$ mm$^3$, multi slice acquisition of 170 slices, TR 8.4 ms, TE 3.9 ms, flip angle 90°).

SEEG recordings

Each patient was implanted with several platinum depth electrodes (DIXI medical, Besancon, France) according to the hypotheses regarding the epileptogenic zone based on available noninvasive electroclinical information as summarized in Table 5.1 (column 4). These electrodes had 5 to 18 contacts of 2 mm each that were 1.5 mm apart. The diameter of the electrodes was 0.8 mm. Besides depth electrodes, subdural strips (4 - 8 contacts) were placed in patient 1 and 5. The implantation was performed at the University Hospital Maastricht. A computed tomography (CT) and structural MRI scan (1.5 T MR scanner, Philips Medical Systems, Best, The Netherlands) were acquired to verify the positions of the electrodes and the absence of local bleedings. When no further complications occurred, the long-term recording was performed at Kempenhaeghe. Data were recorded at a sample rate of 600 Hz (Stellate Harmony 6.1C, Natus Medical Inc., San Carlos, USA). For the purpose of this study, an epoch of 15 min was selected that was representative for the interictal epileptiform activity present in the data. During this selected period the patient was awake and no seizure occurred within 2 h of the selection. The data were further processed in a bipolar montage derived from contiguous contacts of the same electrode following the procedures as reported by Bettus et al. (2008). The data were filtered between 1 and 80 Hz.

5.2.3 EEG-fMRI analysis

Both EEG and fMRI data were analyzed using Brain Imaging Analysis Package$^2$. First, EEG data were corrected offline for gradient and ballistocardiographic artifacts

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$^2$http://demunck.info/software/
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according to the methods presented by Gonçalves et al. (2007). Thereafter, the corrected EEG was examined by an experienced EEG specialist who identified the presence of IEDs (spikes, sharp waves, or interictal paroxysms). An IED density function was created indicating the number of IEDs per fMRI scan.

The fMRI data were realigned to the first image, matched to the anatomical scan, and spatially smoothed with a Gaussian kernel with a standard deviation of 5 mm. Data points where the fMRI data were disturbed by abrupt head movements (more than 0.5 mm or 0.5° based on the realignment parameters) were excluded from the time series. Next, the correlation of fMRI signals with the IED density function was modeled within a single GLM using an unknown finite impulse response function representing an estimation of the HRF (de Munck et al. 2007; van Houdt et al. 2010a). In this model, the IED density function and shifted versions of that regressor were included as predictors. The shifted versions were used to account for possible delayed responses of fMRI starting at -4 times TR (i.e. 10 s before the IED was present in the EEG) to +8 times TR (i.e. 20 s after the onset of the IED). For each predictor a coefficient was estimated. Together these coefficients represent an estimation of the HRF corresponding to the observed IEDs. The following confounders were included in the GLM: six motion regressors resulting from realignment, a constant, linear and quadratic trend, six RETROICOR regressors of heart beat (Glover et al. 2000), and thirteen shifted versions of the heart beat intervals (de Munck et al. 2008). An F-test was performed to determine the significance of the parameters of interest accounting for the number of estimated parameters, the number of nuisance effects and the number of data points. The resulting p-values were converted to an FDR, which was used to threshold the statistical maps (Genovese et al. 2002). Finally, the estimated HRFs were clustered using a hierarchical cluster analysis based on similarity of morphology of the HRFs (de Munck et al. 2008). The cluster analysis visualizes potential differences in HRF within regions of significant BOLD activity. For that purpose, a distance table was computed consisting of the distances between estimated response curves of significantly activated voxels (FDR < 5 %). Voxels corresponding to the same cluster were represented with the same color and one average HRF. The number of clusters was determined by visual inspection and truncated when further subdividing did not yield more variation.

