Epilepsy surgery requires precise localization of the epileptic source. EEG-correlated functional MRI (EEG-fMRI) is a new technique showing the haemodynamic effects of interictal epileptiform activity. This study assesses its potential added value in the presurgical evaluation of patients with complex source localization. Adult surgical candidates considered ineligible because of an unclear focus and/or presumed multifocality on the basis of EEG underwent EEG-fMRI. Interictal epileptic discharges (IEDs) in the EEG during fMRI were identified by consensus between two observers. Topographically distinct IED sets were analysed separately. Only patients with significant, positive blood oxygen level-dependent (BOLD) responses that were topographically related to the EEG were re-evaluated for surgery.

Forty-six IED sets from 29 patients were analysed. In eight patients, at least one BOLD response was significant, positive and topographically related to the IEDs. These patients were rejected for surgery because of an unclear focus (n = 3), presumed multifocality (n = 2) or a combination of both (n = 3). EEG-fMRI improved localization in four out of six unclear foci. In patients with presumed multifocality, EEG-fMRI advocated one of the foci in one patient and confirmed multifocality in four out of five patients. In four patients EEG-fMRI opened new prospects for surgery and in two of these patients intracranial EEG supported the EEG-fMRI results. In these complex cases, EEG-fMRI either improved source localization or corroborated a negative decision regarding surgical candidacy. It is thus a valuable tool in the presurgical evaluation of patients. Guidelines for the use of EEG-fMRI in clinical practice are proposed.

Keywords: electroencephalography; functional MRI; epilepsy; epilepsy surgery; epileptic source localization

Abbreviations: BOLD = blood oxygen level-dependent; GFT = Gaussian field theory; IED = interictal epileptic discharge

Received February 2, 2007. Revised May 22, 2007. Accepted May 25, 2007
localization, to either avoid or guide invasive EEG, would clearly benefit patients.

EEG-correlated functional MRI (EEG-fMRI) measures changes in oxygenation in response to (interictal) epileptic events (Krakow et al., 1999; Benar et al., 2002). It may improve the delineation of epileptogenic areas and networks because it provides information that is different from that provided by non-invasive techniques (Federico et al., 2005; Gotman et al., 2006; Kobayashi et al., 2006b, c). Several studies have shown that local blood oxygen level-dependent (BOLD) responses correspond with the source of spiking activity, even if there are no structural MRI abnormalities (Lemieux et al., 2001; Al-Asmi et al., 2003; Bagshaw et al., 2004; Hamandi et al., 2004; Lemieux, 2004; Bagshaw et al., 2006). A study comparing EEG-fMRI with EEG and intracranial stereo-EEG showed that EEG-fMRI information complements scalp EEG information in localizing epileptic sources (Benar et al., 2006). This localizing ability opens the prospects of using EEG-fMRI in the presurgical evaluation of surgery candidates (Gotman et al., 2006; Salek-Haddadi et al., 2006).

However, there are some reservations to the use of EEG-fMRI for source localization: (i) the outcome depends on the haemodynamic response function model chosen and the definition of a significant fMRI result (Benar et al., 2002); (ii) the underlying physiology of a negative BOLD response is uncertain and consequently its localizing value is unclear (Kobayashi et al., 2006b); (iii) a distant positive BOLD response has been found in potentially epileptogenic regions (for instance, a bitemporal BOLD response with unilateral interictal epileptiform discharges, IEDs), but also in probably unrelated areas (for instance, occipital co-activation with frontal IEDs) (Kobayashi et al., 2006c); (iv) fMRI depends on the definition of ‘events’; EEG-fMRI depends on the selection of interictal epileptiform discharges; (v) (EEG-)fMRI can never prove that a certain region is not involved and (vi) fMRI has a low temporal resolution.

