EEG-correlated fMRI and Post-operative Outcome in Focal Epilepsy

Rachel Thornton, Helmut Laufs[*], Roman Rodionov, Sajitha Cannadathu, David W Carmichael, Serge Vulliemoz, Afraim Salek-Haddadi, Andrew W McEvoy, Shelagh M Smith, [2]Samden Lhatoo, [3]Robert D C Elwes, [4]Maxime Guye, Matthew C Walker, Louis Lemieux, John S Duncan

National Society for Epilepsy MRI Unit, Chalfont St Peter, Buckinghamshire, SL9 0RJ and Department of Clinical and Experimental Epilepsy, Institute of Neurology UCL Queen Square, London, WC1N 3BG, UK

National Hospital for Neurology and Neurosurgery, UCL Hospitals NHS Trust, London, WC1N 3BG, UK

[2]Department of Neurology, North Bristol NHS Trust, Frenchay Hospital, Frenchay Road, Bristol, UK

[3]Department of Neurophysiology, Kings College Hospital, Denmark Hill, London, UK

*current address: Department of Neurology and Brain Imaging Center, Johann Wolfgang Goethe-University, Frankfurt am Main, Germany

[4] Centre de Résonance Magnétique Biologique et Médicale (CRMBM), UMR CNRS 6612 & Service de Neurophysiologie Clinique, INSERM U 751,CHU Timone, AP-HM, Faculté de Médecine de Marseille, Université de la Méditerranée, 27 Bd Jean Moulin, 13005 Marseille

Word Count (Abstract): 247

Word Count (Body of Text): 3380

Disclosure: The Authors report no conflict of interest.

.

Abstract

Background: The main challenge in assessing patients with epilepsy for resective surgery is localising seizure onset. Frequently, identification of the irritative and seizure onset zones requires invasive EEG. EEG-correlated fMRI (EEG-fMRI) is a novel imaging technique which may provide localising information with regard to these regions. In patients with focal epilepsy, interictal epileptiform discharges (IED) correlated BOLD (blood oxygen dependent level) signal changes are observed in approximately 50% of patients where IEDs were recorded. In 70% these are concordant with expected seizure onset defined by non-invasive electroclinical information. Assessment of clinical validity requires post-surgical outcome studies which have, to date, been limited to case reports of correlation with intracranial EEG. We assessed the value of EEG- fMRI in patients with focal epilepsy who subsequently underwent epilepsy surgery and related IED-correlated fMRI signal changes to the resection area and clinical outcome

Methods: We recorded simultaneous EEG-fMRI in 76 patients undergoing presurgical evaluation and compared IED-correlated pre-operative BOLD signal change with resected area and post-operative outcome.

Results : 21 patients had activations on EEG fMRI of whom 10 underwent surgical resection. 7/10 patients are seizure free following surgery and the area of maximal BOLD signal change was concordant with resection in 6/7. In the remaining 3, with reduced seizure frequency post-surgically, there were areas of significant IED correlated BOLD signal change outside the resection. 55 patients had no activation on EEG fMRI of whom 42 subsequently underwent resection.

Conclusion: These results show potential value for EEG-fMRI in pre-surgical evaluation.

INTRODUCTION

In refractory focal epilepsy, surgical resection has the best chance of a good outcome if seizure onset is identified and remote from eloquent cortex[1]. The challenge of pre-surgical evaluation rests in accurate delineation of these regions. High-quality structural MRI has increased the identification of underlying pathology in epilepsy, but successful resective surgery is increasingly possible in the absence of MRI abnormalities [2;3], while the epileptogenic zone may extend beyond the margin of abnormal tissue where pathology is seen[1]. Standard non-invasive means can fail to localise seizure onset and invasive EEG recording is often necessary, which is expensive and has associated morbidity [4]. Intracranial recording requires careful patient selection and 70- 90% of such patients will subsequently be offered surgical resection [5]. There is a pressing need therefore, for non-invasive techniques to identify these regions and assist in the planning of invasive recording, which have been developed over recent years.

FDG PET (fluorodeoxyglucose positron emission tomography) and ictal-interictal SPECT (single photon emission computed tomography) are helpful, but lack the spatial resolution of MRI. Neurophysiological approaches (high density EEG, and magneto encephalography (MEG)) have shown concordance with intracranial recording and postoperative outcome; i.e. have some positive predictive value[6;7], but despite excellent temporal resolution, are limited by the accuracy of source localisation.

 EEG-correlated fMRI (EEG-fMRI), whereby EEG and fMRI are acquired simultaneously, reveals regions of blood oxygen level-dependent (BOLD) signal changes associated with inter-ictal (IED) and ictal epileptiform discharges which may provide information about the epileptic network. The methodology combines the spatial resolution of MRI with the temporal resolution of EEG and applying EEG-fMRI to pre-surgical evaluation has been a important motivation for the technique's development [8-12].

To date, clinical validation of EEG-fMRI has consisted of studies comparing IED-correlated BOLD signal change with invasive and non-invasive methods of localising the seizure onset zone [13 11;12, 9 14;15] reporting up to 70% concordance (co-localisation of areas of maximal positive BOLD signal activation and presumed seizure onset at a lobar level)between IED BOLD activations and electro-clinical seizure onset in patients with focal epilepsy.

Comparison of novel localisation techniques in focal epilepsy with intracranial EEG, the current gold standard is considered the best method for validation [16], but the approach has drawbacks. Intracranial EEG records directly from regions of interest, but has reduced spatial coverage owing to the limited number of electrodes which can be implanted. The problem of source reconstruction found in scalp EEG is not abolished as many regions of interest cannot be accurately sampled using current methods. Nevertheless, it remains one of the best methods of identifying the likely irritative and epileptogenic zones before resection. In EEG fMRI research, concordance of activations with the irritative zone recorded during invasive monitoring have been reported in small groups, an important step in establishing the technique's clinical utility [12;14;17]. One group specifically addressed the use of EEG-fMRI in surgical planning[18], carrying out studies in a group of 29 patients previously rejected for surgery with frequent IEDs. They reported useful EEG-fMRI results in 6 patients, 4 of whom proceeded to surgical resection and suggested that EEG-fMRI may contribute to the surgical decision making process when standard methods did not identify a surgical target [18].

.

Here we compared EEG-fMRI results in a group of patients undergoing surgery with post-operative outcome, assessing whether resection of a region exhibiting IED-correlated BOLD activation was associated with post-operative seizure freedom.

METHODS

Patients

76 patients with refractory focal epilepsy undergoing pre-surgical evaluation underwent EEG-fMRI between December 2005 and May 2008.

Clinical course

Patients underwent electro-clinical assessment including video EEG, clinical examination and structural MRI (National Hospital for Neurology and Neurosurgery Epilepsy protocol). The decision regarding electro-clinical localisation and subsequent resection was made by the clinical team and undertaken with curative intent. 6 patients underwent anterior temporal lobe resection, and 4 underwent neocortical resection (2 frontal, 1 parietal, 1 occipital).

The extent of resection, histopathological diagnosis and International League Against Epilepsy (ILAE) outcome [19] were recorded 1 year post-operatively.

