Research Article

EEG-fMRI in the pre-surgical evaluation of temporal lobe epilepsy

Ana C. Coan, MD, PhD[1]; Umair J. Chaudhary, MBBS, MSc, PhD[2]; Frédéric Grouiller[3]; Brunno M. Campos[1]; Suejen Perani[2]; Alessio De Ciantis, MD[2]; Serge Vulliemoz, MD, PhD[4]; Beate Diehl, MD, PhD[2]; Guilherme C. Beltramini[5]; David Carmichael, PhD[2], Roberto Covolan, PhD[5]; Fernando Cendes, MD, PhD[1]; Louis Lemieux, PhD[2]

[1]Neuroimaging Laboratory, Department of Neurology, University of Campinas, Campinas, Brazil

[2]Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, University College London, London WC1N 3BG, and MRI Unit, Epilepsy Society, Chalfont St. Peter, Buckinghamshire SL9 0RJ, United Kingdom

[3]Department of Radiology and Medical Informatics, Geneva University Hospitals, Geneva, Switzerland

[4]EEG and Epilepsy Unit and Functional Brain Mapping Laboratory, Neurology Department, University Hospitals and Faculty of Medicine of University of Geneva, Switzerland

[5]Neurophysics Group, Gleb Wataghin Physics Institute, University of Campinas, Campinas, Brazil

Corresponding author: Louis Lemieux

Corresponding author's address: MRI Unit, Epilepsy Society, Chesham Lane, Chalfont St Peter, Buckinghamshire SL9 0RJ, UK. Fax: + 44 1494 875 666. Corresponding author's e-mail address: louis.lemieux@ucl.ac.uk

Key words: surgery, functional imaging, image analysis

Number of words in abstract: 250

Number of words in main text: 4035

Number of figures: 02

Number of tables: 02

ABSTRACT

Objective: Drug-resistant temporal lobe epilepsy (TLE) often requires thorough investigation to define the epileptogenic zone for surgical treatment. We used simultaneous interictal scalp EEG-fMRI to evaluate its value for predicting long-term post-surgical outcome.

Methods: 30 patients undergoing pre-surgical evaluation and proceeding to temporal lobe (TL) resection were studied. Interictal epileptiform discharges (IEDs) were identified on intra-MRI EEG and used to build a model of hemodynamic changes. In addition, topographic electroencephalographic correlation maps were calculated between the average IED during video-EEG and intra-MRI EEG and used as a condition. This allowed the analysis of all data irrespective of the presence of IED on intra-MRI EEG. Mean follow-up after surgery was 46 months. ILAE outcomes 1 and 2 were considered good and 3 to 6 poor surgical outcome. Hemodynamic maps were classified according to the presence (Concordant) or absence (Discordant) of BOLD change in the TL overlapping with the surgical resection.

Results: The proportion of patients with good surgical outcome was significantly higher (13/16; 81%) in Concordant than in Discordant group (3/14; 21%) (Chi-squared test, Yates correction, p=0.003) and multivariate analysis showed that Concordant BOLD maps were independently related to good surgical outcome (p=0.007). Sensitivity and specificity of EEG-fMRI results to identify patients with good surgical outcome were 81% and 79%, respectively and positive and negative predictive values were 81% and 79%, respectively.

Interpretation: Interictal EEG-fMRI retrospectively confirmed based on the presence of significant BOLD the epileptogenic zone of TLE patients.. Surgical resection including regions of hemodynamic changes in the TL may lead to better postoperative outcome.

INTRODUCTION

Despite unquestionable benefit of surgical treatment for drug-resistant temporal lobe epilepsy (TLE), almost 50% of patients will not achieve seizure freedom 5 years after surgery.[1] The principal aim of the pre-surgical evaluation process is the accurate identification of the epileptogenic zone (EZ) using a variety of non-invasive (including scalp video-EEG, structural MRI, PET and ictal SPECT) and, in some cases, invasive procedures such as intracranial EEG. The technique of simultaneous electroencephalography and functional MRI (EEG-fMRI) can map haemodynamic changes associated with interictal epileptiform discharges (IEDs), which can provide important localizing information in individuals with drug-resistant focal epilepsies.[2-6] A number of studies have sought to define the role of EEG-fMRI in the pre-surgical evaluation and its value in defining the long-term prognosis of TLE and non-TLE patients.[5, 7-10] The difficulty, so far, is that the number of individuals included in such studies is small, partly due to the high proportion of patients for whom the technique was insensitive due to the lack of IEDs on intra-MRI EEG.

In this study, we investigated the value of EEG-fMRI in drug-resistant TLE patients who had undergone epilepsy surgery, even in cases in whom no visually detectable IED are recorded on intra–scanner EEG, by correlating epilepsy-specific voltage maps derived from EEG recorded during long term video-telemetry monitoring with the intra–scanner EEG to reveal haemodynamic changes.[11] Epileptic activity-related Blood Oxygen Level-Dependent (BOLD) network was evaluated in relation to the estimated EZ and spatially confirmed in the post-surgical MRI. Because we evaluated a select group of drug-resistant epilepsy (TLE patients), we propose a simplified EEG-fMRI concordance scheme for possible use in clinical practice, namely the presence or absence of BOLD in the presumed EZ.

SUBJECTS/MATERIALS AND METHODS

Patient selection

Thirty patients were selected retrospectively according to the following criteria: i) diagnosis of drug-resistant TLE and underwent presurgical evaluation with the definition of the estimated EZ in one of the temporal lobes; ii) EEG-fMRI recording for mapping of fMRI BOLD changes related to epileptic discharges acquired between July 2007 and March 2012 in one of the three following centres: University College London, London, UK; University of Geneva, Geneva, Switzerland; University of Campinas, Campinas, Brazil; and iii) availability of clinical long term video-EEG with IEDs recorded; iv) epilepsy surgery with any type of temporal lobe resection and at least 12 months follow-up. All patients gave informed written consent approved by the respective Ethic Committee of each centre.

