EEG-fMRI correlation patterns in the presurgical evaluation of focal epilepsy: A comparison with electrocorticographic data and surgical outcome measures

Petra J. van Houdt a,b, Jan C. de Munck b, Frans S.S. Leijten c, Geertjan J.M. Huiskamp c, Albert J. Colon d, Paul A.J.M. Boon a, Pauly P.W. Ossenblok e,*

a Department of Research and Development, Kempenhaeghe, Sterkselseweg 65, 5591 VE Heeze, The Netherlands
b Department of Physics and Medical Technology, VU University Medical Center, De Boelelaan 1181, 1081 HV Amsterdam, The Netherlands
c Department of Clinical Neurophysiology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
d Department of Research and Development, Kempenhaeghe, Sterkselseweg 65, 5591 VE Heeze, The Netherlands
e Department of Clinical Physics, Kempenhaeghe, Sterkselseweg 65, 5591 VE, The Netherlands

A R T I C L E  I N F O

Article history:
Accepted 9 February 2013
Available online 26 February 2013

Keywords:
EEG-fMRI
BOLD
Intracranial EEG
Electrocorticography
Epilepsy surgery
Interictal spikes

A B S T R A C T

EEG-correlated functional MRI (EEG-fMRI) visualizes brain regions associated with interictal epileptiform discharges (IEDs). This technique images the epileptiform network, including multifocal, superficial and deeply situated cortical areas. To understand the role of EEG-fMRI in presurgical evaluation, its results should be validated relative to a gold standard. For that purpose, EEG-fMRI data were acquired for a heterogeneous group of surgical candidates (n = 16) who were later implanted with subdural grids and strips (ECOG). The EEG-fMRI correlation patterns were systematically compared with brain areas involved in IEDs ECoG, using a semi-automatic analysis method, as well as to the seizure onset zone, resected area, and degree of seizure freedom. In each patient at least one of the EEG-fMRI areas was concordant with an interictally active ECoG area, always including the early onset area of IEDs in the ECoG data. This confirms that EEG-fMRI reflects a pattern of onset and propagation of epileptic activity. At group level, 76% of the BOLD regions that were covered with subdural grids, were concordant with interictally active ECoG electrodes. Due to limited spatial sampling, 51% of the BOLD regions were not covered with electrodes and could, therefore, not be validated. From an ECoG perspective it appeared that 29% of the interictally active ECoG regions were missed by EEG-fMRI and that 68% of the brain regions were correctly identified as inactive with EEG-fMRI. Furthermore, EEG-fMRI areas included the complete seizure onset zone in 83% and resected area in 93% of the data sets. No clear distinction was found between patients with a good or poor surgical outcome: in both patient groups, EEG-fMRI correlation patterns were found that were either focal or widespread. In conclusion, by comparison of EEG-fMRI with interictal invasive EEG over a relatively large patient population we were able to show that EEG-fMRI areas included the complete seizure onset zone in 83% and resected area in 93% of the data sets. No clear distinction was found between patients with a good or poor surgical outcome: in both patient groups, EEG-fMRI correlation patterns were found that were either focal or widespread. Therefore, we expect that EEG-fMRI can play an important role for the determination of the implantation strategy.

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Introduction

Due to recent progress in the field of neuroimaging, focal epilepsy has become known as a network disease affecting different brain regions that are functionally interconnected (Laufs, 2012; Lemieux et al., 2011; Richardson, 2010; Spencer, 2002). Especially for epilepsy surgery candidates the challenge is to characterize the different parts of the network and to determine their role during the generation and propagation of epileptiform activity (Vulliemoz et al., 2009). One relatively new neuroimaging technique that may identify these networks is the simultaneous recording of EEG and functional MRI (EEG-fMRI) (Chaudhary et al., 2013; Kobayashi et al., 2006a; Rosenkranz and Lemieux, 2010). EEG-fMRI reveals regions of blood–oxygenation dependent level (BOLD) changes that are associated with (inter)ictal epileptiform activity observed in the simultaneously recorded EEG. This technique enables the detection and visualization of multiple activated areas and does not depend on source reconstruction models, such as required with scalp EEG or MEG.

So far, EEG-fMRI has mainly been used as a research tool, but is now gradually moving towards a clinical application in presurgical evaluation (Pittau et al., 2012; Thornton et al., 2010; Zijlmans et al., 2007). However, the added diagnostic value of EEG-fMRI still needs...
to be established. The majority of the papers about EEG-fMRI in focal epilepsy used noninvasive gold standards for the evaluation, such as the presumed seizure focus based on clinical information and other noninvasive investigations (Hawco et al., 2007; Lemieux et al., 2008; Liu et al., 2008; Salek-Haddadi et al., 2006; Vulliemoz et al., 2010a) or the scalp topography of interictal epileptiform discharges (IEDs) in the co-registered EEG (Jacobs et al., 2009; Kobayashi et al., 2006b; Moeller et al., 2009; van Houdt et al., 2010; Zijlmans et al., 2007). Those studies that compared EEG-fMRI with invasive EEG recordings or postoperative results involved only a few cases (Benar et al., 2006; Laeyens et al., 2000; Moeller et al., 2009; Pittau et al., 2011; van Houdt et al., 2012; Vulliemoz et al., 2010b; Zijlmans et al., 2007). Four studies with a larger patient population have been published that compared EEG-fMRI with the seizure onset zone in invasive EEG recordings (Grouiller et al., 2011; Hauf et al., 2012; Pittau et al., 2012; Thornton et al., 2011). These studies have demonstrated that one of the significant EEG recordings (Grouiller et al., 2011; Hauf et al., 2012; Pittau et al., 2012; Thornton et al., 2011) showed this concordance to be better for lateral temporal and extratemporal neocortical epilepsy than for mesial temporal lobe epilepsy. Pittau et al. (2012) showed that in 64% of the patients in whom a BOLD response was obtained, EEG-fMRI provided additional information to scalp EEG alone.