EEG-fMRI Acquisition

All patients underwent EEG-fMRI for between 35 and 60 minutes at 1.5 or 3T. Patients lay still in the scanner with their eyes closed and with no instruction regarding vigilance. EEG was recorded continuously during fMRI using MR-compatible systems (Brain Products, Munich, Germany) along with a scanner synchronisation signal and ECG. Sets of 404 T2*-weighted single-shot gradient-echo echo-planar images (EPI; TE/TR 30/3000 msec at 3T; TE/TR 0.5/3000 msec at 1.5T), flip angle 90: 43 (at 3T) and 21 at 1.5T, interleaved slices (thickness: 3mm at 3T; 5mm at 1.5T), FOV 24x24cm^2, 64^2) were acquired continuously on GE MR scanners (GE Medical Systems, Milwaukee). Offline MRI and pulse related artefact were removed from the EEG trace [20,21] and events marked.

fMRI processing and analysis:

The fMRI time-series were realigned, spatially smoothed with a cubic Gaussian Kernel of 8 mm full width at half maximum and analysed using a general linear model (GLM) in SPM5 (www.fil.ion.ucl.ac.uk/SPM) to identify IED-related BOLD changes. Separate sets of regressors were formed for each type of IED allowing identification of specific BOLD effects. Discharges were represented as zero-duration events (unit impulse, or 'delta', functions) convolved with the canonical haemodynamic response function its temporal and dispersion derivatives, resulting in three regressors for each event type[22]. Ictal events were modelled as 3 'blocks' representing earliest electrographic change, clinical seizure onset and post-ictal change on the EEG.

Motion-related effects were included in the GLM as 24 regressors representing 6 scan realignment parameters and a Volterra expansion of these [23], and Heaviside step functions for large motion effects [24]. Additional regressors were included for pulse-related signal changes [25].

F-contrasts were used across three regressors corresponding to each event type with a threshold of $p<0.05$ corrected for multiple comparisons (family-wise error) considered significant. A T-contrast ($p<0.001$ uncorrected for multiple comparison) assessed whether the haemodynamic response function was positive or negative. BOLD responses were considered positive when a positive HRF was plotted for a given cluster. A less stringent significance threshold was used to explore the data ($p<0.001$, uncorrected). EPI data were co-registered to the pre-operative T1-weighted images to create activation map overlays [26]. Clusters of significant BOLD change were labelled anatomically on high resolution EPI images and co-registered with pre-operative structural T1 images.

Post-operative imaging

Postoperative T1-weighted MRI was acquired and co-registered with the pre-operative images allowing visualisation of fMRI activation maps in relation to the area of resection. Concordance was defined for the cluster of BOLD activation containing the global maximum.

.

RESULTS

76 patients underwent EEG-fMRI recordings. 52 (68%) of these have subsequently undergone surgical resection. 34/52 (65%) have reached one year follow up of whom 10 (33%) had significant activation on EEG-fMRI. A further 11 had significant activation on EEG-fMRI, but did not undergo surgery owing to an extensive epileptogenic zone or overlap with motor function (n=5), intra-operative complications (n=1), patient choice (n=1) or awaiting further evaluation (n=4). In 36/52 (69%) patients who were operated and 13/24 (54%) who were not operated, no IEDs were recorded.

Clinical data and EEG-fMRI results are summarised in table 1. The median number of IEDs was 329 (range 22-635)

Table 1

	Scanner (Tesla)	Electro-clinical localisation	Semiology	Structural MRI	Pathology	ILAE outcome	EEG fMRI Activation
1	1.5	L mesial TLE	Epigastric aura, Oroalimentary automatisms.	L HS	HS	1	L anterior temporal lobe (FWE p<0.05)
2	1.5	L mesial TLE. L	Epigastric aura, oroalimentary automatisms, L-manual automatisms.	L HS	HS	1	Anterior portion L inferior temporal gyrus (FWE p<0.05)
3	1.5	L TLE.	From sleep. Nauseated, hyperventilation. L-sided manual automatisms.	L HS	HS	1	L anterior temporal lobe (FWE p<0.05)
4	3	R TLE.	Hyperventilation, confusion. Bilateral manual automatisms.	R HS, previous resection	HS	1	R mesial temporal lobe (unc. p<0.0001)
5	3	Non-lateralised TLE . Ictal icEEG: bilateral EZ	Behavioural arrest, fear, right hand dystonia, head turning to R.	L HS	HS	1 *	R and L lateral temporal lobes (FWE p<0.05)
6	3	R TLE	Hyperventilation, loss of awareness, manual automatisms	R HS	HS	1	Ictal: Right mesial temporal (FWE p<0.05) IED: none
7	3	R posterior epilepsy	Visual hallucination, incontinence, loss of awareness	R occipital FCD	FCD	4	Ictal: Right medial occipital (FWE p<0.05) IED: none
8	3	L FLE. Ictal icEEG, EZ posterior to FCD. Widespread IZ	From sleep, unresponsive, but awake. Rapid blinking. R arm posturing. Head turning to R.	L inferior frontal gyrus FCD	FCD grade 2a	4	L pre-central gyrus and superior temporal gyrus ,
9	3	R PLE	Sensory change left foot, clonic movements left t arm and leg	R parietal FCD	FCD grade 2a	1	Ictal: Maximal right parietal, but widespread (FWE p<0.05) No IED
10	3	R FLE	Speech arrest, head version to L, clonic movements L hand and foot	R frontal atrophy	Normal	4	IED and ictal

Abbreviations: R = right, L = left, TLE = Temporal lobe epilepsy, FLE = Frontal lobe epilepsy, PLE = Parietal lobe epilepsy, icEEG = intracranial electroencephalogram, HS = hippocampal sclerosis, FCD = focal cortical dysplasia *ILAE Outcome 1, no habitual seizures persistent right sided abnormalities on EEG and occasional auras

Case 1

Patient with left mesial temporal lobe epilepsy and left hippocampal sclerosis on structural MRI at 1.5 Tesla. Interictal EEG revealed left temporal spikes. EEG-fMRI showed widespread activation in the left anterior temporal lobe. Comparison with the post-operative T1 weighted MRI showed the IED-related BOLD cluster within the resection margins. The patient is seizure free (ILAE class 1) 38 months post-surgery (Figure1).

Case 2

Patient with left mesial temporal lobe epilepsy and left hippocampal sclerosis on structural MRI. Interictal EEG revealed left temporal spikes. EEG-fMRI showed activation in the left anterior temporal lobe. Comparison with the post-operative scan showed the IED-related BOLD activation contained within the resection. The patient is seizure free (ILAE class 1) 49 months post-surgery.

Case 3:

Patient with left mesial temporal lobe epilepsy and left hippocampal sclerosis. Interictal EEG revealed left temporal spikes. EEG fMRI showed activation in the left anterior temporal lobe. Comparison with the post-operative scan showed the IED related BOLD activation contained within the resection. The patient is seizure free (ILAE class 1) 30 months post-surgery (Figure 2).