The potential value of EEG-fMRI in clinical practice has not yet been investigated. The need for a new diagnostic tool is greatest in patients in whom other source localization techniques have failed to localize a single, circumscribed source—a prerequisite for surgery. We therefore performed EEG-fMRI in a cohort of patients who had been recently rejected for epilepsy surgery because neither EEG nor other non-invasive techniques delineated a single epileptic source. These patients had not undergone invasive EEG. We studied whether EEG-fMRI improved epileptic source localization and its impact on presurgical decision-making in complex cases.

Material and Methods

Patients

Between January 2001 and February 2006, 276 patients older than 16 years with focal epilepsy underwent surgery in the Netherlands. Seventy-one patients rejected for epilepsy surgery were asked to complete questionnaires about their motivation to undergo extra, experimental diagnostic examinations and were asked for permission to access their medical files; 64 patients (90%) responded. Patients from this latter group were selected to undergo EEG-fMRI using the following criteria: (i) having no contraindications for MRI; (ii) having more than 10 IEDs in 40 min of previously recorded EEG; (iii) the reason for rejection was the inability to localize a single source with EEG.

The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht. All patients gave informed consent.

Data acquisition

EEG measurements

Preceding EEG-fMRI, a reference EEG was recorded outside the scanner. An MR-compatible, 31-channel EEG-cap was used with silver ring electrodes and 10 kΩ safety resistors to safeguard against heat induction by radiofrequency pulses (Micromed, Treviso, Italy). A bipolar EEG was co-registered. Data were transmitted to an acquisition computer outside the MRI suite via an MR-compatible head box (Micromed, Treviso, Italy) through an optic fibre cable. EEG was recorded at a 1024 Hz sampling rate, with 22 bits data resolution, and hardware filtered between 0.15 and 268.8 Hz. Online subtraction of MRI artefacts allowed EEG assessment throughout the whole recording (Allen et al., 2000).

MRI measurements

All patients were scanned on a 1.5-T Achieva MR scanner (Philips Medical Systems, Best, The Netherlands) with an 8-channel phased array head coil for signal reception. To reduce motion artefacts, the patient’s head was immobilized in a vacuum-drawn, foam-filled pillow. An anatomical T1-weighted dataset was acquired using a spin-echo (SE) acquisition [field-of-view (FOV) 25 × 25 cm², matrix 256 × 154, multi slice acquisition of 19 slices of 4.0 mm separated by a gap of 0.6 mm, repetition time (TR) 512 ms, echo time (TE) 15 ms, flow angle 90°, flow compensated]. Functional MRI images were recorded with a T2*-weighted single shot gradient echo-planar imaging (EPI) sequence with the following parameters: FOV = 23 × 23 cm², matrix 64 × 63, TR 2.5 s, TE 46 ms, flip angle 90°, 29 adjacent slices, reconstructed voxel size 3.6 × 3.6 × 4 mm³. The duration of a single dynamic scan was 2.5 s and slices were interleaved. At the beginning of each dynamic scan, a trigger pulse was supplied to the EEG software which made accurate matching of the EEG and fMRI time series possible. The aim of each session was to acquire 1024 sequential dynamic scans (40 min).

EEG processing

Imaging and pulsation artefacts were semi-automatically subtracted offline (Allen et al., 1998, 2000). EEG was displayed in both reference and bipolar montages. IEDs (spikes, spike-and-waves, sharp waves) were independently identified by two experienced observers. IEDs with different topographical distributions were classified as separate IED sets and analysed separately. Interobserver agreement was calculated using Cohen’s kappa (Zijlmans et al., 2002). IED sets with a kappa below 0.40 were reviewed by a third observer. If three observers evaluated a set, the IEDs from two observers with the best agreement were used for...

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Further analysis. Consensus IEDs were defined as IEDs identified by at least two observers. These consensus IEDs were used for fMRI analysis. Only IED sets with at least three consensus IEDs were used.

**FMRI processing**

All fMRI data were analysed using the Statistical Parametric Mapping (SPM) software package version 2 (UCL, London, UK) and Matlab version 7.1 (The Mathworks, Natick, MA). Data were processed in a way similar to that described in another study (Salek-Haddadi et al., 2006). Images were slice-time corrected, realigned and spatially smoothed (Gaussian kernel of 7 mm full width at half-maximum). Scan realignment resulted in a time series of six separate rigid body motion parameters.