5.2.4 SEEG analysis

An analytical approach was developed for the analysis of SEEG data that revealed a spatial pattern indicating the electrode contacts that reflected highly synchronized activity during IEDs observed in the data. The approach is based on the assumption that the mutual correlations between electrodes are increased during epileptiform activity (Bettus et al. 2008). Therefore, the correlation between two electrode contacts was estimated using a nonlinear association analysis (Lopes da Silva et al. 1989; Pijn et al. 1990; Wendling et al. 2001; Westmijse et al. 2009) for non-overlapping
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Windows with a length of TR (= 2.5 s). This method takes both linear and nonlinear relationships between signals into account. The choice of the window length is a compromise between the signal-to-noise ratio and temporal resolution. In our SEEG analysis, a window of 2.5 s was chosen, which is of the same order as in the study of Bettus et al. (2008) and results in a time scale comparable to that of fMRI. For each window \( k \), the nonlinear association \( h_{ij}^2(k \cdot TR, k \cdot TR + \tau) \) was calculated between electrode \( i \) and electrode \( j \), where the signal of \( j \) is shifted with delay \( \tau \) (1/fs s) with respect to the signal of \( i \) [equation (5.1)]. \( h_{ij}^2(k) \) is defined as the maximal association over all delays for window \( k \).

\[
h_{ij}^2(k) = \max_{\tau} \left[ h_{ij}^2(k \cdot TR, k \cdot TR + \tau) \right], \quad -\tau_{\text{max}} \leq \tau \leq \tau_{\text{max}}, \quad 0 \leq k \leq K - 1 \tag{5.1}
\]

\( \tau_{\text{max}} = 150 \text{ ms} \) and \( K \) is equal to the number of windows depending on the length of the selected data. The computation of \( h_{ij}^2(k) \) for all combinations of electrode contacts was implemented in Matlab (R2009a, The Mathworks, Inc.) using several functions of the FieldTrip toolbox (Oostenveld et al. 2011). Averaging of the values for electrode \( i \) with all other electrodes yields an association strength function as shown in equation (5.2), similar to the indices as presented by Barrat et al. (2004) and Ortega et al. (2008).

\[
\text{Strength}_i(k) = \frac{1}{N-1} \sum_{j=1,j\neq i}^{N} h_{ij}^2(k), \quad 0 \leq k \leq K - 1 \tag{5.2}
\]

The association strength of a single electrode contact reflects the changes in association over time relative to the other electrode contacts. The underlying assumption is that the association strength is higher when an electrode is involved in the generation of epileptiform activity.

IEDs were identified by visual inspection of the SEEG data by an experienced reviewer. An IED density function was created reflecting for each window the number of IEDs. Separate IED density functions were created when the data contained multiple IEDs with different topographical distributions. Figure 5.1 shows, for a data set with a single IED-type (patient 2), the relation between the IED density function, the computed correlations \( h_{ij}^2(k) \), and the association strength \( \text{Strength}_i(k) \). For this patient, IEDs were visible on electrodes \( p \) and \( q \), but not on electrode \( r \) (Figure 5.1a). The extracted IED density function is shown in Figure 5.1b. Figure 5.1c shows the computed association between electrode \( p \) and \( q \) (\( h_{pq}^2(k) \) in blue) and \( p \) and \( r \) (\( h_{pr}^2(k) \) in green). There is a relatively high (direct) correlation between the IED density function and \( h_{ij}^2(k) \) when IEDs are present on both signals (\( R^2 = 0.45 \) for \( h_{pq}^2(k) \)), while the correlation is low when IEDs are present on only one of the two (\( R^2 = 0.08 \) for \( h_{pr}^2(k) \)). Figure 5.1d shows that there is also a strong direct
Figure 5.1: Illustration of SEEG analysis using the data of patient 2. (a) shows an epoch of ten seconds of the selected SEEG data for that patient. (b) is an example of an epileptiform density function indicating for each window of 2.5 s how many IEDs were present. (c) illustrates the result of the nonlinear association analysis for the combination of electrodes \( p \) and \( q \) in blue and for the combination of \( p \) and \( r \) in green. \( R^2 \) indicates the correlation coefficient between the nonlinear association values and the IED density function. In (d) an example of the association strength is shown in red for electrode \( p \) that results from averaging the association of that electrode with all other electrodes (blue lines). \( R^2 \) now indicates the correlation coefficient between the association strength and the IED density function.

correlation \( R^2 = 0.46 \) between \( \text{Strength}_p (k) \) (in red) and the IED density function. However, due to averaging the values of the association strength are lower than the values of \( h_{ij}^2 (k) \) (in blue).