Case 4:

Patient with right hippocampal sclerosis and previous resection for a right superior temporo-parietal cavernoma. EEG-fMRI revealed activation in the right mesial temporal lobe. Right anterior temporal lobe resection following confirmation of seizure onset on intracranial EEG was carried out. Comparison with the post-operative scan showed the IED related BOLD activation contained within the most recent resection. The patient remains seizure free. (ILAE class 1) 24 months post-surgery

Case 5:

Patient with left hippocampal sclerosis. EEG showed independent right and left temporal IEDs. EEG-fMRI revealed bilateral temporal BOLD activations. Intracranial recording demonstrated 70% of seizures originated from left mesial temporal structures with a further 30% having simultaneous bilateral onset, and left anterior temporal lobe resection was carried out. The patient has had no further complex partial seizures 18 months post-surgery, but medication was unchanged and the EEG remains extremely active over the right temporal electrodes (ILAE 1) (figure 3).

Case 6

Patient with right hippocampal sclerosis. EEG revealed right temporal sharp waves. Interictal EEG-fMRI demonstrated BOLD deactivation in the default mode network, but no activation was observed. Ictal EEG-fMRI demonstrated activation

.

in the right anterior temporal lobe, with deactivation in the right posterior temporal lobe and contralateral hemisphere. Right anterior temporal lobe resection was carried out and the area of maximal activation lay within resection margins. The patient is seizure free (ILAE class 1) 14 months post-surgery.

Case 7:

Patient with right occipital-parietal cortical dysplasia. Electroclinical localisation suggested right occipital onset. During EEG-fMRI two seizures were recorded with widespread posterior slowing on EEG. Maximal BOLD activation was recorded in the right medial occipital lobe associated with the earliest detectable change on EEG. Intracranial recording revealed seizure onset predominantly in the right lateral occipital lobe, but the irritative zone also involved right mesial and left sided contacts. A wedge resection was carried out in the right occipital and parietal lobes and the patient has a reduced number of seizures 12 months following surgery (ILAE class 4).

Case 8:

Patient with FCD in the left middle frontal gyrus on MRI. EEG revealed left frontal spikes and rapid discharges. The lesion was not concordant with the most significant IED correlated left frontal BOLD activation, but an activation at a lower level of significance ($p < 0.001$ uncorrected for multiple comparisons) in the left anterior frontal lobe was observed correlated with rapid discharges on the EEG. Intracranial recording demonstrated an extensive irritative zone with seizure onset anterior to the lesion concordant with the less significant BOLD activation, and independent spikes in inferior frontal lobe and superior temporal depth electrodes. Left frontal lobe resection was carried out and (figure 4) with seizure frequency halved (ILAE class 4) 27 months post-surgery.

Case 9:

Patient with right post-central gyrus FCD on 3T-MRI. Electro-clinical localisation suggested right parietal seizure onset. During EEG-fMRI there were no IEDs, but two electrographic seizures were recorded with build up of fast activity at Fz-F4 followed by right sided slowing. Fast activity was correlated with intense, widespread BOLD signal change in the right paramedian frontal and parietal lobes. Intracranial EEG confirmed seizure onset in the right medial post-central gyrus. The patient is seizure free following resection of FCD (ILAE class 1) 12 months post-surgery.

Case 10

Patient with right frontal atrophy. Electroclinical localisation suggested right frontal seizure onset. During EEG-fMRI, bifrontal spike wave discharges were recorded most marked in F4. Electrographic seizures were recorded with similar EEG appearance. Maximal BOLD activation in the right mesial pre-motor cortex with further clusters in the right supplementary motor area and right orbitofrontal cortex was associated with both ictal and interictal activity. Limited right frontal resection was carried out guided by intracranial EEG, and the region of activation extended beyond resection margins. Seizure frequency was unchanged at 12 months (ILAE class 4).

DISCUSSION

This series of patients with refractory focal epilepsy demonstrates good correspondence between the localisation of IED-related BOLD changes, the area of resection and seizure outcome, with useful information gleaned in 10/42 patients in whom resections were carried out and the requisite follow up period reached. In six of the seven cases that are seizure free post-operatively, the area of resection included the locus of maximum BOLD signal increase. No IED was captured during EEG-fMRI in case 6 but one cluster of ictal-correlated BOLD signal increase lay within the resection margin. In the remaining three patients who continued to have seizures after surgery the areas of maximal BOLD activation did not overlap with the resected area. Although the clinical outcomes in these patients are expected given their diagnoses, these results support the contention that IED and ictal EEG-fMRI BOLD signal change are linked to seizure onset zone in focal epilepsy. The EEG-fMRI data did not contribute to the surgical decision giving an unbiased evaluation of a potential role for the technique in pre-surgical evaluation.

Methodological Considerations

1. EEG fMRI yield and confounding factors

EEG-fMRI relies on the recording of events during the scanning period, a problem shared with both MEG and standard EEG. Events were captured in 40% of the patients in this group, which appears low, but previous studies of EEG-fMRI often exhibit a selection bias, considering only patients with a very active resting EEG[11;12] in contrast to this study.

Our approach to fMRI data modelling is designed to ensure that regional BOLD changes explained by confounding factors are not considered as effects of interest, by incorporating these features in the model. We generally use a stringent threshold of $p < 0.05$ FWE corrected for multiple comparisons, but in one case have reported the uncorrected, but statistically significant result as this is confirmed on intracranial recording. We employ rigid techniques to correct for physiological noise. While the statistical tools used to produce maps of activity are designed to control for rates of false positive findings, lack of significant BOLD activation essentially represents low signal-to-noise ratio (particularly owing to high noise reflecting variance in the baseline) which may be scanner-related or physiological. While conservative measures to correct for physiological noise improve the specificity of the model, smoothing restricts the spatial resolution as do distortions in the EPI data discussed below.

It seems clear that BOLD increases generally reflect increases in neuronal activity, but in the case of epileptic activity recorded on EEG the relationship is not so clear-cut. Previous reports suggest seizures and IEDs associated with a positive BOLD response[27]. Importantly, lack of activation does not allow any firm inferences to be made on the level of brain activity and in particular lack of regional epileptic activity in this context.

.

2. Limits of an interictal study

Caution is required in extrapolating the results of any interictal investigation to make inferences about the epileptogenic zone, although the development of an interictal method that may contribute to identification of the epileptogenic zone has advantages. It is clear that EEG-fMRI does not image the epileptogenic zone even in the context of ictal recordings, but rather that these results are concordant with seizure onset in straightforward cases and may offer hypotheses for further evaluation in complex cases.

3. Comparison of EPI and T1 weighted imaging

Coregistration of T1 images and EPI for the localisation of BOLD signal change is problematic particularly when complicated by changes in brain structure. We addressed this by comparing individualised SPMs of BOLD signal change with each subject's postoperative T1 volume scan, ensuring accurate anatomical localisation of the area of BOLD signal change. Spatial smoothing limits the resolution of EPI, but we found visual comparison adequate to compare activations with the resected region.

Clinical Significance

Previous studies in focal epilepsy demonstrate regions of IED-related BOLD signal change, often concordant with the seizure onset zone determined by electro-clinical localisation both in temporal and extra-temporal lobe epilepsy and our data support these findings [9;11;12;28].