The EEG-fMRI results were not taken into consideration during presurgical investigation . The estimated EZ was defined according to an expert panel discussion based on clinical, electroencephalographic and neuroimaging (19/30, 63%) or intracranial EEG (icEEG) (11/30, 37%) findings. Surgical outcome was defined according to ILAE outcome classification.[12] For the purpose of statistical analysis, ILAE outcomes 1 and 2 (seizure freedom or only auras since surgery) were grouped as good surgical outcome and ILAE 3 to 6 were considered poor surgical outcome.

EEG-fMRI acquisition

MRIs were acquired on 3T (London: 3T Signa Excite HDX, GE Medical Systems; Geneva: 3T Siemens Magnetom Trio; Campinas: 3T Philips Achieva Medical Systems) MRI scanners. The fMRI protocol consisted of BOLD sensitive echo-planar image (EPI) time series lasting 20 to 48 minutes (London: repetition time=3000ms, voxel size=3.75x 3.75x3mm^3, 43 slices; Geneva: repetition time=1500ms, voxel size=3.75x3.75x5.5mm^3 , 25 slices or repetition time=1980ms, voxel size=3x3x3.75mm^3, 32 slices; Campinas: repetition time=2000ms, voxel size=3x3x3mm³, 39 slices). Concomitant EEGs with 32 to 96 channels recorded with MRI compatible electrodes were acquired (Brain Products, Munich, Germany). Patients were asked to lie still with eyes closed. The EEG signal was amplified and digitized using a BrainAmp Amplifier (Brain Products GmbH, Germany).

EEG-fMRI data analysis

EEG and fMRI pre-processing

The fMRI data were processed and analysed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). The fMRI images were realigned, slice timing-corrected, and smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM).

Intra-MRI EEG was reviewed after removing scanner and pulse-related artefacts using Brain Vision Analyzer 2 (Brain Products GmbH, Germany).[13, 14] IEDs on intra-MRI EEG were identified and marked by board certificated neurophysiologists. All inter-ictal epileptiform discharges, including spikes and sharp waves, were marked and used in the statistical model. One patient (#24) had a seizure during EEG-fMRI, which was also identified and marked[15]

Long-term video-EEG monitoring and IED topography correlation maps

In addition to the BOLD signal changes associated with IED recorded during EEG-fMRI, we used a correlation analysis based on the scalp voltage topography map.[11] This method takes into account the average topography of IED recorded outside the scanner to build a predictor of the presence of epileptic activity on the EEG recorded during fMRI. This method then maps BOLD signal variations correlated with the projection of the intra-MRI EEG onto the maps derived from IEDs recorded during long-term video-EEG. The aim of the IED topography correlation method is to model pathological focal brain activity related to the epileptogenic focus i.e. the presence of a topographic distribution that matches that of the epileptiform discharges during EEG-fMRI.

All patients underwent prolonged EEG recordings, with 18 to 96 electrodes outside the MRI scanner. To calculate the IED topography correlation model, the clinical long-term EEG of each patient was used to build an average topographic map of each type of IED. EEGs were reviewed by experienced neurophysiologists (ACC and SV) and right or left temporal IED were marked. Corresponding IEDs were averaged and corresponding topographic maps calculated using the software *Cartool*.[16] The artefact-corrected intra-MRI EEG was interpolated to match the number of electrodes used for the long-term video-EEG and a band pass filter 1-30Hz applied. The correlation between the topographic maps was calculated for each intra-MRI EEG time point, then squared and convolved with the canonical hemodynamic response function (HRF), giving the IED topography correlation predictor of BOLD changes.

General linear model (GLM) building

The fMRI data was analysed in a GLM framework using the software SPM8. For patients with IED during EEG-fMRI, both the IED and IED topography correlation regressors were included in the GLM as effects of interest; for those with

no IED during EEG-fMRI, only the IED topography correlation regressor was included as an effect of interest. In patients with independent bilateral temporal IEDs both right and left IEDs were included in the design matrix separately. IEDs identified and marked on EEG inside the scanner were modelled as zero-duration events and convolved with the canonical HRF and its temporal and dispersion derivatives. The following effects were modelled as regressors of no interest: motion-related effects using 24 regressors (six scan realignment parameters and their Volterra expansion),[17] large motion events (inter-scan movement greater than 0.2mm (for four patients, large motion events were defined as 0.5mm due to model estimability problems), and cardiac pulse effects.[18, 19] To avoid the contamination of physiological BOLD, EEGs were visually inspected and marked for movements and eye blink artefacts. These regressors were also included in the design matrix and convolved with the HRF and its time and dispersion derivatives.[20] For the patient who had a seizure during EEG-fMRI, the event was also included in the model to account for the maximum amount of variance;[15] however, the associated BOLD changes will not be discussed here.

Statistical mapping of IED and IED topography correlation related BOLD effects

F-contrasts were built for IEDs ipsilateral and contralateral to the EZ. For patients with IED on intra-MRI EEG, an F-contrast was evaluated across the IED on intra-MRI EEG and IED topography correlation effects; for those with no IED on intra-MRI EEG, an F-contrast was evaluated for the IED topography correlation effect only. F-contrasts were estimated at conventional statistical threshold of $p<0.05$ (family wise error (FWE) corrected). In addition, in cases when conventional FWE corrected statistical threshold resulted in null maps, the data was further explored with a less stringent statistical threshold of $p<0.001$ (uncorrected for multiple comparisons). We defined a BOLD cluster as any BOLD activation that reached the statistical threshold irrespective of the number of voxels.