The relation between association strength and IEDs is formalized within the GLM framework in order to quantify the variations in \( \text{Strength}_i (k) \) that are exclusively related to IEDs. Similar to the GLM formulation for EEG-fMRI analysis we use...
\[ \mathbf{d} = X \mathbf{h} + S \phi + \mathbf{\varepsilon} \] (5.3)

In this case, \( \mathbf{d} \) represents the association strength; \( X \) is the design matrix consisting of the regressors of interest: the IED density function from the SEEG data and its shifted versions. The IED density function is shifted with the same time intervals as in the EEG-IMRI analysis (i.e. -10 to 20 s after IED onset) to enable the comparison of EEG-IMRI and SEEG at the same time scales. \( \mathbf{h} \) are the coefficients corresponding to each shifted version of the IED density function, together they represent an IRF. If the association strengths at different electrodes appear to be the main explanatory factor for observed differences in HRF then the convolution of these IRFs with a standard canonical HRF should match these differences. The confounders \( S \) consist of a constant, a linear, and quadratic trend, while \( \phi \) are the corresponding coefficients and \( \mathbf{\varepsilon} \) is the vector of assumed uncorrelated noise. If multiple IED-types were present in the data, a regression analysis was performed separately for each IED-type, and the other density functions were included as confounders in the model. An F-test was applied to yield a correlation value and a \( p \)-value for each electrode that could be compared to the EEG-IMRI results. The correlation values indicate the contribution of each electrode to the IEDs detected in the SEEG data relative to the other electrodes. The \( p \)-values were transformed in FDR values to correct for the number of electrodes.

5.2.5 Visualization of SEEG results

A semi-automatic procedure was developed for the visualization of the SEEG results (Figure 5.2). First, the post-implantation MRI and CT were matched upon the pre-implantation MRI acquired during the EEG-IMRI procedure. The post-implantation MRI clearly showed the trajectories of the implanted electrodes (Figure 5.2a). These trajectories were manually indicated by drawing points in different slices of the post-implantation MRI (yellow dots in Figure 5.2b). Special attention was paid to indicate the tip of the electrode as accurately as possible verified visually at the CT. Thereafter, a line was fitted through this point cloud (Figure 5.2c). Since the distance between the contact points on the electrodes is fixed and the tip of the electrode was indicated, the coordinates of the center of each electrode contact could be estimated from their distance to the tip along the fitted line. Mathematical details about the estimation of the line and coordinates of the electrodes are described in Appendix A. The coordinates were visualized by dots on the pre-implantation MRI (Figure 5.2d), using a certain tolerance level (in mm) with respect to the selected slice. Since a bipolar montage was used, the result of each bipolar derivation was plotted in the middle of the two contiguous electrodes. The correlation values were visualized with color-coded dots for each electrode contact, yielding the spatial correlation pattern of the IEDs occurring in the SEEG data (Figure 5.2d). This spatial correlation pattern represents the contribution of all electrodes to the IEDs in the SEEG.
data. An FDR threshold of 5% was applied to visualize only significant correlations. Nonsignificant correlations were indicated by black dots.