Although the EEG-fMRI correlation pattern includes the seizure onset zone in most cases, usually more brain regions are activated than just the seizure onset zone (e.g. Pittau et al., 2012, Salek-Haddadi et al. 2006, Vulliemoz et al., 2009). Therefore, the interpretation and clinical relevance of the EEG-fMRI correlation pattern remains to be further clarified. Since almost all EEG-fMRI studies are interictal, a first logical step in the validation process of EEG-fMRI would be the comparison with interictal events recorded with invasive EEG. This has not been performed for a large patient population yet. The goal of this study is to increase our understanding of the EEG-fMRI correlation patterns at both the individual patient level and the group level, and to examine its use in clinical decision making.

The results are first viewed from an EEG-fMRI perspective, whether significant BOLD regions overlap with the distribution of IEDs in electrocorticography (ECoG) data. We specifically investigated whether EEG-fMRI reflects also the temporal origin of IEDs, because this may have more localizing value than propagation of the activity (Ray et al., 2007). The results were also viewed from an ECoG perspective, asking which information from the interictal ECoG is or is not revealed by EEG-fMRI. Since interictal ECoG is usually not the primary parameter for decision making for epilepsy surgery, EEG-fMRI results were finally related to the location of the seizure onset zone, resected area, and the degree of seizure freedom after surgery.

Material and methods

Patients

For this study, we selected patients with refractory epilepsy who participated in different EEG-fMRI studies carried out between 2007 and 2011. Patients referred to the Dutch Epilepsy Taskforce were asked to participate in one of these EEG-fMRI studies. Inclusion criteria for all studies were 1) patients older than 12 years, 2) more than 10 IEDs per hour in a previous routine EEG, and 3) they were candidates for epilepsy surgery. For this study, we selected those patients in whom IEDs were found in the EEG during fMRI acquisition, who underwent ECoG recordings, and for whom post implantation CT scans or digital pictures of the implantation were available. Data sets for which the quality of EEG or fMRI data was not sufficient due to too much motion were also excluded. Table 1 summarizes the demographic and clinical details of the 16 patients included (8 male, age 25.1 ± 8.2 years). All patients had MRI visible lesions, except patients 8 and 11. Electrode placement was based on the electroclinical hypothesis (column 4, Table 1) obtained from the results of the non-invasive preoperative work-up. Although the clinical neurophysiologist was aware of the EEG-fMRI results, these results were not included in the hypothesis. Patient 8 was not operated on due to complications on the second day of subdural grid recordings, whereas patient 11 was not operated on due to the presence of multifocal seizure onset zone overlapping with functional areas. The EEG-fMRI study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and VU University Medical Center; all patients gave informed consent.

Acquisition of EEG-fMRI data

EEG-fMRI data were acquired at three institutes (Kempenhaeghe [KH], Hze; University Medical Center Utrecht [UMCU], Utrecht; VU University Medical Center [VUmc], Amsterdam). The patients were asked to lie relaxed with their eyes closed during the recording. The length of the fMRI recordings varied between 20 and 45 min depending on the subject’s endurance. Most patients were scanned at a 3 T MR scanner (Achieva, Philips Medical Systems, Best, The Netherlands) of KH or UMCU with a T2*-weighted EPI sequence; TR = 2.5 s; TE = 35 ms; flip angle = 90°; voxel size 3.3 × 3.3 × 3 mm3; 31–33 adjacent slices; bottom-to-top slice order (patients 1, 3–5, 7, 8, 16) or interleaved slice order (patients 2, 9–14). Patients 6 and 15 were scanned at the 1.5 T MR scanner (Magnetom Sonata, Siemens, Erlangen, Germany) of VUmc with a TR = 3 s; TE = 60 ms; flip angle = 90°; voxel size 3.3 × 3.3 × 3 mm3; 24 slices with a 10% gap; bottom-to-top slice order. For each patient an anatomical T1-weighted scan was available for the visualization of the EEG-fMRI results. All institutes used the same MR-compatible EEG amplifier (MicroMed, Treviolo, Italy) to acquire EEG data during scanning. EEG was recorded using a 32-channels (UMCU) or 64-channels EEG cap (KH, VUmc) positioned according to an extended 10–20 system with a sampling rate of 1024 Hz (UMCU) or 2048 Hz (KH, VUmc). ECG was co-registered either as a bipolar signal included in the EEG data (KH, UMCU) or as a separate data file with MR compatible sensors (VUmc).

Acquisition of ECoG data

ECoG data were acquired either during surgery (acute ECoG, n = 4) or prior to surgery (chronic ECoG, n = 12) at the UMCU. Subdural grids or strips (Ad-Tech, Racine, QI, USA and Brain-electronics, Houten, The Netherlands) were used consisting of platinum or stainless steel electrodes with an interelectrode distance of 1 cm. Patients who underwent chronic ECoG were implanted with 80–120 electrodes (patients 2–4, 6–8, 10–15). ECoG was sampled at 512 Hz. The positions of the electrodes were determined by matching a post-implantation CT image to the anatomical MRI acquired during EEG-fMRI recording using Brain Imaging Analysis Package (http://demunck.info/software/). An MRI cortical surface rendering was created and the electrode positions and labels were manually determined using the point toolbox of the software, such that each electrode could be described in MRI coordinates.

In four patients who underwent acute ECoG during surgery (patients 1, 5, 9, 16), a grid with 20 electrode contacts was used that was replaced several times during the recording. In patients 9 and 16 a subdural strip of 8 contacts was also used. General anesthesia was induced with a mixture of propofol, a synthetic opioid and atracurium. For ECoG recording, the level of propofol was lowered till the ECoG recording showed a continuous pattern, while ensuring that the patient stayed unconscious (Zijlmans et al., 2012). The position of the grid was manually determined using the point toolbox of the software, such that the positions and labels of the electrodes could be indicated in the anatomical scan.
Interictal ECoG analysis