Validation of the technique's clinical use must now depend on demonstrating added value and can be achieved by comparing the EEG-fMRI findings with those of intra-cranial EEG. However, successful demonstration of a new localisation technique's capability to predict post-surgical outcome remains the gold standard against which all localisation methods are judged. In this series we demonstrated that resections which completely removed the region in which IED correlated BOLD signal change were generally associated with seizure freedom, while the finding that areas of significant BOLD activation lying outside of the resection was predictive of poorer outcome in this unbiased sample. It can be argued that the outcomes are unsurprising given the diagnoses, especially in patients with hippocampal sclerosis, but this is a test that any new technique must pass.

In case 5, bilateral activations were observed in relation to runs of left temporal IED, while electroclinical evaluation suggested bilateral seizure foci. .Despite the lack of seizures post surgically, routine scalp EEG remained very active following resection with frequent runs of IEDs, an independent predictor of poor outcome[7;29] This lends support to the theory that multiple EEG-fMRI activations may be predictive of poor outcome in surgery [18]. Cases 7, 8 and 10, where the most significant activations lay outside the region of resection and the epileptogenic and irritative zones were confirmed to be extensive on intracranial recording, lend further support to this hypothesis.

In cases 6 and 9 interpretation is more difficult as ictal activity was recorded during EEG-fMRI. BOLD activations were more widespread, but spatially concordant with seizure onset, similar to previous reports of ictal EEG-fMRI in focal epilepsy [30;31]. Although the areas of activation were more widespread than the resected area, it is notable that the area of most significant early ictal correlated positive BOLD signal change was within the resected tissue in both cases.

Deactivations

This study focused on positive BOLD signal change, similar to previous investigations which assessed concordance of BOLD signal change and seizure focus. W observed deactivations remote from the seizure onset zone in 7/10 cases. This work did not focus on BOLD deactivations which evidence suggests may be represent regions functionally connected with the irritative zone and reflect neuronal inhibition[32-34]. Deactivations in these cases were predominantly limited to the contralateral hemisphere and the 'default mode network', similar to previous reports of IED associated EEG fMRI, which suggested that such deactivations may represent a sub-clinical suspension of the resting state related to interictal events [33].

Non-resected group

In 24 patients resection was not carried out including 11 who had activations on EEG-fMRI. The results are not discussed in detail here, but it is notable that in those patients in whom the seizure onset zone was found to be extensive on intracranial recording, EEG fMRI activations were also generally widespread. It is notable that fewer events were recorded in the group that underwent resection compared to those that did not and in particular a greater proportion of patients who underwent resection had no IEDs compared to those who did not (69% vs. 54% of patients with no IEDs). This reflects the case mix, in particular the higher proportion of patients in the resected group with mesial temporal lobe epilepsy, in whom fewer IEDs are observed on scalp recordings in general.

Further Work

These results suggest that the EEG-fMRI has potential use as a clinical tool, particularly in the sub-group of patients in whom the EEG is active, but localisation using conventional means is difficult. Further work is required to establish its validity in larger patient groups with specific syndromes, in particular those undergoing intra-cranial recording[18] and also to identify those sub-groups in whom the technique adds most value to existing methods of pre-surgical assessment. Larger studies with longer post-operative follow up periods will add to the evidence base. Improvement in EPI acquisition and co-registration between MRI modalities may be able to extend the usefulness of EEG-fMRI.

Conclusion

Our results suggest that localisation based on EEG-fMRI of interictal and ictal activity may be a useful adjunct to the pre-operative work up of patients in whom surgery for focal epilepsy is being considered, particularly when standard data does not indicate a clear-cut focus. We demonstrate good concordance of IED-correlated BOLD with the seizure onset zone

.

and the observation that the presence of IED-correlated BOLD activations remote from the seizure onset zone is associated with poorer outcome is particularly interesting. These findings support the argument that EEG-fMRI may have a valuable role in pre-surgical evaluation in focal epilepsy.

Copyright Licence Statement

.

FIGURE LEGENDS

Figure 1

Patient 1:

A. EEG-fMRI. Left temporal spike correlated activation overlaid on EPI in individual space (p<0.05 FWE corrected for multiple comparisons, SPM postitive z = 6.89) Crosshair at global maximum.

B. Event related response for the same IED correlated BOLD at global maximum. Event (spike) related haemodynamic response + 90% confidence interval (dashed lines). Time = time in seconds after event.

C. Post operative T1 weighted image showing resected region in same location as BOLD response.

Fig 2

Patient 3

A. EEG-fMRI. Left temporal spike correlated activation overlaid on EPI in individual space (p<0.05 FWE corrected for multiple comparisons, z = inifinite). Crosshair at global maximum.

B. Plotted response for the same events at global maximum. Event (spike) related haemodynamic response + 90% confidence interval (dashed lines). Time = time in seconds after event.

C. Post operative T1 weighted image showing resected region in same location as BOLD response.

Figure 3

Patient 5

A. EEG-fMRI. Left and right temporal activation on EPI in individual space (p<0.05 FWE corrected for multiple comparisons SPM-F test, z = 5.39). Crosshair at global maximum

B. Plotted response for the same events at global maximum. Event (spike) related haemodynamic response + 90% confidence interval (dashed lines). Time = time in seconds after event.

C. Post operative T1 weighted image showing resected region on contralateral side to global maximum

Figure 4

Patient 8. Left frontal lobe epilepsy.

A. Left fronto-temporal correlated BOLD activation overlaid on high resolution EPI (FWE corrected for multiple comparisons, p<0.05, z = 6.8). Crosshair at global maximum.

B. Plotted response for same events.

C. Same (yellow) and left frontal polyspike correlated activation (green, p<0.0001, uncorrected, z= 4.17)shown over T1 weighted MRI.

D. Post-operative T1-weighted MRI. All images at 3T in individual space.

LEGENDS:supplemental data files

Supplemental Data Figure 1s

Patient 2

A. EEG-fMRI. Left temporal spike correlated activation overlaid on EPI in individual space (p<0.05 FWE corrected

for multiple comparisons, z = 5.13). Maximal BOLD response indicated by position of crosshair. .

B. Plotted response for the same events at global maximum. Event (spike) related haemodynamic response + 90%

confidence interval (dashed lines). Time = time in seconds after event.

C. Post operative T1 weighted image showing resected region in same location as BOLD response.

Figure 2s

Patient 4

A. EEG-fMRI. Right temporal activation on EPI in individual space (p<0.0001 uncorrected for multiple comparisons

z = 3.29). Crosshair at global maximum

B. Plotted response for the same events at global maximum. Event (spike) related haemodynamic response + 90%

confidence interval (dashed lines). Time = time in seconds after event.
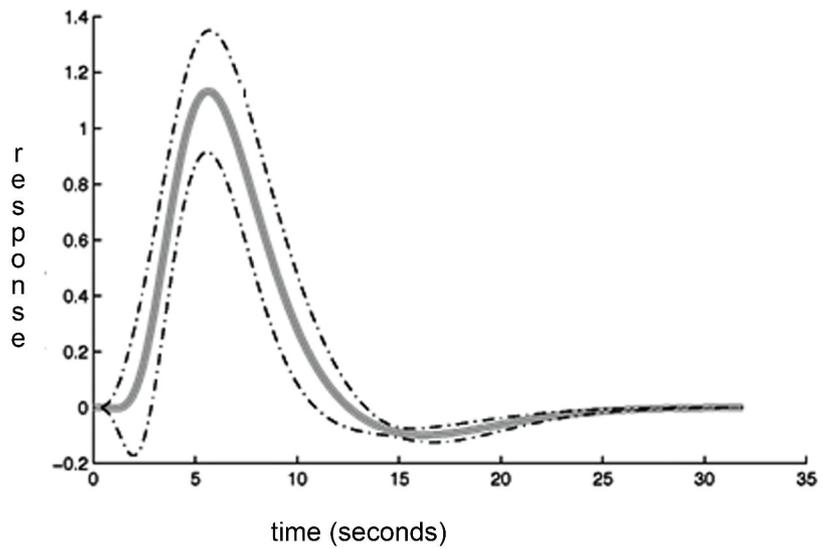
C. Post operative T1 weighted image demonstrates activation is concordant with right anterior temporal lobe

subsequently resected. Posterior region of resection is following previous surgery for a cavernoma.