5.3 Results

Both EEG-fMRI and SEEG analysis yield a spatial pattern indicating the brain areas that show changes during the occurrence of IEDs of the patient. The results of these analyses were related to the results of the standard clinical examination of IEDs recorded in the SEEG data and to the clinical profile of each patient, i.e., seizure onset zone, resected area, and postoperative outcome (columns 5, 6 and 7, Table 5.1). For example, for patient 1, left frontotemporal spikes were recorded during EEG-fMRI (Figure 5.3a). Correlation of the events with the fMRI data mainly resulted in a large activated area in the left temporal lobe (Figure 5.3b). Clustering of the HRFs of these significantly activated voxels revealed three distinct clusters as depicted color-coded in Figure 5.3c. The cluster with the most pronounced HRF (red cluster) included the left neocortical temporal area and hippocampus. From the available electroclinical and anatomical investigations, there was a suspicion of a left mesial temporal focus. However, the patient also had an occipital lesion. To exclude the involvement of this lesion, five electrodes were implanted in the left occipital lobe (LB, LL, LM, LO, LS, Figure 5.3e) and one through the hippocampus (LH); different colors indicate different electrodes. Figure 5.3d shows a representative example of the interictal SEEG data illustrating the IEDs that were mainly present at the hippocampal electrode. The results of the quantitative SEEG analysis indicates that the correlations
for the electrodes in the hippocampus were higher than for the electrodes in the occipital lobe (Figure 5.3f). Since the same analysis as for EEG-fMRI was used, an IRF was estimated for each electrode contact. Note that the IRFs were consistent over electrodes and that the responses mainly changed in the window of 0 s (in which the IED occurred; insert in Figure 5.3f). According to the ictal SEEG data, the seizure onset zone was located in the left temporal region (A.C.; column 5, Table 5.1). Therefore, a left temporal resection was performed (column 6, Table 5.1; white contour line in Figure 5.3b, c and f), which rendered the patient seizure-free (follow-up of 17 months, column 7, Table 5.1). EEG-fMRI supported these clinical findings, because no significant activations were revealed in the occipital region. In particular the positive HRF cluster depicted in red was located partially within the resected area.

The results of the other four patients are summarized in Figure 5.4 to 5.7. The upper panel of each figure illustrates the implantation of the electrodes as based on the electroclinical hypotheses of each patient (Table 5.1). Representative examples of SEEG recordings were chosen to illustrate the visually identified IEDs. The location and number of these IEDs are indicated between brackets in the legend of the implantation figures. A brace means that IEDs were simultaneously present on electrode contacts of different depth electrodes. An asterisk in the legend indicates that the regression analysis for that IED-type revealed significant correlations. The bottom panel of each figure illustrates the EEG-fMRI and SEEG spatial patterns for the same slices. These slices were selected in such a way that they show all significant areas obtained with EEG-fMRI and all significantly active electrodes as yielded by SEEG analysis. The “warm” colors (red, yellow) in the EEG-fMRI figure indicate clusters with a positive peak in the shape of the HRF, further referred as “positive HRF “, whereas “cold” colors (blue, green) indicate clusters with a negative peak in the HRF, referred as “negative HRF “. The resected area is indicated with a white contour line in both figures.

To determine the seizure onset zone of patient 2, six depth electrodes were implanted in the right temporal and occipital regions for this patient (Figure 5.4). In the SEEG recordings, three different IED-types were identified of which two are indicated in the recording shown in Figure 5.4. Only five useful minutes of SEEG data were available for the automatic analysis during which the patient was awake and IEDs were present. The IEDs were abundant during sleep, but too frequent for a successful regression analysis. The IEDs simultaneously present at the RH, RSL, RSA, and RSP electrodes were less frequent than the other types (#7 vs. #13 and #24), but much more generalized and dominant in amplitude. For this IED-type, the regression analysis revealed significant correlations, which were present at the temporal electrode contacts. According to the ictal SEEG data, the seizure onset zone was identified in the right temporal region. Therefore, a right temporal resection was performed, which rendered the patient seizure free (follow-up of 21 months). The resected area overlaps with both the most active SEEG electrodes and with a
Figure 5.3: EEG-fMRI and SEEG results of patient 1. Correlation of the IEDs (a) resulted in significant activations in the left temporal lobe (b). Clustering yielded three different clusters where the cluster with the most pronounced HRF corresponded to activations in the left temporal neocortical focus and left hippocampus (c). The white contour line indicates the resected area. Six depth electrodes were implanted. A representative epoch of the IEDs is shown in (d), while the spatial orientation of the electrodes is visualized in (e); different colors represent different depth electrodes, which were plotted with a tolerance level of 5 mm. The legend indicates between brackets the number of IEDs that were present on the LH depth electrode. (f) illustrates the significant correlation pattern revealed by the regression analysis for those IEDs. Furthermore, the insert in (f) shows the IRFs for the electrode contacts that were significantly active during IEDs.
Results