Postoperative MRIs

To assess the spatial relationship between the BOLD changes and area of surgical resection, the former was co-registered with the patient's postoperative MRI using affine transformations and bilinear interpolation modified in order to give a smoother cost function,[21] using SPM8.

EEG-fMRI BOLD concordance

For each patient, the concordance of the BOLD maps was evaluated for: i) IEDs ipsilateral to the estimated EZ (applicable to all cases); and ii) IEDs contralateral to the estimated EZ (when available). The concordance of the BOLD maps was assessed in relation to the area of surgical resection, irrespective of IED field distribution. Each SPM map was

classified as either: Concordant, when one or more BOLD clusters were located in the estimated EZ (temporal lobe) and overlapped with the area of surgical resection or was within up to 2 cm of the resection margin;[22] Discordant: all BOLD clusters were located remote from the estimated EZ and area of surgical resection. Patients with no BOLD clusters detected were classified as Discordant. Previous studies have demonstrated that although fMRI is a reliable technique to map the brain topography, there can be a spatial difference as much as 10 times its plane resolution, as compared to electrophysiologically defined activity.[22] Therefore, accounting for the intrinsic localization uncertainty, we limited the concordance assessment area to up to 2 cm of the surgical margins identified in the post-surgical MRI.

Statistical analysis

Descriptive statistics were used to assess frequencies. The distribution of age of onset and duration of epilepsy was assessed using T-test. We assessed the association and relationship between postsurgical outcome and concordance of IED-related BOLD maps using Chi-squared test (with Yates correction) and Pearson's correlation coefficient respectively. We performed multivariate analysis (general linear model) to evaluate the association of postsurgical outcome with concordance of IED-related BOLD changes, the presence of IEDs on the intra-MRI EEG, unilateral or bilateral IEDs, aetiology, duration of epilepsy and duration of follow-up.

Sensitivity was defined as the ratio of the number of patients with good postsurgical outcome and Concordant BOLD maps over the number of patients with good postsurgical outcome. Specificity was defined as the ratio of the number of patients with poor surgical outcome and Discordant BOLD maps over the number of patients with poor surgical outcome. Positive predictive value was defined as the ratio of the number of patients with Concordant BOLD maps and good surgical outcome over the number of patients with Concordant BOLD maps. Negative predictive value was defined as the ratio of the number of patients with Discordant BOLD maps and poor surgical outcome and the number of patients with Discordant BOLD maps.

RESULTS

30 patients (16 females) fulfilled the selection criteria (median age of 32 years, range 13-51). The median postsurgical follow-up period was 46 months (range 12-80). Sixteen patients had good postsurgical outcome (ILAE class 1: 12 and class 2: 4). Fourteen patients had poor postsurgical outcome (ILAE class 3: 4, class 4: 8 and class 5: 2). The detailed clinical data of patients are described in Table 1.

TABLES

Table 1: Clinical data of temporal lobe epilepsy patients submitted to surgical treatment.

	Gender	Age of epilepsy onset (years)	Age at scan (years)	Epilepsy duration (years)	Structural MRI	icEEG	Histology	Surgical outcome	Follow-up (months)
1	M	13	18	5	Normal	Yes	Non-specific findings	1	72
2	F	3	46	43	L HS (mild atrophy of TL)	No	HS	1	12
3	M	9	20	11	R temporal polar lesion	No	Ganglioglioma	1	55
4	M	17	21	4	L HS, multiples tubers	No	HS + FCD IIB	3	48
5	M	10	48	38	L HS	No	HS	1	33
6	F	4	47	43	R HS	No	HS	1	31
7	M	10	13	3	L H microsystic lesion	No	DNET	1	12
8	M	10	33	23	R HS, PNH	No	HS	1	12
9	F	17	19	2	L temporal epidermoid cyst	No	Epidermoid cyst	3	39
10	M	2	20	19	Normal	No	Gliosis	2	32
11	M	33	48	15	Resection cavity on L TL	Yes	Cavernoma	1	12
12	F	7	18	11	Resection cavity on R TL	No	Low grade glial neuronal tumor	1	50
13	F	16	50	34	R HS	No	HS + FCD IIA	2	42
14	F	17	46	29	R HS	No	HS	2	41
15	F	15	29	14	L TL atrophy	Yes	HS	1	68
16	F	14	23	9	Normal	Yes	Gliosis	4	66
17	F	28	42	14	R HS	No	HS	4	33
18	F	5	36	31	L HS	No	HS	4	55
19	M	5	33	28	L HS	No	HS	4	67
20	F	21	26	5	Normal	Yes	Non-specific findings	5	51
21	F	27	27	1	R TL inferior lesion	No	DNET	1	36
22	F	3	28	25	Normal	Yes	Gliosis	1	61
23	F	4	51	47	R HS	No	HS	2	31

24	M	1	50	49	L HS	No	HS	3	33
25	F	15	24	9	Normal	Yes	Non-specific findings	4	75
26	M	10	28	18	Normal	Yes	L H end folium sclerosis	3	50
27	F	6	31	25	Normal	Yes	L H end folium sclerosis	5	60
28	M	7	30	23	R HS	No	HS	4	80
29	M	19	24	5	Normal	Yes	FCD IIA	4	47
30	F	24	31	7	Normal	Yes	Gliosis	4	65

MRI: magnetic resonance imaging; icEEG: intracranial electroencephalography; M: male; F: female; L: left; R: right; HS: hippocampal sclerosis; HS: hipocampal sclerosis; TL: temporal lobe; FCD: focal cortical dysplasia; DNET: dysembryoblastic neuroepitelial tumor; PNH: periventricular nodular heterotopia; H: hippocampus.