A semi-automatic procedure was applied for the analysis of the ECoG data to facilitate an objective comparison with EEG-fMRI correlation patterns. The procedure visualizes which electrodes are activated during the occurrence of IEDs in ECoG data and at which electrodes the interictal activity becomes visibly first (early onset). Mathematical details about this method are described in appendix A. The estimation of the interictally active electrodes is based on the semi-automatic analysis developed for stereo-EEG data as described in Van Houdt et al. (2012) using the assumption that mutual correlations between signals are increased during IEDs (Bettus et al., 2008). For each patient, a ten minute sample was selected during awake resting-state, not within one hour of a seizure. This epoch was selected in such a way that all IED-types were present that were identified in the ECoG analysis during clinical assessment of the data, while keeping a balance between normal background ECoG and IEDs (i.e. no overabundance of IEDs). A nonlinear association analysis (Pijn et al., 1990; Wendling et al., 2001) was performed for nonoverlapping sliding windows of 2.5 s (Fig. 1, step 1), yielding for each window $k$ and for each pair of electrodes ($ij$) a maximal association value $h_{ij}(k)$ and a corresponding time delay $\tau_{ij}(k)$ (Fig. 1, step 2). Then, an average association value was computed for each electrode, called the association strength, representing the association of that electrode relative to the other electrodes (Fig. 1, step 3). Next, a regression analysis was performed to investigate which changes in association strength time series can be explained by the occurrence of IEDs (Fig. 1, step 5). This model uses the association strength as explained variable (similar to the fMRI signals in EEG-fMRI analysis) with the IEDs in the data as predictor (Fig. 1, step 4). The advantage of this method is that it does not require a selection of specific background windows such as, e.g., in the study by Wendling et al. (2001). The resulting correlation value indicates to what extent a certain electrode is involved during IEDs relative to the other electrodes (Fig. 1, step 3). Involvement is visualized by color-coded dots scaled by the correlation value and results in an activation map representing the spatial distribution of IEDs over the cortex. Electrodes with a significant correlation (FDR < 5%) are further referred to as interictally active electrodes; non-significant correlations are indicated by black dots. If multiple IED-types were present in the data, the analysis was performed for each IED-type separately, consequently yielding an activation map for each type.

Table 1

Summary of demographic and clinical details.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>MRI abnormalities</th>
<th>Lateralization</th>
<th>Electroclinical hypothesis</th>
<th>Seizure onset zone</th>
<th>Resected area</th>
<th>Engel score</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 34 M</td>
<td>T cavernoma</td>
<td>L</td>
<td>T</td>
<td>–</td>
<td>T</td>
<td>1D</td>
<td>–</td>
<td>Cavernoma</td>
</tr>
<tr>
<td>2 13 F</td>
<td>TSC</td>
<td>L</td>
<td>F</td>
<td>Bilateral F</td>
<td>F</td>
<td>4B</td>
<td>–</td>
<td>Tuber</td>
</tr>
<tr>
<td>3 33 F</td>
<td>P dysplasia in operculum</td>
<td>L</td>
<td>PC</td>
<td>PC</td>
<td>PC</td>
<td>2B</td>
<td>–</td>
<td>FCD</td>
</tr>
<tr>
<td>4 25 F</td>
<td>PO tumor</td>
<td>L</td>
<td>TO onset with propagation to T</td>
<td>mT, fT</td>
<td>TO</td>
<td>1A</td>
<td>Astrocytoma</td>
<td></td>
</tr>
<tr>
<td>5 41 M</td>
<td>mf dysplasia</td>
<td>F</td>
<td>f</td>
<td>mf</td>
<td>mf</td>
<td>1A</td>
<td>–</td>
<td>Dysplasia</td>
</tr>
<tr>
<td>6 30 F</td>
<td>mf lesion</td>
<td>R</td>
<td>mf</td>
<td>mf</td>
<td>f</td>
<td>4B</td>
<td>–</td>
<td>MCD</td>
</tr>
<tr>
<td>7 22 F</td>
<td>mT dysplasia</td>
<td>R</td>
<td>T posterior or anterior</td>
<td>T basal</td>
<td>T</td>
<td>1A</td>
<td>–</td>
<td>MCD</td>
</tr>
<tr>
<td>8 17 M</td>
<td>Resection based on PO gangliocytoma</td>
<td>L</td>
<td>PO</td>
<td>No conclusion</td>
<td>No operation</td>
<td>No operation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9 16 M</td>
<td>T tumor</td>
<td>L</td>
<td>T</td>
<td>–</td>
<td>T</td>
<td>No operation</td>
<td>–</td>
<td>No operation</td>
</tr>
<tr>
<td>10 31 F</td>
<td>Susception of mild cortical dysplasia</td>
<td>R</td>
<td>TO</td>
<td>mT, fT</td>
<td>T</td>
<td>IA</td>
<td>–</td>
<td>NGGL</td>
</tr>
<tr>
<td>11 34 M</td>
<td>Negative</td>
<td>L</td>
<td>0 onset with propagation to T, C, and mf</td>
<td>O, P, T</td>
<td>No operation</td>
<td>No operation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>12 23 M</td>
<td>Deep white matter abnormality in right hemisphere</td>
<td>R</td>
<td>f or TO</td>
<td>mf, f, P, C</td>
<td>F</td>
<td>3A</td>
<td>–</td>
<td>MCD</td>
</tr>
<tr>
<td>13 28 M</td>
<td>Enlargement of right ventricle</td>
<td>R</td>
<td>T posterior</td>
<td>T, mT</td>
<td>T</td>
<td>1B</td>
<td>–</td>
<td>Normal</td>
</tr>
<tr>
<td>14 19 F</td>
<td>Negative</td>
<td>L</td>
<td>mf or IF</td>
<td>f</td>
<td>f</td>
<td>1A</td>
<td>–</td>
<td>Normal</td>
</tr>
<tr>
<td>15 23 M</td>
<td>Prefrontal resection based on DNET</td>
<td>R</td>
<td>F</td>
<td>mf, P, C</td>
<td>F</td>
<td>3A</td>
<td>–</td>
<td>DNET</td>
</tr>
<tr>
<td>16 12 F</td>
<td>MTS</td>
<td>L</td>
<td>T</td>
<td>–</td>
<td>T</td>
<td>1A</td>
<td>–</td>
<td>MTS</td>
</tr>
</tbody>
</table>

Abbreviations: sex: M = male; F = female. MRI abnormalities: m = mesial; f = frontal; p = parietal; O = occipital; T = temporal; MTS = mesial temporal sclerosis; TSC = tuberous sclerosis complex; DNET = dysembryoplastic neuroepithelial tumor; lateralization: L = left; R = right; electroclinical hypothesis: m = mesial; l = lateral; F = frontal; P = parietal; C = central; O = occipital; T = temporal; seizure onset zone: based on ECoG recordings; determined only for patients with chronic ECoG recordings; Engel score: follow-up > 1 year after surgery. Pathology: DNET = dysembryoplastic neuroepithelial tumor; MCD = malformations of cortical development; FCD = focal cortical dysplasia; Taylor-type; MTS = mesiotemporal sclerosis.