Figure 3s

Patient 6: activation

A. Pre-operative early ictal BOLD activation overlaid on EPI image. (SPM F-test, corrected for multiple

comparisons FWE p<0.05, z = 7.26). Crosshair at global maximum.

B. Plotted response for the same events at global maximum. Event (early ictal EEG change) related

haemodynamic response + 90% confidence interval (dashed lines). Time = time in seconds after event onset. Note

response in right posterior temporal lobe and contralateral hemisphere is negative. No interictal BOLD response

was observed in this patient.

C. post-operative resection seen on T1-weighted coronal MRI.

Figure 4s

Patient 7

A. Pre-operative early ictal BOLD activation overlaid on EPI image (SPM F-test corrected for multiple comparisons

FWE p<0.05, z =.7.96) Crosshair at global maximum.

B. Plotted response for the same events at global maximum, Event (early ictal change) related haemodynamic

response + 90% confidence interval (dashed lines). Time = time in seconds after event onset. Note response in

contralateral hemisphere is negative. No interictal BOLD response was observed in this patient.

.

C. Site of seizure onset (green) and irritative zone (red) overlaid on volume rendering of T1 weighted MRI.

D. Post-operative resection seen on T1-weighted coronal MRI (single illustrative slice shown).

Figure 5s

Patient 9: Right parietal lobe epilepsy

A. Pre-operative early ictal BOLD activation overlaid on EPI image. (SPM F-test, corrected for multiple comparisons FWE p<0.05, z = 48.2). Crosshair at global maximum.

B. Plotted response for the same events at global maximum. Event (spike) related haemodynamic response + 90% confidence interval (dashed lines). Time = time in seconds after event.

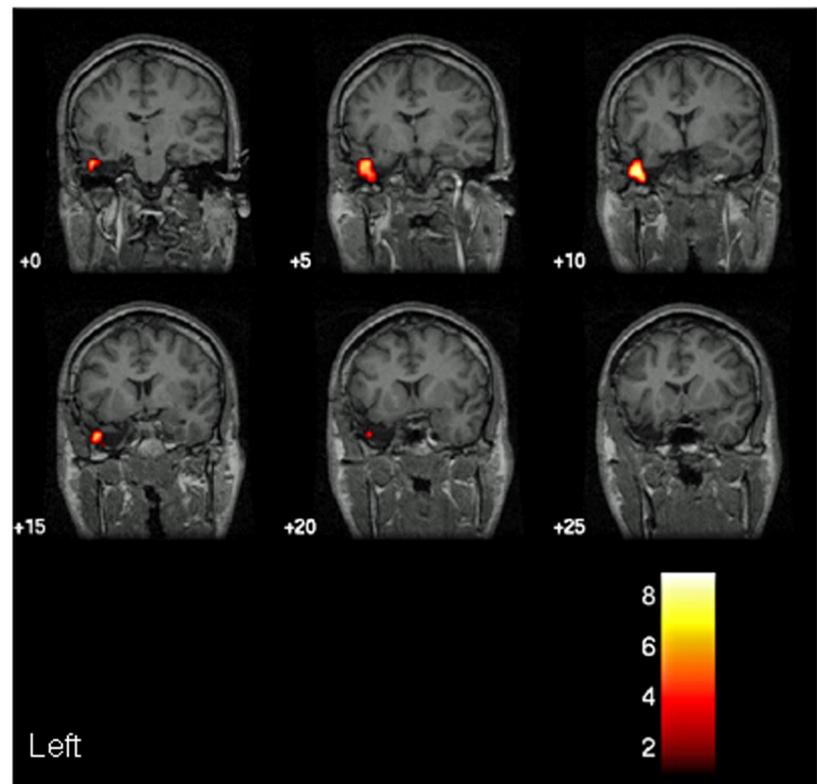**C. Post-operative resection seen on T1-weighted coronal MRI. Note resection is posterior to maximal ictal EEG-fMRI activation, but includes region of significant BOLD signal change.**

Figure 6s

Patient 10: Right frontal lobe epilepsy

A. Interictal and electrographic seizure- correlated BOLD activation (SPM F-test, corrected for multiple comparisons FWE p< 0.05, z=

B. Plotted response for the same events at global maximum. Event (spike) related haemodynamic response + 90% confidence interval (dashed lines). Time = time in seconds after event.