The BOLD response following IEDs was modelled in an event-related design using a canonical haemodynamic response function with a temporal derivative. If there were prolonged bursts of interictal epileptiform activity, event duration was taken into account (Bagshaw et al., 2005). The motion parameters were included as confounders in design matrices. FMRI data were filtered with a high-pass filter with time constant 128 s and an auto-regressive filter (AR1-model).

**Analysis of IED sets**

Statistical parametric maps were created using an F-test (Friston et al., 1998) with correction for multiple comparisons using Family Wise Error, a method based on Gaussian field theory (GFT). Results with a P-value <0.05 were considered significant. We determined which IED sets contained a significant BOLD response, and then assessed the topographical concordance between significant BOLD responses and EEG activity: (i) same area, ipsilateral; (ii) same area, contralateral; (iii) ipsilateral, different area, (iv) no concordance. We distinguished between positive and negative BOLD-responses. Additionally, it was evaluated in how many IED-sets a significant BOLD-response was found when selecting all IEDs (i.e. depicted by any of the two observers).

**Clinical evaluation of EEG-fMRI results**

For each patient the former reason for rejection was categorized into: (i) inability to delineate a clear focus (including presumed frontal foci with unknown lateralization); (ii) multiple potential distinct foci (mainly a priority problem) or both.

Only when the consensus-IEDs showed a significant (P < 0.05 GFT) BOLD response with a positive sign (Kobayashi et al., 2006b), the result was considered robust. Of the patients with at least one robust result, the EEG-fMRI results of only those patients with a BOLD response in the region that could be expected on basis of the IED (defined as topographically related) were re-evaluated in two ways:

First, the potential added value for the two categorized localization problems was assessed apart from clinical interpretation. To access the extent of the BOLD-response in the localization of a single focus and to access all possible (co-) activated areas in case of presumed multifocality, the uncorrected maps of voxels with P < 0.001 were considered together with the statistically corrected results (Fig. 1). Possible outcomes were: (i) with regard to source localization (category 1): EEG-fMRI showed a circumscribed focus in the expected region, whereas EEG did not (Table 2: ‘improved’); focus localization remaining unclear (‘not improved’); (ii) With regard to multifocality (category 2): EEG-fMRI indicated a single focus (‘unifocal’); multifocality was confirmed, consistent with the EEG (‘multifocal’); a significant BOLD response was unifocal, but the BOLD responses that were not corrected for multiple comparisons (P < 0.001), were multifocal (‘probably multifocal’).

As a second step, the EEG-fMRI results were reported back to the Dutch Collaborative Epilepsy Surgery Program, the national forum of clinical experts who review all applications for epilepsy surgery in the Netherlands. The members had been informed about EEG-fMRI and the current study and were asked to handle EEG-fMRI results like those of any novel diagnostic procedure. The following data were presented: (i) all available clinical data; (ii) reason for rejection; (iii) from the EEG-recording during fMRI a characteristic EEG example, the number of IEDs and interobserver agreement; (iv) EEG-fMRI results as statistical parametric maps projected onto a glass brain or structural T1-image. The necessity for invasive EEG studies and surgery was then discussed.

**Results**

Of 64 patients, 29 fulfilled the selection criteria for EEG-fMRI (mean age: 36.6; 13 women). Of these, 13 patients (45%) had no structural lesion on 1.5 T MRI including coronal FLAIR images. A total of 34 EEG-fMRI sessions were performed. EEG-fMRI was repeated in five patients: in three because artefacts made EEG or fMRI interpretation impossible, in one patient, generalized IEDs were so abundant that it was difficult to define focal discharges (the procedure was repeated after benzodiazepine administration that suppressed some, but not all of the IED activity) and in one to verify prior results (512 dynamic scans; this patient was asked to perform motor and sensory tasks to estimate the proximity of the focus to
the motor and sensory cortex). The technically best measurements were used for analysis in these five patients. The vacuum-drawn pillow could not be used for two patients because of their head size, which led to increased movement artefacts and in one patient to discontinuation after 702 dynamic scans because of discomfort. In two other patients discomfort also led to discontinuation after 896 and 680 dynamic scans. In nine patients the measurement was done in two sessions of 512 dynamic scans each for practical reasons.