50% (6/12) of patients with hippocampal sclerosis, 100% (6/6) of patients with tumors, 33% (1/3) of patients with focal cortical dysplasia and 33% (3/9) of patients with non-specific findings (including gliosis and end folium sclerosis) had good postsurgical outcome.

During long-term video-EEG and intra-MRI EEG, all patients had IEDs exclusively localized on anterior, middle or posterior temporal region either ipsilateral to the EZ or in the bilateral temporal regions.

Fifteen (50%) patients had IEDs ipsilateral to the EZ (mean: 20 IEDs; range: 1-257) during the intra-MRI EEG recording and the fMRI analysis was performed for the intra-MRI IEDs and IED topography correlation effect. For the remaining 15 patients (50%), the fMRI analysis was performed for the IED topography correlation effect only using the EEG topography derived from IED ipsilateral to the EZ recorded on long-term video-EEG monitoring.

Eight patients had bi-temporal IEDs in the long term video-EEG monitoring and 4 of them also had bitemporal IED during intra-MRI EEG. For these 8 patients, BOLD contrasts maps were also created for the IED contralateral to the EZ (4 with fMRI analysis performed for the intra-MRI IEDs and IED topography correlation effect and 4 with fMRI analysis performed for the IED topography correlation effect only).

BOLD Map Concordance

BOLD maps for IEDs ipsilateral to the EZ

We assessed the concordance of IED-related BOLD maps with the area of surgical resection and compared the concordance with post-surgical outcome as summarized in Table 2.

Table 2: IED-related BOLD changes detected and surgical outcome in patients with TLE.

	Marker type	Spikes in the intra-	Statistical analysis	BOLD cluster: global maxima	Other BOLD clusters (p<0.001, uncorrected)	BOLD in DMN areas	BOLD concordance
1	LT IED	152	p<0.05, FWE corr	**L Temporal Lobe**	LI, RT, RP, AntCing, RF, LF, RI, LP, RO, LO	Bilateral Precuneus	Concordant
2	LT IED	no spike	p<0.001, unc	**L Hippocampus**	LF, RF	none	Concordant
3	RT IED	89	p<0.05, FWE corr	**R Temporal Lobe**	RP, LP, RF, LF, LI	Bilateral Precuneus	Concordant
4	LT IED	no spike	p<0.05, FWE corr	**L Temporal Lobe**	LF, RF, RP, RT, RO, AntCing, LP, LO, OE	Bilateral Precuneus	Concordant
5	LT IED	no spike	p<0.05, FWE corr	Posterior CIngulate (DMN)	**LT,** LF, RP, LP, RF, RI, RT, LI	Contralateral Precuneus	Concordant
6	RT IED	39	p<0.001, unc	Anterior Cingulate (DMN)	**RT**, RP, RF, RO, LP, LF, RI, LO	Ipsilateral Precuneus	Concordant
7	LT IED	532	p<0.05, FWE corr	Anterior Medial Frontal (DMN)	**LT**, RP, AntCing, RF, RI, RT, RO, LO, LF, LI, LP	AMF, Bilateral Precuneus	Concordant
8	RT IED	no spike	p<0.05, FWE corr	R Precuneus (DMN)	**LT**, RF, LP, RT, LF, PostCing	Bilateral Precuneus	Concordant
9	LT IED	no spike	p<0.05, FWE corr	L Precuneus (DMN)	**LT**, RP, RF, LP, RT, LF, PostCing	Ipsilateral Precuneus	Concordant
10	LT IED	147	p<0.001, unc	R Posterior Temporal	**LT**, RO, LO, LI, RF	none	Concordant
11	LT IED	21	p<0.05, FWE corr	Anterior Medial Frontal (DMN)	**LT,** LP, RP, RO, RT, RF, LO, LF, AntCing	AMF, Ipsilateral Precuneus	Concordant
12	RT IED	no spike	p<0.001, unc	R Insula	**Rhip**, RP, RF, LP, LF, PostCing, LT	Ipsilateral Precuneus	Concordant
13	RT IED	no spike	p<0.001, unc	**R Temporal Lobe**	LO, LP, LF	none	Concordant
14	RT IED	5	p<0.001, unc	R Insula	**Rhip**, AntCing, LP, RF, LT, LO, LF, RO	Ipsilateral Precuneus	Concordant
15	LT IED	34	p<0.001, unc	R Frontal Lobe	**LT**, RF, RP, LP, PostCing	none	Concordant
16	LT IED	30	p<0.001, unc	**L Temporal Lobe**	LF, RF, RO	none	Concordant
17	RT IED	1	p<0.001, unc	R Temporal Lobe	RI	none	Discordant
18	LT IED	3	p<0.001, unc	R Precuneus (DMN)	RT, RP, LP, RO, LO, LT, RF, LF	Ipsilateral Precuneus	Discordant
19	LT IED	23	p<0.001, unc	R Precuneus (DMN)	none	Contralateral Precuneus	Discordant
20	LT IED	no spike	p<0.001, unc	Anterior Medial Frontal (DMN)	RF, LF, LP	AMF	Discordant
21	RT IED	no spike	p<0.001, unc	L Frontal Lobe	LP, AntCing, RF, RP, RT, LI	Ipsilateral Precuneus	Discordant
22	LT IED	11	p<0.001, unc	R Frontal Lobe	LF, AntCing, RF, RO, RP, LT	none	Discordant
23	RT IED	15	p<0.05, FWE corr	R Posterior Temporal	RO, RP, LO, LP, AntCing, RF	Bilateral Precuneus	Discordant
24	LT IED	17	p<0.05, FWE corr	R Frontal Lobe	AntCing, RP, LF, LP, RO	Contralateral Precuneus	Discordant
25	LT IED	no spike	p<0.001, unc	L Frontal Lobe	LF, LT, RP	Contralateral Precuneus	Discordant
26	LT IED	567	p<0.001, unc	R Occipital Lobe	RF, LF, RP, LP	none	Discordant
27	LT IED	no spike	p<0.001, unc	L Caudate	RCaud, RP, LI, LF	Contralateral Precuneus	Discordant
28	RT IED	no spike	p<0.001, unc	no BOLD		none	Discordant
29	RT IED	no spike	p<0.001, unc	no BOLD		none	Discordant
30	LT IED	no spike	p<0.001, unc	no BOLD		none	Discordant