Positive HRF cluster (indicated in red). However, the EEG-fMRI and SEEG results are more widespread than the resected area. In fact, EEG-fMRI also revealed a positive HRF cluster in the right occipital lobe and negatively activated voxels that seem to be scattered through the brain or located outside brain tissue. Furthermore, the EEG-fMRI results were shifted relative to the spatial correlation pattern of the interictal SEEG data.

For patient 3 (Figure 5.5), EEG-fMRI revealed one large cluster with a positive HRF posterior to the lesion and negative HRF clusters mainly in the left and right occipital lobes. According to the clinical hypotheses for this patient, depth electrodes were implanted in the right hemisphere (n = 8) and in the left temporal lobe through the hippocampus (n = 1). Multiple IED-types were identified in the selected SEEG data (Figure 5.5), but a significant correlation pattern was only obtained for three of them (IEDs at RZ+RO, at LH, and at RH). Figure 5.5 shows the spatial correlation pattern of the IEDs simultaneously present at RZ and RO. Comparison with the SEEG recordings illustrates that the maximal correlations (at RZ and RO) coincided with the electrode contacts showing maximal amplitude. The positive HRF cluster of EEG-fMRI partially corresponded to the spatial pattern of the IEDs recorded at the RZ and RO electrodes; no depth electrode was positioned exactly through the positive HRF cluster, but the surrounding electrode contacts were active during IEDs. However, the electrode contacts with the highest correlation values were located more occipitally and within the resected area. The EEG-fMRI area was located exactly at the edge of the resection. The patient has been seizure-free for 9 months now.

For patient 4 (Figure 5.6), EEG-fMRI yielded a positive HRF cluster posterior to the lesion (in right insula) that extended to the right temporal lobe (red cluster). A negative cluster was obtained in the contralateral temporal lobe together with some small negative clusters spread throughout the brain (mainly at the edges). This patient was implanted with nine electrodes; two major IED-types were visible in the SEEG recordings (at RO and RP, and at RH). The automated SEEG analysis revealed for both types a spatial pattern that shows the same maxima as identified visually from these recordings. Figure 5.6 shows that the positive HRF cluster corresponded well to these spatial correlation patterns. The seizure onset zone was located in the right temporal region and extended to the right insula. Resection of this area rendered the patient seizure-free (follow-up 7 months). In addition, the area with positive HRF was located within the resected area and at the edge of the resection.