EEG analysis
A total of 46 IED-sets were analysed. The number of consensus IEDs varied from 3 to 286 (mean 49). Twenty-four studies were evaluated by a third observer because of low interobserver agreement ($k < 0.40$), which resulted in a kappa value higher than 0.40 in two studies. The final interobserver agreement varied from 0.13 to 0.78 (mean 0.44). In one patient no identifiable IEDs occurred during scanning.

fMRI results
A significant BOLD response was found in 17 consensus-IED sets (37%) from 15 patients (Table 1). Of the remaining 29 IED sets, 19 contained fewer than 10 consensus IEDs. Eleven patients (13 IED sets) had a robust outcome i.e. a positive significant BOLD response to consensus IEDs. In eight patients, at least one robust fMRI result was highly topographically related to the IED and these patients were included for further clinical consideration.

When all IEDs from any observer were considered, 26 out of 46 IED sets (57%) showed a significant BOLD response. Positive BOLD responses that were topographically incongruent with the EEG were found in the occipital region or in the mesial structures, together with a diffuse negative BOLD response. Positive BOLD responses were also localized to a more confined source than expected from the EEG. This patient underwent surgery during which acute electrocorticography showed fairly circumscribed IEDs as well as a prolonged, spontaneous electrographical discharge, confirming a seizure onset zone left frontotemporally (Fig. 2b). After resection of a low-grade glioma and anterior temporal lobectomy, the patient experienced sporadic seizures only (Engel II after 6 months of follow-up).

In patient 29, a frontal source was hypothesized but could not be lateralized. EEG-fMRI revealed a BOLD response in the left frontal lobe, to left-sided as well as to right-sided frontal interictal discharges (Fig. 3). He was offered further evaluation by means of implantation of a subdural electrode-grid, but this has been delayed because of a recent improvement in seizure control.

Clinical interpretation
Robust and topographically related EEG-fMRI results were first interpreted in the light of the source localization problem (Table 2). In four out of six foci not clearly localized on EEG, EEG-fMRI showed a circumscribed focus. In four out of five patients with presumed multifocality, EEG-fMRI was also indicative of multifocality, but in one patient clearly favoured one single source.

As a second step these EEG-fMRI results were presented to the clinical forum.

In patient 10, with presumed multifocality and a widespread EEG focus, one of the foci (located left frontotemporally) predominated in EEG-fMRI and could also be localized to a more confined source than expected from the EEG. This patient underwent surgery during which acute electrocorticography showed fairly circumscribed IEDs as well as a prolonged, spontaneous electrographical discharge, confirming a seizure onset zone left frontotemporally (Fig. 2b). After resection of a low-grade glioma and anterior temporal lobectomy, the patient experienced sporadic seizures only (Engel II after 6 months of follow-up).

In patient 29, a frontal source was hypothesized but could not be lateralized. EEG-fMRI revealed a BOLD response in the left frontal lobe, to left-sided as well as to right-sided frontal interictal discharges (Fig. 3). He was offered further evaluation by means of implantation of a subdural electrode-grid, but this has been delayed because of a recent improvement in seizure control.

Patient 1 showed a parasagittal EEG-focus that could be associated with either a confined deep-lying source or a more widespread superficial focus. EEG-fMRI revealed a circumscribed BOLD response involving the medial postcentral gyrus, with an extension into the midline (Fig. 4). Because the focus was median and close to the leg area, surgery was considered too risky. Further steps have not been decided for yet.