IED: interictal epileptiform discharges; BOLD: blood oxygen level dependent; TLE: temporal lobe epilepsy; L: left; R: right; T: tesla; FWE: family-wise error corrected; ipsi: ipsilateral to the epileptogenic zone; TL: temporal lobe; GM: global maxima; DMN: default mode network; EZ: epileptogenic zone; icEEG: intracranial EEG. LF: left frontal; RF: right frontal; LT: left temporal; RT: right temporal; LI: left insula; RI: right insula; LP: left parietal; RP: right parietal; LO: left occipital; RO: right occipital; AntCing: anterior cingulum; PostCing: posterior cingulum; Rhip: right hippocampus; RCaud: right caudate nucleus. AMF: anterior medial frontal.

16/30 (53%) patients had Concordant BOLD maps and their postsurgical outcomes were ILAE class 1 in 10/16, class 2 in 3/16, class 3 in 2/16 and class 4 in 1/16 (Fig 1).

14/30 (47%) patients had Discordant BOLD maps, and their postsurgical outcomes were ILAE class 1 in 2/14, class 2 in 1/14, class 3 in 2/14, class 4 in 7/14 and class 5 in 2/14 (Fig 2).

Sensitivity and specificity to predict good surgical outcome were 81% and 79%, respectively. Postsurgical outcome was significantly different between patients with Concordant and Discordant IED-related BOLD changes (Chi-squared test, Yates correction, $p<0.003$) and moderate correlation was observed between Concordant results and good surgical outcome (Pearson's correlation coefficient, $p=0.598$, $p=0.000$). The positive predictive value was 81% and negative predictive value, 78%.

There was no difference between patients with Concordant and Discordant maps for the presence of IEDs in intra-MRI EEG (Fisher exact test, $p=1.00$), number of IEDs on intra-MRI EEG (two-sample t-test, $p=0.705$), occurrence of bilateral temporal IEDs (Fisher exact test, $p=0.470$), aetiology (Fisher exact test, $p=0.284$), age of epilepsy onset (two-sample t-test, $p=0.950$) or duration of epilepsy (two-sample t-test, $p=0.768$). Univariate analyses showed higher frequency of good surgical outcome in patients with Concordant BOLD maps (Fisher exact test, $p=0.003$) and tumors (Fisher exact test, $p=0.022$) and shorter post-surgical follow-up time in those with good outcome (two-sample t-test, $p=0.046$). However, multivariate analysis showed that Concordant BOLD maps ($p=0.001$) and shorter follow-up time ($p=0.005$) were the only variables independently associated with good surgical outcome.

BOLD maps for IEDs contralateral to the EZ

BOLD maps for IEDs contralateral to the EZ were Discordant in all cases.

Distribution of BOLD clusters

The distribution of BOLD clusters for each patient is detailed in Table 2. Seven patients had global maximum BOLD cluster localized within 2 cm of the area of surgical resection. Nine patients had global maximum BOLD cluster

localized in areas of the default mode network (DMN). With a statistical threshold of p<0.001, uncorrected, three patients had no detected BOLD cluster and one had only one BOLD cluster. The remaining patients had at least two different BOLD clusters and these are described in Table 2.

DISCUSSION

In this study we used EEG-fMRI to map BOLD changes related to epileptic patterns on scalp EEG in patients with drug-resistant TLE using a methodological advancement, which made it possible to evaluate all individuals submitted to the technique even in the absence of IED during the scan.[11] We have demonstrated that this technique can be used to reveal BOLD patterns with high positive and negative predictive values for good and poor postsurgical outcome in TLE, independent from other factors that affect the surgical prognosis. Therefore this technique has significant clinical potential for presurgical evaluation of patients with drug-resistant TLE.

Previous reports have shown the importance of EEG-fMRI in the definition of the EZ [2-5] and the understanding of network abnormalities in epilepsies.[2-5, 23-26] Despite its promising as a pre-surgical evaluation tool for drug-resistant epilepsies, there are few studies evaluating the long-term prognosis of seizure control after epilepsy surgery.[8-10, 27] So far, the major difficulty in establishing the use of EEG-fMRI in the pre-surgical workup of drug-resistant epilepsies is the high number of lost exams due to the absence of IED during fMRI acquisition.[28] In line with previous work [11], the use of IED voltage topography correlation approach in the present report allowed us to study a larger cohort of patients due to the higher yield it provides. In this approach, we built a patient-specific EEG voltage map corresponding to an average IED recorded during the clinical video-EEG and we then calculate the presence (correlation) of this topography at each time-point of the EEG-fMRI recording. This allows to map BOLD changes related to the presence of EEG voltage topography concordant with IED without any visible IED detected on the scalp EEG and the reliability of the methods has been validated invasively.[11]] The use of the IED topography correlation approach substantially increases the number of patients who will benefit from the use of EEG-fMRI in the pre-surgical workup.