For patient 5 (Figure 5.7), left parietal IEDs in the EEG revealed a positive HRF cluster in the left parietal lobe, while small negative clusters were present in the left and right temporal lobe, left and right occipital lobe, and right frontal lobe. The patient was implanted with twelve depth electrodes and subdural strips. Large IEDs were simultaneously present at the LH and LST contacts, while IEDs with a lower amplitude were visible at electrode LST, LSO, and LE. A spatial pattern was obtained for the dominant IEDs (LH+LST) with the automated analysis showing significant
Figure 5.4: Summary of the results of patient 2. The upper plot shows the location of the three implanted depth electrodes (RM, RL, and RH) and three subdural strips (RSL, RSP, and RSA) and a representative example of their recordings; different colors indicate different needles (tolerance level of 6 mm). The legend indicates between brackets the number of IEDs that were present on a certain electrode. A brace means that these IEDs were simultaneously present on multiple electrodes. An asterisk indicates that the results of the regression analysis were significant for that type. The lower plot represents the spatial patterns obtained with EEG-fMRI (top) and SEEG (bottom), showing that there is an overlap between the EEG-fMRI area in the right temporal lobe (red cluster) and the active depth electrodes indicated in yellow. The number and location of IEDs is given in the corner of the EEG-fMRI and SEEG figures. Abbreviations: T-R = right temporal.
Figure 5.5: Summary of the results of patient 3. The upper plot shows the location of the nine implanted depth electrodes (tolerance level of 6 mm). The lower plot illustrates that the positively activated area in the right temporo-occipital lobe determined with EEG-fMRI (in red) is surrounded by active depth electrodes. For a detailed description of the figure we refer to the legend of Figure 5.4. Abbreviations: TO-R = right temporo-occipital.
Figure 5.6: Summary of the results of patient 4. The upper plot shows the location of the nine implanted depth electrodes (tolerance level of 6 mm). From the lower plot it can be concluded that the positively activated EEG-fMRI area (in red) from the insula to the temporal lobe is concordant with the active electrodes determined with SEEG analysis. For a detailed description of the figure we refer to the legend of Figure 5.4. Abbreviations: FT-R = right fronto-temporal.
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Figure 5.7: Summary of the results of patient 5. The upper plot shows the location of the seven implanted depth electrodes (LE, LH, LS, LO, LX, LY, RH) and 5 subdural strips (LST, LSP, LSO, RSL, and RSB) with a tolerance level of 6 mm. The lower plot indicates that there is no concordance between the EEG-fMRI areas and the active depth electrodes. For a detailed description of the figure we refer to the legend of Figure 5.4. Abbreviations: TP-L = left parieto-temporal.

correlations at the LH and LY electrodes. No regions of significant BOLD were found in the vicinity of these active electrodes. For this patient, a right temporal resection was performed, but the postoperative MRI and postoperative outcome are not available yet. However, the HRF clusters will most certainly not be located within the resected area. After surgery, the patient appeared to be seizure-free (follow-up of 5 months), but auras have re-occurred.

To summarize, the EEG-fMRI results indicated that multiple activated BOLD areas were obtained in all patients. Clustering of the HRFs showed that the HRF is similar
within neighboring voxels. For four of the five patients (patient 1-4), at least one area was located close to or overlapping with active electrodes determined from SEEG, which were areas with a positive HRF. The areas of significant BOLD that were not located in the vicinity of depth electrodes, were mainly characterized by negative HRFs. These results are summarized in the last two columns of Table 5.1, where the location of the positive HRF clusters (column 8) and most active depth electrode contacts (column 9) were determined at lobar level, showing concordance between EEG-fMRI and interictal SEEG for four of the five patients. This table also illustrates that the positive HRF cluster confirmed at least one of the electroclinical hypotheses for all patients. In addition, these HRF clusters were located near the seizure onset zone and within the resected area in three of the five patients.

5.4 Discussion

Our results provide further evidence that EEG-fMRI is a valuable additional tool in the preoperative work-up, especially to guide the implantation of depth electrodes. Contrary to earlier studies (Bénar et al. 2006; Grova et al. 2008; Pittau et al. 2011), in this study the concordance of EEG-fMRI and intracranial EEG data is based on a quantitative statistical analysis of SEEG signals that reveals a spatial correlation pattern of IEDs present in these data. In four out of five patients, the EEG-fMRI areas correspond with the IEDs recorded from depth electrodes, as determined from the analysis of SEEG recordings. Especially the results of patient 1 illustrate that with EEG-fMRI it is possible to answer clinical questions (i.e. the exclusion of the occipital lesional area as epileptic focus) that could not be answered with other noninvasive techniques. The discordance in patient 5 might be explained by a weak representation of mesial temporal spikes on scalp EEG. During EEG-fMRI usually one (dominant) type of IEDs is present, whereas in SEEG multiple types of IEDs can be identified. Therefore, EEG-fMRI does not always give a complete picture of the irritative zone, as identified by the SEEG recordings. For all patients, the most likely epileptogenic zone was located in the same area as the irritative zone, which further supports the use of EEG-fMRI in clinical practice. However, the relatively short postoperative follow-up time prevents final conclusions with regard to the epileptogenic zone in all patients.