Table 1 Summary of IED sets that showed a significant BOLD-response to consensus IEDs

<table>
<thead>
<tr>
<th>Study</th>
<th>EEG</th>
<th>N (kappa)</th>
<th>Positive BOLD</th>
<th>Negative BOLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>CP-r</td>
<td>286 (0.74)</td>
<td>CP-r, OC</td>
<td>–</td>
</tr>
<tr>
<td>2.1</td>
<td>F-r</td>
<td>155 (0.75)</td>
<td>C-r, F-r, T-r</td>
<td>G</td>
</tr>
<tr>
<td>3.1</td>
<td>F-l</td>
<td>196 (0.38)</td>
<td>F-l</td>
<td>–</td>
</tr>
<tr>
<td>3.2</td>
<td>F-l/G</td>
<td>220 (0.66)</td>
<td>M</td>
<td>G</td>
</tr>
<tr>
<td>4.1</td>
<td>F-b</td>
<td>9 (0.44)</td>
<td>F-b</td>
<td>–</td>
</tr>
<tr>
<td>10.1</td>
<td>F-l</td>
<td>55 (1.00)</td>
<td>F-r</td>
<td>–</td>
</tr>
<tr>
<td>12.1</td>
<td>FT-l</td>
<td>66 (0.65)</td>
<td>OC, P-b</td>
<td>–</td>
</tr>
<tr>
<td>13.1</td>
<td>P-b$</td>
<td>181 (0.34)</td>
<td>P-b</td>
<td>–</td>
</tr>
<tr>
<td>14.1</td>
<td>FT-r</td>
<td>12 (0.48)</td>
<td>T-r</td>
<td>–</td>
</tr>
<tr>
<td>15.1</td>
<td>F-r</td>
<td>241 (0.62)</td>
<td>M</td>
<td>G</td>
</tr>
<tr>
<td>17.1</td>
<td>T-r</td>
<td>222 (0.76)</td>
<td>OC</td>
<td>–</td>
</tr>
<tr>
<td>18.1</td>
<td>F-l</td>
<td>41 (0.61)</td>
<td>–</td>
<td>P-l</td>
</tr>
<tr>
<td>21.1</td>
<td>FT-I</td>
<td>21 (0.75)</td>
<td>OC</td>
<td>–</td>
</tr>
<tr>
<td>26.1</td>
<td>FT-I</td>
<td>13 (0.42)</td>
<td>–</td>
<td>P-l</td>
</tr>
<tr>
<td>28.1</td>
<td>FT-I</td>
<td>12 (0.32)</td>
<td>–</td>
<td>P-l</td>
</tr>
<tr>
<td>29.1</td>
<td>F-l</td>
<td>84 (0.50)</td>
<td>F-l</td>
<td>–</td>
</tr>
<tr>
<td>29.2</td>
<td>F-r</td>
<td>28 (0.42)</td>
<td>F-l</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: In superscript the topographical concordance between EEG localization and BOLD response is given: $^*$ same area, ipsilateral, $^1$ same area, contralateral, $^2$ ipsilateral, different area, no concordance. CP = centro-parietal, OC = occipital (bilateral), C = central, FT = frontotemporal, P = (latero-)parietal, T = temporal, G = generalized, F = frontal, M = mesial (basal ganglia and interhemispheric), l = left, r = right, b = bilateral, m = midline. $^*$pt 13 had spatially and morphologically distributed IEDs over both parietal regions, which were also clustered with a spike-clustering software (Van ‘t Ent et al., 2003; Liston et al., 2006). These different clusters also showed biparietal BOLD responses.
### Table 2  Patients re-evaluated for surgery