Our results demonstrate that the presence of IED-related BOLD changes within or in the immediate vicinity of surgical target, revealed using EEG-fMRI, is strongly related to long-term surgical outcome in a large cohort of TLE patients. The prognosis of seizure control after surgery in TLE is heterogeneous, with a significant number of patients presenting seizure recurrence after a long follow-up and the factors influencing the outcome are not fully understood.[1, 29] The use

of invasive EEG is necessary for the determination of the EZ in a significant number of patients what increases the costs and morbidity.[30,31] The development and improvement of noninvasive localization techniques may reduce the morbidity and costs involved in preoperative evaluations by better targeted implantations through improved definition of the EZ, and identification of good surgical candidates or those who would benefit from intracranial EEG.[32]

Differently from previous studies, we were able to control different aspects that might also influence the surgical outcome, as aetiology and epilepsy duration. We demonstrated that the use of combined scalp EEG-fMRI can predict surgical outcome with high accuracy in TLE patients when BOLD changes overlapped the area of surgical resection, indicating they are from the EZ. Previous studies had similar results in smaller groups of heterogeneous drug-resistant patients,[7-10] or in patients with FCD,[5] but no studies had evaluated the use of EEG-fMRI as a potential pre-surgical tool in a large series of TLE. Importantly, we could demonstrate that the BOLD concordance is associated with good surgical outcome independent of other known variables as aetiology and epilepsy duration.

In the present study, we assessed the spatial relationship between the BOLD maps and the area of resection by considering all significant BOLD clusters equally. This contrasts to a method we and others have used previously in which a special emphasis was given to the BOLD cluster containing the voxel with the highest degree of statistical significance, an approach in principle well suited to summarise patterns which can extend across multiple lobes.[5, 8, 9] Also, in our group's previous studies, we used a type of concordance scheme that takes into account the presence of BOLD changes in the presumed (or confirmed) EZ but also in distant regions [5,8]; this reflected a wish to answer broader questions related to the possible meaning of the BOLD maps associated with epileptic activity. In the present study, we started from a more select group of TLE and propose a simplified test's result. We reasoned that a more targeted approach based on the assessment of the presence or absence of BOLD changes within the surgical target area would be suited for the specific purpose of assessing outcome predictive power.

In TLE, extra-temporal findings are reported in the results of a range of non-invasive and invasive pre-surgical localization techniques. Indeed, TLE is associated with a well-known network of cortical and subcortical abnormalities appreciated by functional and structural imaging as well as intracranial EEG.[25, 33] Likewise, in EEG-fMRI studies significant BOLD abnormalities are observed outside the EZ and a consistent network of IEDs-related haemodynamic changes has been demonstrated.[25]. Also, both positive and negative IED-related BOLD changes can be observed in the EZ and, therefore, we did not differentiate between them.[34] With this approach, commonly, BOLD clusters

localized in areas of the default mode network (DMN) will be observed, often, as the global statistical maxima. The suppression of activity of regions of the DMN related to IEDs has been consistently demonstrated in different epilepsy syndromes,[24, 25, 35] especially in TLE; however the significance and importance of these findings are not fully understood. The consistent observation of IED-BOLD changes in areas of the DMN corroborates the idea of a common functional network associated with the epileptiform abnormalities in patients with TLE.

Methodological considerations

Although different modalities of EEG-fMRI statistical analysis exist, it is still not clear which is the best clinical approach. The canonical HRF is the most widely used and previous studies have demonstrated it appropriately detects the EZ in patients with epilepsy [5,11]. The use of modified HRF can increase the extent and degree of BOLD detection [10,36]; however this may represent a variety of phenomena, including artefacts or propagated epileptiform activity [37]. One may argue that some of the widespread hemodynamic changes observed in EEG-fMRI studies are findings due to artefacts. However, in recent years different approaches have been proposed to eliminate false results, including corrections for movements, cardiac artefacts and physiological noise.[18-20] In fact, in this work we have attempted to model such confounding effects thoroughly, in line with our philosophy of measuring and modelling as many effects as possible.[17, 18, 20] Therefore, with appropriate modelling of the fMRI signal, we significantly limited the possibility of false positive results and increased the possibility of a specific patient benefiting from EEG-fMRI study. In this context, we believe it was worth considering the potential clinical significance of the results with a less strict statistical threshold (FWE uncorrected). Indeed, differently from many previous methodological EEG-fMRI studies[6,20,36-38], our current analysis is focused on the possible clinical use of EEG-fMRI. The use of corrections for multiple comparisons decreases the odds of false positive results. In the present study, however, we had the gold standard data to define the false positives: the long-term surgical outcome. By choosing a statistical threshold level *a priori* and testing the predictive value at this level against the outcome data we limit the scope for bias. This is in contrast to a study in which different thresholding strategies would be compared; such a methodological study be best performed on data from a larger group of patients, with the results of the optimization performed on part of the group would be applied to data from the rest of the group.

The visual detection of IEDs is subjective, leading to inter-observer-related variability in the results of the fMRI analysis [38]. In our study, the use of the topographic map is a first step to decrease this bias. In the future, the combination of this technique with automated IED detection [39,40] could improve the EEG-fMRI analysis decreasing this variability

and the amount of time needed for its analysis. One limitation of the topography map, is the mismatch in the spatial sampling of the EEG between the recordings inside and outside the scanner, a problem which is addressed by interpolation over the scalp. This is a practical solution, which allows data recorded under different circumstances and in different scanners to be included in the analysis, but which can result in sub-optimal estimates of the correlation. Also, the use of the topographic map might contribute to balance the dispersion of the number of IEDs among patients (which varied from zero to 567 in our study). This large variability of the number of IEDs is indeed observed in every EEG-fMRI study and it could contribute to an uneven bias to the BOLD maps. In our study, however, besides the use of the topographic map, no significant difference in the number of IEDs was observed between patients with good or poor surgical outcome

Finally, one limitation of our study is the use of retrospective data. Further longitudinal studies, comparing EEG-fMRI results with other neuroimaging modalities, should be performed in order to define their specific contribution to the presurgical evaluation of patients with drug-resistant epilepsies.