The procedures developed in this study to assess the concordance between EEG-fMRI and SEEG data contains several novel elements. First, we developed a strategy for the quantitative analysis of IEDs in the SEEG data such that these data are analyzed within the same GLM framework at the same spatiotemporal domain as the EEG-fMRI data. The method is based on the assumption that the appearance of IEDs in the SEEG data are associated with increased activity of the epileptic network. The nonlinear association analysis, which was used to quantify the mutual coupling between underlying brain regions, has previously been used to investigate the propagation
5.4. Discussion

of seizures (Arthuis et al. 2009; Bartolomei et al. 2001; Meeren et al. 2002; Westmijse et al. 2009). Our results suggest that this method is also useful to reveal information about IEDs, even at a relatively large time scale, which is also supported by the results of Bettus et al. (2008). However, other (non)linear methods to quantify the relation between signals, such as mutual information or phase coherence (e.g. Ortega et al. 2008; Stam 2005), might have been appropriate as well.

Although the SEEG recordings contain clinically more relevant information (i.e. seizures), we specifically investigated the IEDs for the validation of EEG-fMRI results and applied a regression analysis to contrast changes in correlation pattern during IEDs against background activity. The advantage of this approach is that only temporal information of IEDs in the SEEG data is required. When multiple IED-types are present in the data one of them is treated as predictor and the others are treated as confounders, resulting in a spatial pattern of significant correlation values for each IED-type. In practice, this approach appears to reveal a statistically significant spatial pattern for the most dominant and frequently occurring IED-types that corresponds to the electrode contacts active during IEDs as was visually determined during the clinical examination of the SEEG recordings. A significant spatial pattern was usually not found for IED-types that were less frequent relative to the other IED-types or those that were masked in amplitude by other more dominant IED-types. Since it will be likely that the most dominant and frequent IEDs in the SEEG data also occur in the scalp EEG during fMRI, we consider the current version of our model well suitable for validation of EEG-fMRI spatial patterns. However, extensions of the model are needed for a quantitative assessment of clinical SEEG data. For example, it could be useful to calculate the association strength only for neighboring electrodes as was proposed by Ortega et al. (2008).

In addition, the visualization of the EEG-fMRI results was improved, because the cluster algorithm enabled the combination of the spatial (i.e. correlation pattern) and temporal information (i.e. estimated HRF for each voxel) in a single image. Although the cluster algorithm did not use the spatial origin as a priori information, our results indicate that neighboring voxels show similar HRFs. We consider our approach, which requires only one step to reveal spatial information and the shape of the HRF, as a particular advantage compared to other commonly used methods that require several subsequent steps (e.g. Bagshaw et al. 2005; Jacobs et al. 2008).

Our results indicate that the variation in shape of the HRF is large between subjects. The sign of the HRF was the only parameter which we observed to be consistent among the concordant HRF clusters for the five patients studied. We did not investigate other HRF parameters [e.g. time-to-peak and amplitude (Lindquist et al. 2007)], because our population was too small for a systematic comparison. Nevertheless, our results are in line with other studies which suggest that the positively activated BOLD areas are most likely related to the focus (Lemieux et al. 2008; Moeller et al. 2009; Salek-Haddadi et al. 2006). This issue is still under debate,
because negative BOLD responses have also been reported close to the epileptogenic foci (Bénar et al. 2006; Kobayashi et al. 2006c; Rathakrishnan et al. 2010; Vulliemoz et al. 2009). It was not possible to systematically investigate the relationship between positive and negative HRF clusters, because the regions with negative HRF did not lie within the vicinity of depth electrodes for most of our data sets. Therefore, prospective studies are necessary to investigate whether both positive and negative HRFs are directly related to IEDs.