EEG-fMRI analysis

The analysis of the EEG-fMRI data was performed with the Brain Imaging Analysis Package, similar to the procedures described in Van Houdt et al. (2012). Briefly, EEG data were corrected for image artifacts and ballistocardiographic artifacts using the methods as described by de Munck et al. (2013). From the EEG, a reference function was extracted representing the timing of IEDs during the EEG-fMRI acquisition. Separate reference functions were created for IEDs with different shape or topology assuming that these different IED-types have different sources. The reference function was correlated to the preprocessed fMRI data through a general linear model framework. Studies in epilepsy patients have shown that the shape of the hemodynamic response function (HRF) varies among patients (Jacobs et al., 2009). In fact, the peak time of the HRF may have localizing value towards the onset site of the IEDs (Hawco et al., 2007; Jacobs et al., 2009; Pittau et al., 2011). Therefore, the parameters of the HRF were estimated from the data using a finite impulse response model (de Munck et al., 2007) instead of using a set of fixed HRFs. An F-test was used to calculate the level of correlation between the data and the reference function, while taking the number of estimated parameters, the number of confounders and the number of data points into account. The resulting p-values were converted to the false discovery rate (FDR) (Genovese et al., 2002), which was used to threshold the statistical maps (FDR < 1%). As a final step, a cluster algorithm was applied to visualize differences in the shape of the HRF for different brain regions. The voxels within a single cluster were indicated with the same color and a corresponding average HRF. Clustering was truncated based on visual inspection when further subdividing did not yield more variation. We used this clustering approach to explore whether the shape of the HRF yields more information about the functional role of an area (i.e. related to the onset or propagation of epileptic activity).

The procedure visualizes which electrodes are activated during the occurrence of IEDs in ECoG data and at which electrodes the interictal activity becomes visible first (early onset). Mathematical details about this method are described in appendix A. The estimation of the interictally active electrodes is based on the semi-automatic analysis developed for stereo-EEG data as described in Van Houdt et al. (2012) using the assumption that mutual correlations between signals are increased during IEDs (Bettus et al., 2008). For each patient, a ten minute sample was selected during awake resting-state, not within one hour of a seizure. This epoch was selected in such a way that all IED-types were present that were identified in the ECoG analysis during clinical assessment of the data, while keeping a balance between normal background ECoG and IEDs (i.e. no overabundance of IEDs). A nonlinear association analysis (Pijn et al., 1990; Wendling et al., 2001) was performed for nonoverlapping sliding windows of 2.5 s (Fig. 1, step 1), yielding for each window $k$ and for each pair of electrodes ($ij$) a maximal association value $h_{ij}(k)$ and a corresponding time delay $\tau_{ij}(k)$ (Fig. 1, step 2). Then, an average association value was computed for each electrode, called the association strength, representing the association of that electrode relative to the other electrodes (Fig. 1, step 3). Next, a regression analysis was performed to investigate which changes in association strength time series can be explained by the occurrence of IEDs (Fig. 1, step 5). This model uses the association strength as explained variable (similar to the fMRI signals in EEG-fMRI analysis) with the IEDs in the data as predictor (Fig. 1, step 4). The advantage of this method is that it does not require a selection of specific background windows such as, e.g., in the study by Wendling et al. (2001). The resulting correlation value indicates to what extent a certain electrode is involved during IEDs relative to the other electrodes (Fig. 1, step 6). Involvement is visualized by color-coded dots scaled by the correlation value and results in an activation map representing the spatial distribution of IEDs over the cortex. Electrodes with a significant correlation (FDR < 5%) are further referred to as interictally active electrodes; non-significant correlations are indicated by black dots. If multiple IED-types were present in the data, the analysis was performed for each IED-type separately, consequently yielding an activation map for each type.

Our method made it possible to study the temporal onset of IEDs as well (Ray et al., 2007). The location of the early onset of IEDs was estimated in the second part of the analysis (Fig. 1, steps 7–9). Time delays $\tau_{ij}(m)$ between two electrodes $i$ and $j$ can be interpreted as the direction of information flow between two signals representing neuronal propagation (Wendling et al., 2001). A nonlinear association analysis was performed for windows of 1 s centered around the IEDs.
(Fig. 1, step 7), and the delays $\tau_{ij}(m)$ were subsequently used to estimate the moment in time at which an IED was measured at each electrode (Fig. 1, step 8). The estimated time points are represented in the same way as the interictally active electrodes with color-coded dots: early onset is indicated with bright colors whereas later time points are indicated with dark colors. The analysis was performed for each IED separately. An example of the onset pattern is shown in step 9 of Fig. 1 with the corresponding ECoG signals.

**Surgery related parameters**

The location of the seizure onset zone was visually determined by the neurophysiologist based on the ECoG data. The location of the resected area was established from a postoperative MRI matched to the anatomical MRI acquired during the EEG-fMRI experiment. A contour line was drawn to indicate the edges of the resection. The contour line was overlaid on the EEG-fMRI correlation patterns and ECoG activation maps. As a measure for postoperative outcome, the Engel-score was determined at least one year after surgery (Engel et al., 1993). An Engel-score of 1 or 2 was considered good surgical outcome, whereas an Engel-score of 3 or 4 was considered poor surgical outcome.

**Comparison of results**

Since the spatial domains of EEG-fMRI and ECoG are different (voxels vs. electrodes), results were compared at the level of the underlying anatomical brain regions. For that purpose a digital atlas of the brain was matched to the anatomical MRI of each patient using linear transformation and rotation. We used the anatomic automatic labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) available from the MRcron software (www.mccauslandcenter.sc.edu/mricro/mricon/). This atlas divided the brain into 90 brain regions. According to neurosurgical practice these brain regions were merged into ten larger anatomical regions for each hemisphere defined by gyri and sulci comparable to the definitions described by Agirre-Arrizubieta et al. (2009): lateral temporal region (TL); mesial temporal region (TM); inferior, medial, and superior frontal gyri (FL); orbitofrontal region (FO); interhemisperic region (IH); central region (C); parietal region (P); occipital region (O); subcortical structures (B); insular region (Ins). Inline Supplementary Table S1 provides a detailed list of the ten anatomical brain regions and their corresponding AAL brain regions.