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age/sex</th>
<th>MRI</th>
<th>Seizure onset</th>
<th>Ictal onset EEG</th>
<th>Interictal</th>
<th>Clinical problem</th>
<th>Category*</th>
<th>EEG-fMRI</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20F</td>
<td>–</td>
<td>arousal, sensation L leg</td>
<td>parasagittal</td>
<td>parasagittal</td>
<td>distribution unclear</td>
<td>1</td>
<td>deep parasagittal (u + c)</td>
<td>improved</td>
</tr>
<tr>
<td>2</td>
<td>25F</td>
<td>–</td>
<td>1 staring</td>
<td>unclear</td>
<td>R frontocentral MEG R central PET R hemisph</td>
<td>R hemisph, focus unclear</td>
<td>1</td>
<td>widespread R hemisph (u + c)</td>
<td>not improved</td>
</tr>
<tr>
<td>3</td>
<td>25F</td>
<td>–</td>
<td>1 automatisms, aphasic</td>
<td>unclear</td>
<td>L frontal, R temp PET - frontal</td>
<td>R temp and L frontal frontal focus unclear</td>
<td>2</td>
<td>L frontal (u + c) and R temp (u) frontal focus confined (u + c)</td>
<td>probable multifocal improved</td>
</tr>
<tr>
<td>9</td>
<td>58F</td>
<td>WML Lowering consciousness</td>
<td>R frontal, L temp SPECT bifrontal</td>
<td>frontal</td>
<td>frontal and L temp frontal focus unclear</td>
<td>2</td>
<td>frontal (u + c), L temp (u) wide-spread frontal focus (u + c)</td>
<td>probable multifocal not improved</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>17M</td>
<td>tumour</td>
<td>epigastric aura</td>
<td>R frontal</td>
<td>L temp biparietal PET - bifrontal</td>
<td>L frontotemp, L temp and R frontal</td>
<td>2</td>
<td>L frontotemporal (u + c)*</td>
<td>unifocal</td>
</tr>
<tr>
<td>13</td>
<td>17F</td>
<td>lesion</td>
<td>1 aura</td>
<td>L temp biparietal</td>
<td>R frontal</td>
<td>L temp and R temporal</td>
<td>1</td>
<td>frontotemporal (u + c)</td>
<td>improved</td>
</tr>
<tr>
<td>14</td>
<td>41F</td>
<td>–</td>
<td>2 tongue apraxia epigastric aura</td>
<td>R temp</td>
<td>biparietal PET - bitemporal</td>
<td>bitemporal</td>
<td>2</td>
<td>R temp (u + c), bitemporal (u)</td>
<td>probable multifocal</td>
</tr>
<tr>
<td>29</td>
<td>24M</td>
<td>MTS L</td>
<td>1 head turn to L 2 myoclonias R hand</td>
<td>L frontotemp</td>
<td>frontal focus unclear</td>
<td>1</td>
<td>L frontal (u + c)</td>
<td>improved</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** F = female, M = male, WML = white matter lesions, MTS = mesiotemporal sclerosis, L = left, R = right, temp = temporal, hemisph = hemisphere. *Category 1 = localization of focus unclear, category 2 = multiple distinctive presumed foci. #right frontal negative BOLD response. u = fMRI not corrected for statistical significance (P < 0.001 for each voxel), c = fMRI corrected according to GFT (P < 0.05).
In patient 3, interictal and ictal EEG activity was found in multiple areas, with bifrontal paroxysms with an unstable maximum over the left side. EEG-fMRI showed a predominant left basofrontal focus (Fig. 5a). On the basis of the EEG-fMRI findings, the patient received subdural electrode strips and depth electrodes implanted through bilateral burr-holes (Van Veelen et al., 1990). IEDs were widespread on interictal intracranial EEG. Ictal onset activity, however, was found to arise from the left frontal lobe and spread rapidly to different sites. This was concordant with

**Fig. 2** Patient 10. (a) Results uncorrected for multiple comparisons are shown ($P < 0.001$, $T > 3.1$ or $<-3.1$) projected onto selected slices in a structural image. Positive BOLD is shown in yellow—red, negative BOLD in green—blue (MRCro, Rorden, USA). The significant positive BOLD response was found in the left frontal lobe, while there was a negative BOLD response in the right frontal lobe. A, B and C: cross-hair in positive maximum. D cross-hair in negative maximum $P < 0.001$ ($T = 3.1$). (b) Schematic drawing of intra-operatively measured surface EEG. The interictal epileptiform discharges (spikes) are shown in blue with maximum amplitude in dark blue. The onset of an electrographical seizure is shown in red.
the EEG-fMRI results showing a predominant left baso-frontal focus (Fig. 5b). This patient was considered not eligible for surgery, because there was overlap between the ictal onset zone and Broca’s area.