Furthermore, we observed that the variations in HRF are not accompanied by similar variations in the IRFs of the SEEG data for the five patients studied. The IRFs, shown in Figure 5.3 for one patient, were consistent across the five patients and demonstrate that the statistically significant responses were similar for different electrodes and all had a maximal response occurring in the windows of 0 s. If differences in HRF observed with EEG-fMRI would be exclusively explained by differences in underlying nonlinear association patterns in SEEG data, the IRFs of SEEG would show similar variations. However, all IRFs were similar for different electrodes, and, therefore, other explanations for the differences in HRF should be raised, such as the underlying neurovascular anatomy (Handwerker et al. 2004). Another possibility is that differences in HRF are associated with timing information of the SEEG data on a very short time scale. To investigate this possibility in future research, the developed method can be extended by using the time delays $\tau_{ij}(k)$ in equation (5.1), for instance as in the studies of Wendling et al. (2001) and Bartolomei et al. (2008).

5.4.1 Conclusions

This study systematically compared results of EEG-fMRI and SEEG by analyzing both modalities within the same spatiotemporal domain and by projecting the results on the anatomical MRI of the patient. The SEEG analysis revealed a spatial correlation pattern of the most frequent and dominant IEDs, while clustering of the HRFs in EEG-fMRI data enabled the visualization of differences in shape of the HRF across the brain. Therefore, our approach is a promising way to systematically compare EEG-fMRI and invasive EEG recordings, and is potentially a valuable tool for the validation of EEG-fMRI in larger patient populations.

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Appendix

The points that indicate the trajectory of a depth electrode do not form an exact straight line due to the manual selection of these points (Figure 5.2c). A line can be fitted through the point cloud assuming that noise is introduced in each direction. Therefore, this is a total least squares problem that can be solved by a singular value decomposition. For that purpose, a matrix \( X \) was created from the coordinates of the points, where each column represented either the x, y, or z-coordinate of the points, and with \( n \) rows according to the number of points that were selected. The line was expressed using a parametric representation (equation (A.1)).

\[
\begin{pmatrix}
x \\
y \\
z
\end{pmatrix}
= \begin{pmatrix}
m_1 \\
m_2 \\
m_3
\end{pmatrix} + \lambda \begin{pmatrix}
p_1 \\
p_2 \\
p_3
\end{pmatrix}
\] (A.1)

The coordinates of \( m \) represent an arbitrary point on the line; we chose the mean of the point cloud. Vector \( p \) represents the direction vector of the line. Therefore, the coordinates of a particular point on the line are specified by \( \lambda \). In this problem, the values of vector \( p \) were determined by calculating the maximal singular value of the matrix \( X \) where \( m \) is subtracted off (equation (A.2))

\[
W = \left[ X(:, 1) - m_1 \ X(:, 2) - m_2 \ X(:, 3) - m_3 \right] \\
A = \frac{1}{n} \cdot W^T \cdot W
\] (A.2)

Once the equation of the line is known, the coordinates of the contacts (\( = \) center of each contact) on that line can be determined. To estimate the coordinates of the first contact, a point on the line was found closest to the point in the cloud that was indicated as the tip of the electrode. These coordinates \((x_1, y_1, z_1)\) were used to calculate \( \lambda_1 \) from equation (A.1). Thereafter, the distance \( D \) between the centers of two contacts \((= 3.5 \text{ mm})\) was used to calculate \( \lambda_2 \) for the second contact as illustrated in equation (A.3).

\[
|\lambda_2 p| = |\lambda_1 p| + D
\] (A.3)

This process was repeated until the coordinates of all contacts on that electrode were determined.