Conclusions

We demonstrated that the presence of BOLD change in the area of surgical resection is highly associated with the probability of seizure-freedom. The presence of IED-related BOLD change within or in the immediate vicinity of the EZ/area of surgical resection predicts seizure-freedom in 81% of the cases, while its absence predicts seizure recurrence in 78% of the cases. We propose that EEG-fMRI as part the presurgical evaluation of TLE patients may be an independent predictor of good surgical outcome if a BOLD change is observed in the presumed EZ.
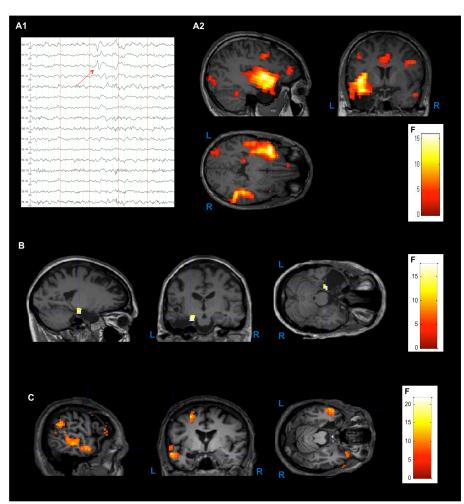
REFERENCES

1. de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 2011;378:1388-95.

2. Federico P, Archer JS, Abbott DF, et al. Cortical/subcortical BOLD changes associated with epileptic discharges An EEG-fMRI study at 3 T. Neurology 2005;64:1125-30.

3. Jacobs J, Kobayashi E, Boor R, et al. Hemodynamic Responses to Interictal Epileptiform Discharges in Children with Symptomatic Epilepsy. Epilepsia 2007;48:2068-78.

4. Moeller F, Tyvaert L, Nguyen DK, et al. EEG-fMRI: adding to standard evaluations of patients with nonlesional frontal lobe epilepsy. Neurology 2009;73:2023-30.

5. Thornton R, Vulliemoz S, Rodionov R, et al. Epileptic networks in focal cortical dysplasia revealed using electroencephalography-functional magnetic resonance imaging. Ann Neurol 2011;70:822-37.

6. Caballero-Gaudes C, Van de Ville D, Grouiller F, et al. Mapping interictal epileptic discharges using mutual information between concurrent EEG and fMRI. Neuroimage 2013;68:248-62.

7. Zijlmans M, Huiskamp G, Hersevoort M, et al. EEG-fMRI in the preoperative work-up for epilepsy surgery. Brain 2007;130:2343-53.

8. Thornton R, Laufs H, Rodionov R, et al. EEG correlated functional MRI and postoperative outcome in focal epilepsy. J Neurol Neurosurg Psychiatry 2010;81:922-7.

9. An D, Fahoum F, Hall J, et al. Electroencephalography/functional magnetic resonance imaging responses help predict surgical outcome in focal epilepsy. Epilepsia 2013;54:2184-94.

10. van Houdt PJ, de Munck JC, Leijten FS, et al. EEG-fMRI correlation patterns in the presurgical evaluation of focal epilepsy: a comparison with electrocorticographic data and surgical outcome measures. Neuroimage 2013;75:238-48.

11. Grouiller F, Thornton RC, Groening K, et al. With or without IEDs: localization of focal epileptic activity by simultaneous electroencephalography and functional magnetic resonance imaging. Brain 2011;134:2867-86.

12. Wieser HG, Blume WT, Fish D, et al. Commission on Neurosurgery of the International League Against Epilepsy (ILAE). ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. Epilepsia 2001;42:282-6.

13. Allen PJ, Polizzi G, Krakow K, et al. Identification of EEG events in the MR scanner: the problem of pulse artifact and a method for its subtraction. Neuroimage 1998;8:229-39.

14. Allen PJ, Josephs O, Turner R. A method for removing imaging artifact from continuous EEG recorded during functional MRI. Neuroimage 2000;12:230-9.

15. Chaudhary UJ, Carmichael DW, Rodionov R, et al. Mapping preictal and ictal haemodynamic networks using video-electroencephalography and functional imaging. Brain 2012;135:3645-63.

16. Brunet D, Murray MM, Michel CM. Spatiotemporal Analysis of Multichannel EEG: CARTOOL. Comput Intell Neurosci 2011;2011:2.

17. Friston KJ, Williams S, Howard R, et al. Movement-related effects in fMRI timeseries. Magn Reson Med 1996;35:346-55.

18. Lemieux L, Salek-Haddadi A, Lund TE, et al. Modelling large motion events in fMRI studies of patients with epilepsy. Magn Reson Imaging 2007;25:894-901.

19. Liston AD, Lund TE, Salek-Haddadi A, et al. Modelling cardiac signal as a confound in EEG-fMRI and its application in focal epilepsy studies. Neuroimage 2006; 30:827-34.

20. Chaudhary UJ, Rodionov R, Carmichael DW, et al. Improving the sensitivity of EEG-fMRI studies of epileptic activity by modelling eye blinks, swallowing and other video-EEG detected physiological confounds. Neuroimage 2012;61:1383-93.

21. Collignon A, Maes F, Delaere D, et al. Automated multi-modality image registration based on information theory. In Information processing in medical imaging 1995;3:264-74.

22. Disbrow EA, Slutsky DA, Roberts TP, et al. Functional MRI at 1.5 tesla: a comparison of the blood oxygenation level-dependent signal and electrophysiology. Proc Natl Acad Sci USA 2000;97:9718–23.