In three patients (patients 9, 13 and 14) EEG-fMRI results confirmed the existence of multiple epileptic sources, which corroborated the earlier decision to refrain from further investigations (Fig. 6). In patient 2, EEG-fMRI results collateralized with previous investigations, but did not result in the identification of a more confined focus.

Thus, in four patients (14%) EEG-fMRI results opened new prospects of surgery, which has been performed in one patient so far.
Discussion

This study is the first to investigate the value of EEG-fMRI in clinical practice. EEG-fMRI has the potential to improve source localization in complex cases, especially in patients with an unclear focus on EEG. However, we showed that the technique is also useful in patients with presumed multifocality, as EEG-fMRI can emphasize one of the foci. EEG-fMRI can tip the scales in favour of surgery in complex cases but it can also play a role in avoidance of invasive electrode implantations.

We deliberately took a conservative approach to EEG-fMRI, possibly underestimating its clinical potential by lowering its overall yield. We considered EEG-fMRI results that met strict criteria, to avoid the influence of spurious

![Fig. 5 Patient 3. (a) Results uncorrected for multiple comparisons are shown (P < 0.001, F > 3.5). Data are projected onto a glass brain and selected slices in a structural image are shown. Cross-hair in (positive) maximum, positive BOLD shown in grey—black and yellow—red. A significant positive BOLD response was found in the left frontal lobe. (b) Intracranial EEG. No localized interictal activity was found. Seizures started on the dorsal basolateral side of the frontal lobe (1) and spread basofrontally left (2), thereafter spreading to distant sites.](image-url)
results. This is reflected in the scrutiny of IED identification: although 57% of the IED sets showed a BOLD response if IEDs from any observer were taken, this was the case for only 37% of the IED sets when consensus had been reached. We also discarded topographically unrelated and negative BOLD responses to enhance interpretation and avoid speculation.

When studying a cohort of patients rejected because source localization failed with a number of established methods, the *a priori* chance that any novel technique, especially one based on interictal EEG, has a high impact, is low. For instance, in spite of our selection criterion of a minimum of 10 IEDs in previously recorded EEGs, there was a paucity of IEDs in the actual EEG-fMRI recording in several patients. This partly explains the low overall yield in comparison to that of other studies (Lemieux *et al.*, 2001; Bagshaw *et al.*, 2004). It is likely that the concordance between EEG spike field distribution and the BOLD response will be higher in patients with a clear-cut EEG focus, but then new techniques are not needed for clinical decision-making in these patients.

Our yield of EEG-fMRI would have been higher if we had used less strict selection criteria. EEG-fMRI depends on the number of EEG spikes during MRI acquisition. Clearly, our requirement that there be minimally 10 IEDs in previously recorded EEG does not guarantee the presence of enough IEDs in the actual EEG-fMRI conditions in several patients. If there are scarce events, the signal-to-noise ratio will be low in fMRI, leading to false negative results. Also, this study assesses the current added value, as outcome depends on the ‘state of the art’ of EEG-fMRI. We expect the clinical yield of EEG-fMRI to increase with ongoing improvement of insight and knowledge of registration and analysis techniques.

We defined clinical value as neutrally as possible, in recognition of the fact that practices differ between epilepsy centres, especially in the availability and use of intracranial EEG (Siegel, 2004). We hypothesize that EEG-fMRI will prove particularly useful in the first steps of clinical interpretation, in delineating an unclear EEG source and defining multifocality. However, the decision regarding surgical candidacy or the need for additional investigations will reflect the philosophy of individual centres. Although the threshold for invasive EEG recordings is relatively high in the Netherlands, the surgery-rejection rate is similar to that reported in other countries (Berg *et al.*, 2003) and all non-invasive source localization techniques like specific MR sequences, PET, SPECT, MEG, as well as intracranial EEG monitoring with subdural electrodes are available.