Inline Supplementary Table S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.02.033.

In this way, significantly activated BOLD regions and interictally active ECoG electrodes could each be described by a set of anatomical brain regions. This approach is schematically illustrated in Fig. 2. BOLD regions that were not located in one of these brain regions (e.g. in white matter, cerebellum, or ventricles) were discarded from further analysis. We defined active EEG-fMRI areas when more than 1% of the voxels in a brain area were significantly involved. The threshold of 1% corresponds to an average activation of $0.64 \text{ cm}^3$, which is similar to the criterion of 5–12 contiguous voxels used in other studies (e.g. Bagshaw et al., 2006; Benar et al., 2006; Pittau et al., 2011; Rathakrishnan et al., 2010). Brain regions were specified as interictally active ECoG areas when one or more electrodes within that brain region (e.g. in white matter, cerebellum, or ventricles) were significantly activated. In case more than one IED-type was present in the ECoG data of a patient, the interictally active regions of all types were grouped. Next, it was determined for each data set whether the active EEG-fMRI areas were covered with ECoG electrodes, whether these regions were concordant with interictally active ECoG areas, or whether they were discordant. Furthermore, from an ECoG perspective it was determined whether all interictally active ECoG brain regions were found by EEG-fMRI. A general level of concordance between EEG-fMRI and interictal ECoG patterns was obtained by merging the results of all data sets.
Finally, a comparison was made between EEG-fMRI correlation patterns and the surgical parameters. For each data set it was determined whether the EEG-fMRI correlation pattern involved the same brain regions as the seizure onset zone and/or resected area. In a similar way, the interictally active ECoG areas were compared with the seizure onset zone and resected area. The EEG-fMRI and ECoG results were also linked to the level of seizure freedom to examine whether there is a distinction in the results of patients with a good or poor surgical outcome.

Results

General results

In the EEG during fMRI acquisition a single IED-type (with more than 3 IEDs) was identified for almost all patients, except for patient 16 in whom two IED-types were present, resulting in 17 IED-correlated fMRI analyses. The number of activated EEG-fMRI regions ranged from 1 to 13. For each patient, clustering of the estimated HRFs of these significant BOLD regions resulted in 3 to 6 clusters with varying shape and sign of the average HRF. In the selected ECoG data of these patients, 1 to 7 different IED-types were present, but the regression analysis yielded only significant results for frequently occurring or widespread IEDs. For patient 9, ECoG analysis did not reveal any significant results, probably because too little contrast was present to reach significance in the regression analysis due to continuous spiking in the ECoG data. This patient was therefore excluded from the comparison with interictal ECoG. For more detailed information about the individual results of EEG-fMRI and interictal ECoG analysis, we refer to Inline Supplementary Table S2.

Inline Supplementary Table S2 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.02.033.

EEG-fMRI vs. interictal ECoG

Individual level

Table 2 shows a color-coded summary of the EEG-fMRI and interictal ECoG findings expressed in brain regions (columns) for all data sets (rows). From these results it immediately appears that for each data set at least one active EEG-fMRI region was concordant with interictally active ECoG regions (in green), except for data set 16.2. This table also shows that discordant results (in red) were obtained in 5 data sets, whereas in ten data sets one or more interictally active ECoG regions were not present in the EEG-fMRI correlation pattern (in yellow). In
Fig. 3. EEG-fMRI correlation pattern (first column) and ECoG results (second and third column) for patients 1–3. The white contour line indicates the resected area. The color bars indicate the height of the correlation coefficient for the EEG-fMRI correlation pattern and for the ECoG activation map. For the ECoG onset map, the color bar indicates the delay of IED activity for a particular electrode relative to other electrodes. Early onset (i.e. negative time values) is indicated with bright colors whereas later time points are indicated with dark colors. For patient 2, the interictal onset areas were highly variable between individual IEDs, therefore, no onset areas were shown for this patient.

Fig. 4. Illustrative case showing the EEG-fMRI results (top row) and ECoG results (bottom row) for patient 4. Panel (a) shows the IEDs identified during EEG-fMRI. Panel (b) shows the correlation pattern resulting from the fMRI analysis. In (c) the results of the HRF clustering are shown; each color corresponds to a different cluster and a different average HRF shown in (d). Positive HRF clusters are indicated with warm colors (red, yellow, orange) and negative clusters with cold colors (blue, green). Panel (f) represents the interictally active areas from the ECoG analysis. The color bar indicates the height of the correlation coefficient. Panel (g) represents the onset area of the IEDs in the ECoG data. Early onset (i.e. negative time values) is indicated with bright colors whereas later time points (i.e. positive time values) are indicated with dark colors.
most data sets, as expected, EEG-fMRI revealed regions that could not be validated, because they were not covered with subdural grids or strips (in blue). Furthermore, Table 2 shows that according to the EEG-fMRI results, the data sets can be divided into two groups: a group with a single EEG-fMRI activation area and a group with a widespread correlation pattern usually involving multiple brain regions. The first group, with a single BOLD region, consisted of three patients (patients 1–3). In all of them the single region was concordant with the interictally active ECoG area which was also focal (Fig. 3). For the remaining thirteen data sets EEG-fMRI revealed a more widespread correlation pattern. For each of these data sets at least one region was concordant with interictally active ECoG areas. One of these concordant regions was also concordant with the early onset of the IEDs, suggesting that EEG-fMRI reflects a pattern of onset and propagation of IED activity.