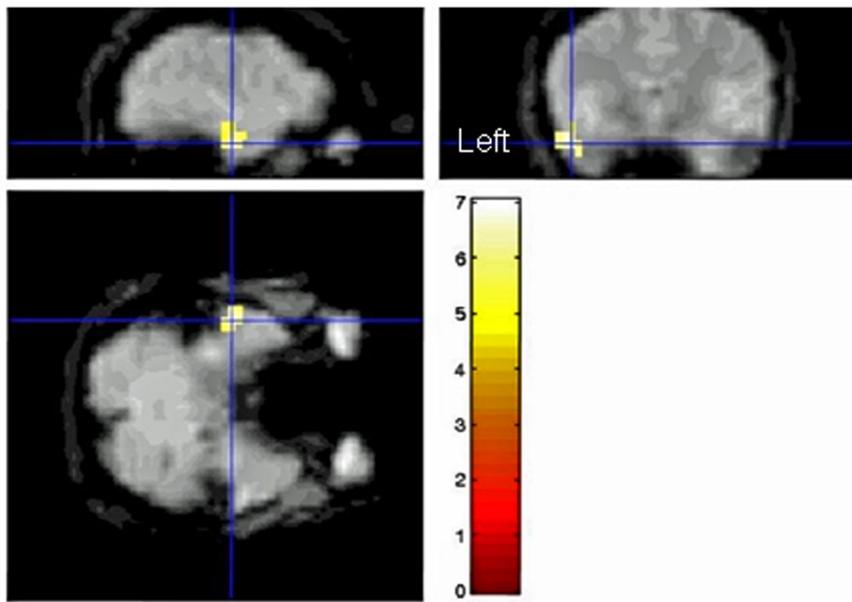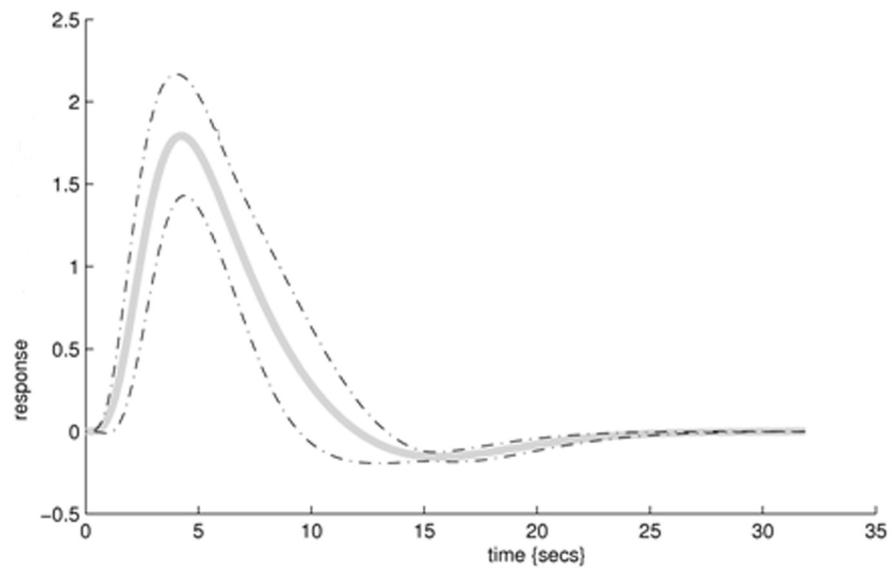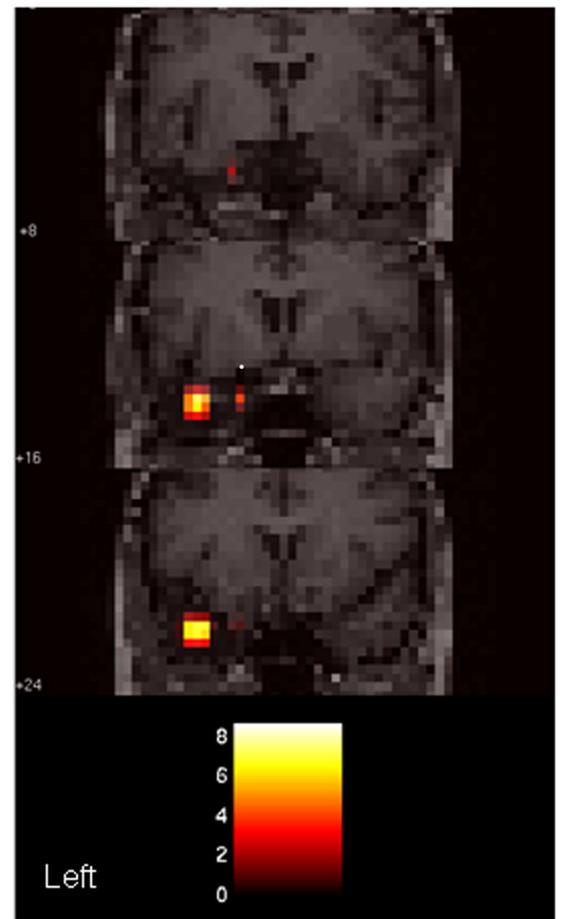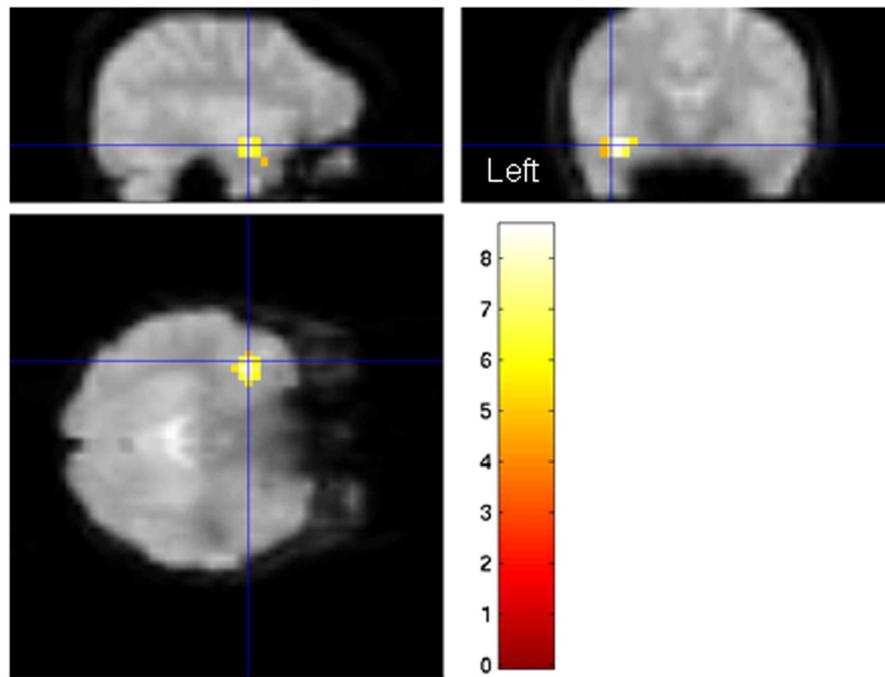**C. Post-operative resection seen on T1 weighted MRI.**

Reference List

1. Rosenow F, Luders H. Presurgical evaluation of epilepsy. *Brain* 2001;**124**:1683-700.

2. Siegel AM, Jobst BC, Thadani VM, Rhodes CH, Lewis PJ, Roberts DW, Williamson PD. Medically Intractable, Localization-related Epilepsy with Normal MRI: Presurgical Evaluation and Surgical Outcome in 43 Patients. *Epilepsia* 2001;**42**:883-8.

3. McGonigal A, Bartolomei F, Regis J, Guye M, Gavaret M, Fonseca AT-D, Dufour H, Figarella-Branger D, Girard N, Peragut JC, Chauvel P. Stereoelectroencephalography in presurgical assessment of MRI-negative epilepsy. *Brain* 2007;awm218.

4. Hamer HM, Morris HH, Mascha EJ, Karafa MT, Bingaman WE, Bej MD, Burgess RC, Dinner DS, Foldvary NR, Hahn JF, Kotagal P, Najm I, Wyllie E, Luders HO. Complications of invasive video-EEG monitoring with subdural grid electrodes. *Neurology* 2002;**58**:97-103.

5. Cossu MMD, Cardinale FMD, Castana LMD, Citterio AMD, Francione SMD, Tassi LMD, Benabid ALM, Lo Russo GMD. Stereoelectroencephalography in the Presurgical Evaluation of Focal Epilepsy: A Retrospective Analysis of 215 Procedures. [Article]. *Neurosurgery* 2005;**57**:706-18.

6. Knowlton RC, Elgavish R, Howell J, Blount J, Burneo JG, Faught E, Kankirawatana P, Riley K, Morawetz R, Worthington J, Kuzniecky RI. Magnetic source imaging versus intracranial electroencephalogram in epilepsy surgery: a prospective study. *Ann.Neurol.* 2006;**59**:835-42.

7. Knowlton RC, Elgavish RA, Bartolucci A, Ojha B, Limdi N, Blount J, Burneo JG, Ver HL, Paige L, Faught E, Kankirawatana P, Riley K, Kuzniecky R. Functional imaging: II. Prediction of epilepsy surgery outcome. *Ann.Neurol.* 2008;**64**:35-41.