Some of the EEG-fMRI results raise questions of the mechanisms underlying interictal spike generation. For example, negative BOLD responses which in our patients were confined to specific brain regions that are not topographically related to the IED distribution. Current explanations of negative BOLD responses are that they either reflect a concurrent change in the default state of the brain, favouring certain regions (Raichle *et al.*, 2001; Gotman *et al.*, 2005; Laufs *et al.*, 2006) or reflect a redistribution of cortical blood resources (Harel *et al.*, 2002). The frequently encountered occipital and generalized negative BOLD response is consistent with the first explanation. The negative BOLD responses in patients

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**Fig. 6** Patient 13. Results uncorrected for multiple comparisons are shown (*P* < 0.001, *F* > 70). Data are projected onto a glass brain and selected slices in a structural image are shown. Cross-hair in (positive) maximum, positive BOLD shown in grey–black and yellow–red. Significant positive results were found right and left parietal.
18, 26 and 28 occurred in arterial water-shed areas, and thus might be explained by intrahemispheric reallocation of blood (van der Zwan et al., 1993). The negative BOLD response in the contralateral frontal lobe in patient 10 might be due to interhemispheric steal via the anterior communicating artery, as has been reported in patients with unilateral carotid artery stenosis (Vriens et al., 2001). Like their negative counterparts, positive BOLD responses that were not topographically related to IEDs were seen in specific constellations. Such a positive BOLD response was seen in the mesial structures together with a generalized negative BOLD response, as reported previously in (secondarily) generalized epilepsy and sporadically in focal epilepsy. Like negative BOLD responses, positive distant BOLD responses were also frequently seen in the occipital region. This is probably a patient-independent finding: the occipital region is sensitive to both negative and positive changes in the default state of the brain and to changes in blood flow. Recently, it was found that the occipital oxygenation relates to changes in the alpha rhythm (de Munck et al., 2007). Interictal activity may influence the generators of the alpha rhythm, causing a change in occipital blood flow.

On the basis of our results we propose the following clinical guidelines for application of EEG-fMRI:

1. The best indication is for source localization in (i) extratemporal (MRI-negative) epilepsy and (ii) when questions about the depth of the source arise;
2. In the case of presumed multifocality, EEG-fMRI will likely confirm this hypothesis, but incidentally it can favour one of the putative sources;
3. A priori allocation of a region of interest is crucial: topographically unrelated co- (de)activation may lack a clinical relevance;
4. EEG-fMRI can guide invasive electrode placement;
5. In addition to robust results, uncorrected data should also be reviewed.

EEG-fMRI is essentially an inexpensive technique, requiring minimal investment in additional hardware and software. It provides additional information about the epileptic source in the presurgical work-up of complex cases, influencing clinical decision-making either by strengthening or refining the source localization hypothesis derived from other non-invasive techniques. The impact of any additional successful resection is high, both in terms of quality of life of the patient and on society if the patient is young and may return to work.

Our study prompts the need for subsequent studies comparing source localization with EEG-fMRI to other techniques and to extend knowledge about the underlying physiology of topographically distant and negative BOLD responses. The yield of EEG-fMRI may increase by using improved fMRI sequences and decreasing the number of EEG artefacts, using improved software and by increasing patient comfort during acquisition. The question of how to identify epileptiform EEG events (consensus versus non-consensus) and how to evaluate events with a different topographic distribution also needs to be addressed. Provocative measures (such as sleep deprivation or medication) that influence the number of IEDs may be relevant to increase the diagnostic yield of EEG-fMRI.

Acknowledgements

This project was supported by the Netherlands Organization for Scientific Research (NWO) grant no. 945-05-039. We thank all patients, their treating neurologists and the members of the Dutch Collaborative Epilepsy Surgery Program for their participation.

References