HRF clustering was applied to the data of patients with a widespread correlation pattern to examine whether onset and propagation regions could be separated based on the shape of the HRF. In six patients (4–9) HRF clustering distinguished the onset region from propagation regions as a single HRF cluster of neighboring voxels. An illustrative case is patient 4, presented in Fig. 4. In this patient, EEG-fMRI analysis of the IEDs identified during scanning (Fig. 4a) yielded significant BOLD areas in the left lateral temporal region, in the left parietal region near the lesion of the patient (Fig. 4b), and in the left thalamus (insert Fig. 4c). Clustering of the HRFs in these significant voxels showed that each BOLD area is characterized by a different HRF (Figs. 4c and d). Positive HRF clusters were obtained in the left thalamus and left lateral temporal region (cluster 1–3 in Fig. 4d), while negative HRFs were found in the left posterior temporal region and parietal region (cluster 5 and 6 in Fig. 4d). Cluster 4 was not located in one of the specified brain regions (edge of the brain). Electrode grids were implanted across the temporal and parietal lobes (Fig. 4f), overlapping HRF clusters 2, 5, and 6. Fig. 4f shows the IEDs that were marked in the ECoG data, which were presumably of the same type as the IEDs of the EEG-fMRI recording. Analysis of these IEDs shows maximal activity in the left frontotemporal and left parietal region (Fig. 4f), showing overlap with the EEG-fMRI areas. Furthermore, the estimated onset of the IEDs was located at the lateral temporal electrodes (Fig. 4g). Therefore, of the concordant HRF clusters (cluster 2, 5, and 6), only the positive HRF cluster (cluster 2 in Fig. 4d) was also concordant with the early onset area of the IEDs in ECoG. The results of the other patients are shown in Supplementary Fig. 1.

For the other data sets, clusters were more widespread and usually involved other brain regions (10–16.1). In those patients, the interictally active ECoG areas were widely distributed as well (see Supplementary Table S1). An example is shown in Fig. 5 for patient 10 illustrating that multiple brain regions were obtained with EEG-fMRI. HRF clustering did not reveal a clear separation of different activated brain regions. Many different IED-types were present in the ECoG data of this patient, each involving different brain regions. We refer to Supplementary Fig. 2 for the figures of the other patients.

**Group Level**

Table 3 summarizes the results of the comparison between EEG-fMRI and ECoG at group level. Since insular regions and subcortical structures cannot be reached with grid electrodes, 16 brain regions were compared for each data set, resulting in 256 brain regions in total. Only 32% of the 256 brain regions were covered with subdural electrodes. However, significant BOLD activations were found in 28% of the regions that were not covered with electrodes. These regions,
was removed, while only part of the seizure onset zone was removed. In all patients who underwent resective surgery, the interictally active ECoG areas were located within the resected area. In 6 data sets the interictally active ECoG areas were larger than the seizure onset zone. In patients 2, 11, 15, the interictal results only reflected the distribution of the IED-types present in the ECoG data. Nevertheless, it corresponded to propagation of interictal activity. These results suggest that the EEG-fMRI correlation pattern reflects an interictal epileptic network (Laufer, 2012; Vulliemoz et al., 2009).

To put the results of the comparison of EEG-fMRI into perspective, the interictal ECoG results were also compared to the seizure onset zone and resected area. In 75% of the data sets the interictally active ECoG areas included the complete seizure onset zone. In patients 2, 11, 15, the interictal results only reflected part of the seizure onset zone. In 6 data sets the interictally active ECoG areas were larger than the seizure onset zone. In all patients who underwent resective surgery and in whom ECoG data were analyzed (n = 14), part of the interictally active ECoG areas were located within the resected area. Finally, in 9 data sets (81%) the complete seizure onset zone was removed, while only part of the seizure onset zone was removed in patients 12 and 15 and a lesionectomy was performed in patient 4, which did not include the seizure onset zone.

From a clinical perspective it is important to know whether EEG-fMRI correlates with the primary parameter of the presurgical evaluation, i.e. seizure onset zone, as well as with surgical outcome measures, the resected area and degree of seizure freedom. Table 4 shows a comparison between EEG-fMRI results, interictal ECoG results, seizure onset zone, and resected area. The EEG-fMRI correlation patterns included the complete seizure onset zone in 83% of the data sets. In patient 2, only the left frontal region showed up in EEG-fMRI, while the seizure onset zone was identified bilaterally in the frontal lobe. For patient 15, only EEG-fMRI activations were found in the frontal region and not in the parietal and central regions. In 93% of the data sets, at least one EEG-fMRI region was located within the resected area. Note that in 12 data sets (75%) the EEG-fMRI region that was located within the resected area was also the region that was concordant with the onset of the IEDs in the ECoG data.

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## Table 3

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>EEG-fMRI</th>
<th>No ECoG electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (onset area)</td>
<td>Inactive</td>
<td>Total</td>
</tr>
<tr>
<td>EEG-fMRI</td>
<td>34 (18)</td>
<td>11</td>
<td>48</td>
</tr>
<tr>
<td>Inactive</td>
<td>15 (8)</td>
<td>23</td>
<td>125</td>
</tr>
<tr>
<td>Total</td>
<td>49 (26)</td>
<td>34</td>
<td>173</td>
</tr>
</tbody>
</table>

**EEG-fMRI vs. surgical parameters**

From a clinical perspective it is important to know whether EEG-fMRI correlates with the primary parameter of the presurgical evaluation, i.e. seizure onset zone, as well as with surgical outcome measures, the resected area and degree of seizure freedom. Table 4 shows a comparison between EEG-fMRI results, interictal ECoG results, seizure onset zone, and resected area. The EEG-fMRI correlation patterns included the complete seizure onset zone in 83% of the data sets. In patient 2, only the left frontal region showed up in EEG-fMRI, while the seizure onset zone was identified bilaterally in the frontal lobe. For patient 15, only EEG-fMRI activations were found in the frontal region and not in the parietal and central regions. In 93% of the data sets, at least one EEG-fMRI region was located within the resected area. Note that in 12 data sets (75%) the EEG-fMRI region that was located within the resected area was also the region that was concordant with the onset of the IEDs in the ECoG data.

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## Table 4

Concordance from a clinical perspective. A comparison is made between the EEG-fMRI and ECoG results.