8. Lemieux L, Salek-Haddadi A, Josephs O, Allen P, Toms N, Scott C, Krakow K, Turner R, Fish DR. Event-related fMRI with simultaneous and continuous EEG: description of the method and initial case report. *NeuroImage* 2001;**14**:780-7.

9. Krakow K, Woermann FG, Symms MR, Allen PJ, Lemieux L, Barker GJ, Duncan JS, Fish DR. EEG-triggered functional MRI of interictal epileptiform activity in patients with partial seizures. *Brain* 1999;**122 (Pt 9)**:1679-88.

.

10. Jacobs J, Jacobs J, Boor R, Jansen O, Wolff S, Siniatchkin M, Stephani U. Localization of Epileptic Foci in Children with Focal Epilepsies using 3-Tesla Simultaneous EEG-fMRI Recordings. *Clinical Neurophysiology* 2007;**118**:e50-e51.

11. Salek-Haddadi A, Diehl B, Hamandi K, Merschhemke M, Liston A, Friston K, Duncan JS, Fish DR, Lemieux L. Hemodynamic correlates of epileptiform discharges: an EEG-fMRI study of 63 patients with focal epilepsy. *Brain Res.* 2006;**1088**:148-66.

12. Al Asmi A, Benar CG, Gross DW, Khani YA, Andermann F, Pike B, Dubeau F, Gotman J. fMRI Activation in Continuous and Spike-triggered EEG-fMRI Studies of Epileptic Spikes. *Epilepsia* 2003;**44**:1328-39.

13. Benar CG, Grova C, Kobayashi E, Bagshaw AP, Aghakhani Y, Dubeau F, Gotman J. EEG-fMRI of epileptic spikes: Concordance with EEG source localization and intracranial EEG. *NeuroImage* 2006;**30**:1161-70.

14. Lazeyras F, Blanke O, Perrig S, Zimine I, Golay X, Delavelle J, Michel CM, de Tribolet N, Villemure JG, Seeck M. EEG-triggered functional MRI in patients with pharmacoresistant epilepsy. *J Magn Reson.Imaging* 2000;**12**:177-85.

15. Zimine I, Seghier ML, Seeck M, Lazeyras F. Brain activation using triggered event-related fMRI. *NeuroImage* 2003;**18**:410-5.

16. Guye M, Ranjeva JP, Le Fur Y, Bartolomei F, Confort-Gouny S, Regis J, Chauvel P, Cozzone PJ. 1H-MRS imaging in intractable frontal lobe epilepsies characterized by depth electrode recording. *NeuroImage* 2005;**26**:1174-83.

17. Seeck M, Lazeyras F, Michel CM, Blanke O, Gericke CA, Ives J, Delavelle J, Golay X, Haenggeli CA, de Tribolet N, Landis T. Non-invasive epileptic focus localization using EEG-triggered functional MRI and electromagnetic tomography. *Electroencephalography and Clinical Neurophysiology* 1998;**106**:508-12.

18. Zijlmans M, Huiskamp G, Hersevoort M, Seppenwoolde JH, van Huffelen AC, Leijten FS. EEG-fMRI in the preoperative work-up for epilepsy surgery. *Brain* 2007.

19. Wieser HG, Blume WT, Fish D, Goldensohn E, Hufnagel A, King D, Sperling MR, Luders H, Pedley TA. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia* 2001;**42**:282-6.

20. Allen PJ, Josephs O, Turner R. A Method for Removing Imaging Artifact from Continuous EEG Recorded during Functional MRI. *NeuroImage* 2000;**12**:230-9.
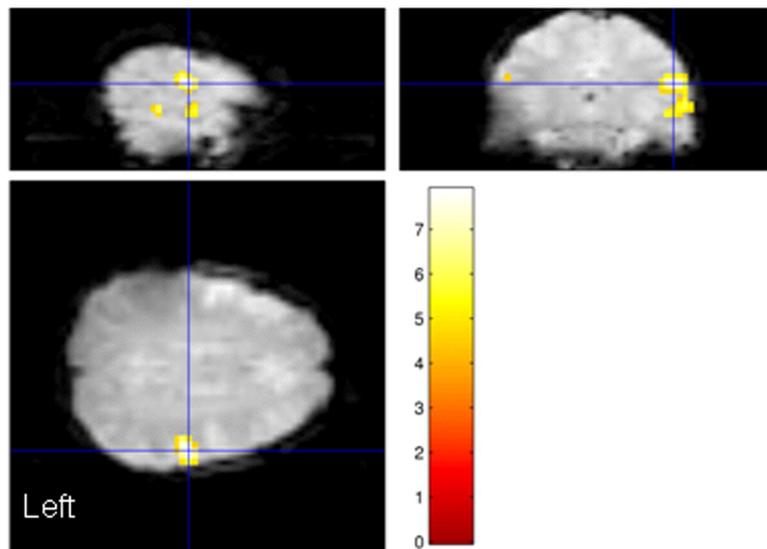
21. Allen PJ, Polizzi G, Krakow K, Fish DR, Lemieux L. Identification of EEG Events in the MR Scanner: The Problem of Pulse Artifact and a Method for Its Subtraction. *NeuroImage* 1998;**8**:229-39.

22. Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-Related fMRI: Characterizing Differential Responses. *NeuroImage* 1998;**7**:30-40.

23. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. *Magn Reson.Med.* 1996;**35**:346-55.

24. Lemieux L, Salek-Haddadi A, Lund TE, Laufs H, Carmichael D. Modelling large motion events in fMRI studies of patients with epilepsy. *Magn Reson.Imaging* 2007;**25**:894-901.

25. Liston AD, Lund TE, Salek-Haddadi A, Hamandi K, Friston KJ, Lemieux L. Modelling cardiac signal as a confound in EEG-fMRI and its application in focal epilepsy studies. *NeuroImage* 2006;**30**:827-34.

26. Ashburner J, Friston K. Multimodal Image Coregistration and Partitioning--A Unified Framework. *NeuroImage* 1997;**6**:209-17.

27. Salek-Haddadi A, Friston KJ, Lemieux L, Fish DR. Studying spontaneous EEG activity with fMRI. *Brain Research Reviews* 2003;**43**:110-33.

28. Kobayashi E, Bagshaw AP, Grova C, Gotman J, Dubeau F. Grey matter heterotopia: what EEG-fMRI can tell us about epileptogenicity of neuronal migration disorders. *Brain* 2006;**129**:366-74.

29. Godoy J, Luders H, Dinner DS, Morris HH, Wyllie E, Murphy D. Significance of sharp waves in routine EEGs after epilepsy surgery. *Epilepsia* 1992;**33**:285-8.

30. Salek-Haddadi A, Merschhemke M, Lemieux L, Fish DR. Simultaneous EEG-Correlated Ictal fMRI. *NeuroImage* 2002;**16**:32-40.

31. Kobayashi E, Hawco CS, Grova C, Dubeau F, Gotman J. Widespread and intense BOLD changes during brief focal electrographic seizures. *Neurology* 2006;**66**:1049-55.

32. Aghakhani Y, Kobayashi E, Bagshaw AP, Hawco C, Benar CG, Dubeau F, Gotman J. Cortical and thalamic fMRI responses in partial epilepsy with focal and bilateral synchronous spikes. *Clinical Neurophysiology* 2006;**117**:177-91.

33. Laufs H, Hamandi K, Salek-Haddadi A, Kleinschmidt AK, Duncan JS, Lemieux L. Temporal lobe interictal epileptic discharges affect cerebral activity in "default mode" brain regions. *Hum.Brain Mapp.* 2006.

.

34. Stefanovic B, Warnking JM, Kobayashi E, Bagshaw AP, Hawco C, Dubeau F, Gotman J, Pike GB. Hemodynamic and metabolic responses to activation, deactivation and epileptic discharges. *NeuroImage* 2005;**28**:205-15.
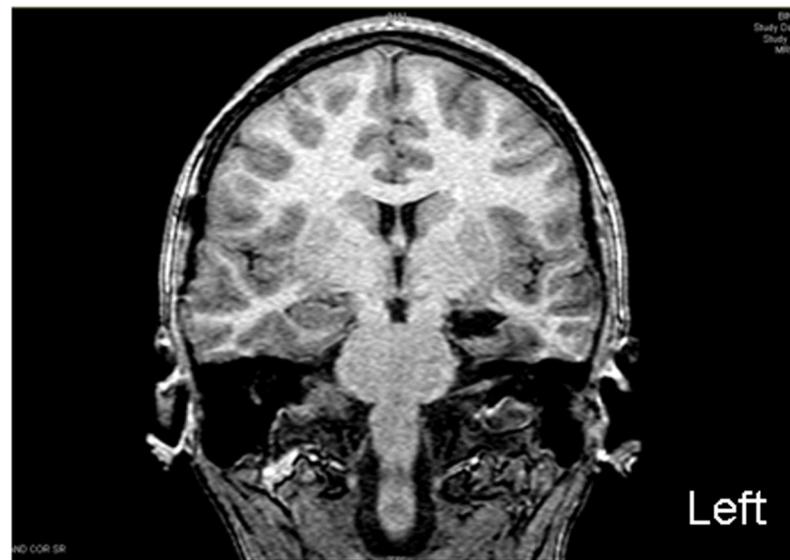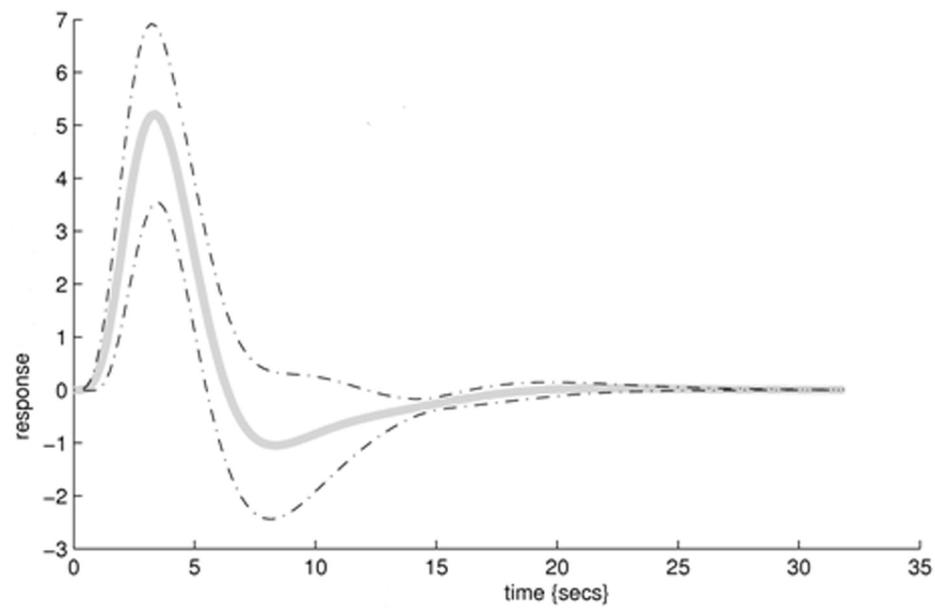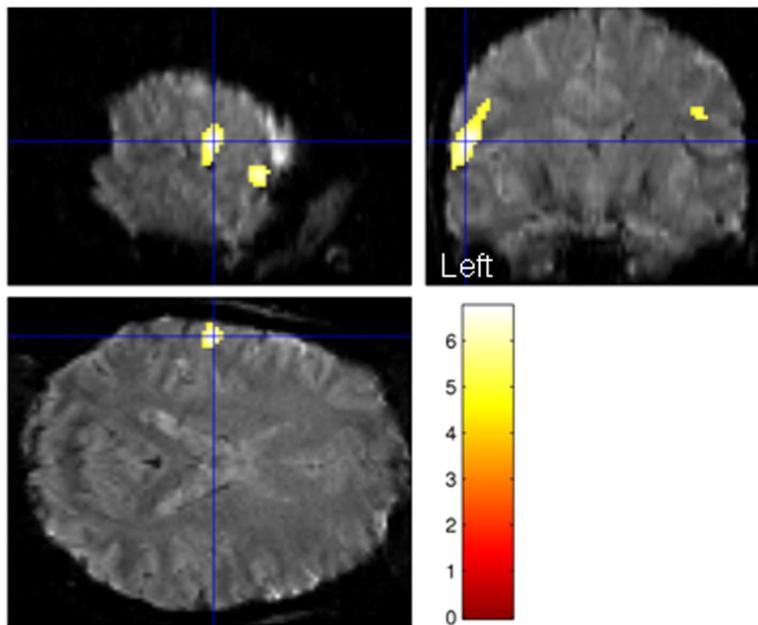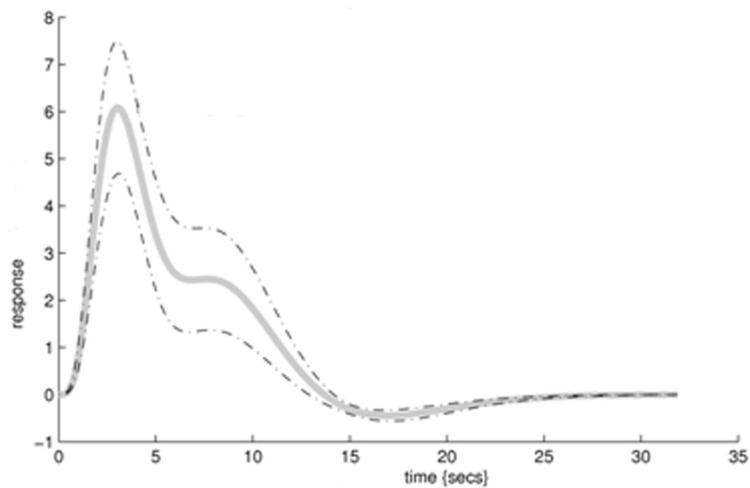
Left

response

time (seconds)

Left

Left

3C

Left

Left

response

time {secs}

4A

4B

4C

4D

p< 0.0001
unc .
z= 4.17

p< 0.05
FWE
Z = 6.8

Left

time {secs}

response