<table>
<thead>
<tr>
<th></th>
<th>Seizure onset zone</th>
<th>Resection area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active EEG-fMRI regions</td>
<td>(n = 12)</td>
<td>83%</td>
</tr>
<tr>
<td>ECoG Intercitically active regions</td>
<td>(n = 16)</td>
<td>75%</td>
</tr>
<tr>
<td>Early onset</td>
<td>(n = 16)</td>
<td>75%</td>
</tr>
<tr>
<td>Seizure onset zone</td>
<td>(n = 12)</td>
<td>x</td>
</tr>
</tbody>
</table>

The Engel score (>one year after surgery) was 1 or 2 for 9 patients, while the Engel score was 3 or 4 for 5 patients. No clear distinction was found between the EEG-fMRI results of patients with a good or poor surgical outcome: in both patient groups, EEG-fMRI correlation patterns were found that were focal or widespread and with either a positive or negative HRF.

**Discussion**

To our knowledge, this study is the first that systematically assessed the concordance between EEG-fMRI and the interictally active areas as determined with ECoG for a large patient population. The results confirm earlier findings that in most patients the EEG-fMRI pattern consists of multiple activated regions (e.g. Pittau et al., 2012, Vulliemoz et al., 2009). Of the 16 patients a single focal region was found only in 3. In all patients at least one EEG-fMRI region overlapped with the interictically active ECoG areas. Some EEG-fMRI regions appear to be related to the onset of IEDs in the ECoG data, whereas others were related to propagation of interictal activity. These results suggest that the EEG-fMRI correlation pattern reflects an interictal epileptic network (Laufer, 2012; Vulliemoz et al., 2009). A previous study, in which scalp and intracranial EEG were measured simultaneously, has suggested that the onset of scalp IEDs is more localizing than the peak of the IEDs as it almost always correlated with the seizure onset zone (Ray et al., 2007). Therefore, our finding that the EEG-fMRI correlation pattern generally includes the onset of IEDs is a promising added value of EEG-fMRI in presurgical evaluation, in particular when the onset is located in deeper lying cortical structures, which are usually not visible from scalp EEG or MEG.

The EEG-fMRI correlation pattern did not reflect the distribution of all IED-types present in the ECoG data. Nevertheless, it corresponded to the most frequent and dominant IEDs in the ECoG data, which are usually the IEDs that are clinically more relevant (Ray et al., 2007). Furthermore, the EEG-fMRI correlation pattern included the seizure onset zone in most data sets (83%). The good overlap between EEG-fMRI and the seizure onset zone is comparable to other studies (Grouiller et al., 2011, Pittau et al., 2012, Thornton et al., 2011). Together, these findings indicate that the sensitivity of EEG-fMRI is high and confirm the important role EEG-fMRI may play in decision-making of implantation strategies, as suggested by Zijlmans et al. (2007).

The level of concordance as estimated in this study depends on several choices made for the comparison. First, by dividing the EEG-fMRI pattern into anatomical brain regions, a single activated area might be divided into multiple brain regions of which some can be concordant and others discordant with ECoG patterns. In this way, information is lost about the connection of EEG-fMRI voxels and we cannot examine whether a concordant area extends over other brain regions as well. This may underestimate the subjective concordance level determined from visual inspection. The concordance level may also be influenced by the size of the defined brain regions which shows a large variation (see Supplementary Table S1). For example, the lateral frontal region is large with respect to the orbitofrontal region. However, we believe that further subdividing the regions makes the interpretation of Supplementary Table S2 more difficult. Furthermore, the figures that are provided for each patient, show a good concordance between EEG-fMRI and ECoG within the lateral frontal region. In addition, the parcelation method is in line with other recent EEG-fMRI studies also summarizing EEG-fMRI concordance at sublobar level (e.g. Ghaliouf et al., 2011, Lemieux et al, 2008, Pittau et al., 2012).

The level of concordance may also be influenced by the thresholds used for the EEG-fMRI and ECoG correlation patterns. We used FDR-values to threshold the data, as there are currently no standards for the statistical thresholds in EEG-fMRI analysis. Applying a more stringent threshold for EEG-fMRI correlation patterns will result in lower sensitivity and higher specificity if the region of statistical maximum is a concordant region. However, from Inline Supplementary Table S2...
it appears that this is not the case for 6 of the 17 data sets. Sensitivity may be improved by using a fixed number of activated voxels (Hauf et al., 2012). From a practical point of view, it is important to keep the purpose of EEG-fMRI in mind: when the goal of EEG-fMRI is to guide the implantation of subdural electrode grids, a high sensitivity is more important than a high specificity.

The systematic evaluation of EEG-fMRI is compromised by the limited spatial sampling of ECoG recording. EEG-fMRI generally yields more areas than covered with ECoG electrodes. Therefore, the function of these regions cannot be validated. We expected the number of “unknown” brain regions to be larger for patients who received acute ECoG than for chronic ECoG, because implantation during acute ECoG is usually restricted to one or two brain regions. However, in this study similar numbers of unknown brain regions were obtained for patients with acute and chronic ECoG recording (see Table 2). Subdural grids can cover only neocortical and interhemispheric regions, but not deeper lying structures. Prospective studies, preferably in combination with depth electrodes are necessary to determine precise values for sensitivity and specificity of EEG-fMRI. The absence of an absolute gold standard is a general problem in the evaluation of new noninvasive techniques in presurgical evaluation (Burch et al., 2012). Intracranial findings such as from ECoG recordings present the best available gold standard. Further insight can be gained from simultaneous ECoG-fMRI recordings (Carmichael et al., 2012; Vulliemoz et al., 2011). Although our population is quite a heterogeneous group, it is representative for the complex epilepsy patients that are presented for epilepsy surgery requiring invasive EEG recordings. To determine the role of EEG-fMRI during the decision making of implantation strategies, a comparison of EEG-fMRI with ECoG is important despite these limitations.

Clustering of the HRF seems useful to predict the extent of the areas involved with interictal epileptiform activity: when the EEG–fMRI correlation pattern was widespread without clear HRF clustering, the interictally active ECoG areas were also widespread. Furthermore, clustering may highlight relevant areas that were not noticed before. For example, in patient 5 (see Supplementary Fig. 2), clustering separately the mesial frontal region from other areas activated with EEG–fMRI. This region appeared to be concordant with the early onset of IEDs in the ECoG data. Without clustering, this region would not have been noticed in the widespread correlation pattern, especially because the maximal BOLD response was located in the parietal and temporal regions.

The shape of the HRF of concordant clusters is highly variable among patients. This suggests that the use of a standard HRF model may lead to false negative fMRI results (e.g. Josephs et al., 1997; Lu et al., 2007; van Houdt et al., 2010). Previous studies focused on those areas with the maximal t- or F-statistic (e.g. Kobayashi et al., 2006a; Salek-Haddadi et al., 2006). Our results confirm the suggestion by Vulliemoz et al. (2009) that the maximal t-statistic is not always the area that is most closely related to the presumed epileptiform focus (see Inline Supplementary Table S2). Due to these variable results, it seems difficult to decide without a priori information which HRF cluster is clinically important. For instance, we investigated whether the shape of the HRF is predictive for the role within the network (onset vs. propagation), but we did not obtain consistent results. The sign of the HRF does not seem to correlate with the level of concordance; both positive and negative HRFs are related to concordant regions. This has also been observed by others and is still a topic of debate (Pittau et al., 2011, Rathakrishnan et al., 2010). Other characteristics of the HRF shape were also not predictive for concordance. For example, both canonical and noncanonical HRF clusters were concordant with the ECoG data and the seizure onset zone, which deviates from the results by Lemieux et al. (2008), who suggested that noncanonical HRFs were most likely not related to the focus of activity. Therefore, it seems that the shape of the HRF is not directly dependent on the underlying epileptiform activity, suggesting a much more complex relation. This relation is currently an important topic of research in more fundamental research as well (e.g. Conner et al., 2011; Rosa et al., 2010; Siero et al., 2011).

Conclusions

This study is the first systematic study to the interpretation of the EEG-fMRI correlation patterns in presurgical evaluation. By comparison of EEG-fMRI with interictal invasive EEG over a large patient population we were able to show that the EEG–fMRI correlation patterns are spatially accurate at the level of neurosurgical units (i.e. anatomical brain regions) and reflect the underlying network of IEDs. Compared to high resolution EEG and MEG source localization, EEG-fMRI is able to reveal activations in the mesial structures. Therefore, we expect that EEG–fMRI may play an important role in surgical planning in complex patients, especially to determine the implantation strategy.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.02.033.

Acknowledgments

This project was supported by the Dutch Epilepsy Foundation (grant 07-16) and the Central Nervous System and Imaging (CSI) project that has received funding from the ENIAJ Joint Undertaking (grant no. 120209) and from the national programs of Austria, Hungary, Italy, and The Netherlands. The ECoG recordings were performed at the University Medical Center Utrecht. We especially acknowledge Cyrille Ferrier and Peter van Rijen for their contribution to the recordings used in this study. Furthermore, we would like to thank Jan Verwoerd from Philips Health Care (Eindhoven, The Netherlands) for his assistance regarding the MR imaging sequences, Mike van der Mieren, Marlies Dolmans, and Ine Keulen for the review of the EEGs, Remco Berting and Esther Peeters for their assistance during the fMRI recordings, and Roy Krijn for technical support.

Appendix A. ECoG analysis

The analysis of the IEDs in the ECoG data consists of two parts: the estimation of the interictally active ECoG electrodes and the early onset area. The analysis is implemented in Matlab (R2009a, The Mathworks, Inc.) and uses several functions of the Fieldtrip toolbox (Oostenveld et al., 2011). For both parts of the analysis, the data was first transformed in a Hjorth derivation to reduce the influence of common sources (Hjorth, 1975).

Estimation of the interictally active electrodes was performed with the procedure as described in Van Houdt et al. (2012) that was developed for the purpose of validation of EEG-fMRI results. The goal of the activation map is to indicate which electrode contacts reflect increased activity during the occurrence of IEDs. The approach is based on the assumption that the mutual correlations between electrodes are increased during epileptiform activity (Bettus et al., 2008). Therefore, a nonlinear association analysis was applied for each ECoG window yielding the maximal association $h_{ik}(k)$ and a corresponding time delay $\tau_{ij}(k)$ between electrodes $i$ and $j$ for each 2.5 s window $k$ using Eq. (A.1) (Bartolomei et al., 2001; Lopes da Silva et al., 1989; Meeren et al., 2002; Pijn et al., 1996; Wendling et al., 2001; Westmijse et al., 2009).

$$h_{ik}(k) = \max_{\tau} \left[ h_{ij}(k \cdot \text{TR} + \tau) \right], \quad -\tau_{\max} \leq \tau \leq \tau_{\max}; 0 \leq k \leq K-1.$$  

(A.1)

$\tau_{\max}$ is 150 ms and $K$ is equal to the number of windows depending on the length of the selected data. Averaging of the $h_{ij}(k)$ values for electrode $i$ with all other electrodes reveals an association strength function as shown in Eq. (A.2) (Ortega et al., 2008).

$$\text{Strength}_{i}(k) = \frac{1}{N-1} N \sum_{\tau=1}^{N} h_{ij}(k), \quad 0 \leq k \leq K-1.$$  

(A.2)
In which \( N \) is the number of ECoG electrodes. Next, a general linear model framework was applied to reveal which changes in association strength can be explained by the occurrence of IEDs (Eq. (A.3)).

\[
d = Xh + \Phi p + \epsilon.
\]

(A.3)

In this model, \( d \) represents the association strength function for electrode \( i \). \( X \) is the design matrix consisting of the regressors of interest, which are in this formulation the IEDs present in the ECoG data. The required input from the clinician is the timing of IEDs in the ECoG data, which were marked visually and different markers were used for IED-types with different topologies. From these events, an IED density function was created that was applied as a predictor in the general linear model. Different IED density functions were created for different types of IEDs. If multiple IED-types were present, regression analysis was performed for each type separately, while the other IEDs were used as confounders indicated by \( S \).

For the estimation of the onset area, which are in this formulation the IEDs present in the ECoG data. The required input from the clinician is the timing of IEDs in the ECoG data, which were marked visually and different markers were used for IED-types with different topologies. From these events, an IED density function was created that was applied as a predictor in the general linear model. Different IED density functions were created for different types of IEDs. If multiple IED-types were present, regression analysis was performed for each type separately, while the other IEDs were used as confounders indicated by \( S \).

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