23. Lemieux L, Salek-Haddadi A, Josephs O, et al. Event-related fMRI with simultaneous and continuous EEG: description of the method and initial case report. Neuroimage 2001;14:780-7.

24. Laufs H, Hamandi K, Salek-Haddadi A, et al. Temporal lobe interictal epileptic discharges affect cerebral activity in ''default mode'' brain regions. Human Brain Mapping 2007;28:1023–32.

25. Fahoum F, Lopes R, Pittau F, et al. Widespread epileptic networks in focal epilepsies-EEG-fMRI study. Epilepsia 2012;53:1618-27.

26. Laufs H. Functional imaging of seizures and epilepsy: evolution from zones to networks. Curr Opin Neurol 2012;25:194-200.

27. Donaire A, Capdevila A, Carreño M, et al. Identifying the cortical substrates of interictal epileptiform activity in patients with extratemporal epilepsy: An EEG-fMRI sequential analysis and FDG-PET study. Epilepsia 2013;54:678-90.

28. Pittau F, Dubeau F, Gotman J. Contribution of EEG/fMRI to the definition of the epileptic focus. Neurology 2012;78:1479-87.

29. Janszky J, Janszky I, Schulz R, et al. Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. Brain 2005;128:395-404.

30. Bulacio JC, Jehi L, Wong C, et al. Long-term seizure outcome after resective surgery in patients evaluated with intracranial electrodes. Epilepsia 2012;53:1722-30

31. Arya R, Mangano FT, Horn PS, et al. Adverse events related to extraoperative invasive EEG monitoring with subdural grid electrodes: A systematic review and meta-analysis. Epilepsia 2013;54:828-39.

32. Pittau F, Grouiller F, Spinelli L, et al. The role of functional neuroimaging in pre-surgical epilepsy evaluation. Front Neurol 2014;5:31.

33. Blumenfeld H, McNally KA, Vanderhill SD, et al. Positive and negative network correlations in temporal lobe epilepsy. Cerebral Cortex 2004;14:892-902.

34. Vulliemoz S, Thornton R, Rodionov R, et al. The spatio-temporal mapping of epileptic networks: combination of EEG-fMRI and EEG source imaging. Neuroimage 2009;46:834-43.

35. Gotman J, Grova C, Bagshaw A, et al. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. Proc Natl Acad Sci USA 2005;102:15236-40.

36. Grouiller F, Vercueil L, Krainik A, et al. Characterization of the hemodynamic modes associated with interictal epileptic activity using a deformable model-based analysis of combined EEG and functional MRI recordings. Human brain mapping 2010;31:1157-73.

37. Lemieux L, Laufs H, Carmichael D, et al. Noncanonical spike-related BOLD responses in focal epilepsy. Human brain mapping 2008;29:329-45.

38. Flanagan D, Abbott DF, Jackson GD. How wrong can we be? The effect of inaccurate mark-up of EEG/fMRI studies in epilepsy. Clin Neurophysiol 2009;120:1637-47.

39. Liston AD, De Munck JC, Hamandi K, et al. Analysis of EEG–fMRI data in focal epilepsy based on automated spike classification and Signal Space Projection. Neuroimage 2006;31:1015-24.

40. Pedreira C, Vaudano AE, Thornton RC, et al. Classification of EEG abnormalities in partial epilepsy with simultaneous EEG–fMRI recordings. Neuroimage 2014;99:461-76.
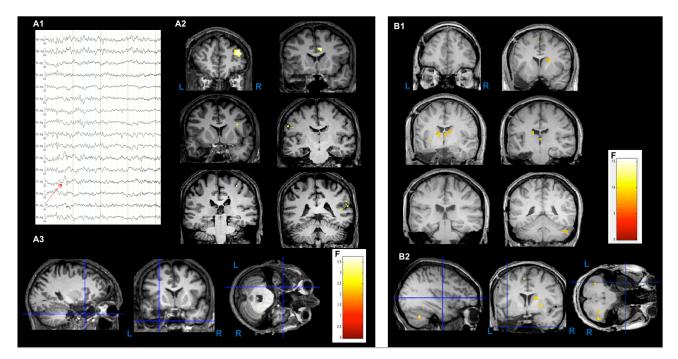
Fig1: Patients with Concordant BOLD responses.

A (Patient 1): Patient with left temporal lobe epilepsy. The patient had normal pre-operatory MRI and the surgical specimens revealed non-specific findings. Surgical outcome ILAE class 1 after a follow-up of 15 months. A1 shows a left temporal spike in the intra-MRI EEG (red arrow); A2 shows the co-register of the BOLD response and the post-operatory MRI*. B (Patient 9): Patient with left temporal lobe epilepsy. The patient had a large epidermoid cyst in the pre-operatory MRI. During surgery, the cyst and the adjacent cortex in the left temporal pole were removed. Surgical outcome ILAE class 1 after a follow-up of 14 months. This patient had no spikes in the intra-MRI EEG. B shows the co-register of the BOLD response and the post-operatory MRI*. C (Patient 5): Patient with left temporal lobe epilepsy. The patient had signs of hippocampal sclerosis in the pre-operatory MRI and this was confirmed in the surgical specimens. Surgical outcome ILAE class 1 after a follow-up of 6 months. This patient had no spikes in the intra-MRI EEG. D shows the co-register of the BOLD response and the post-operatory*.

* All results are shown with a statistical threshold of $p<0.001$ (uncorrected for multiple comparisons).

BOLD: blood oxygen level-dependent; MRI: magnetic resonance imaging; ILAE: International League Against Epilepsy; EEG: electroencephalography; L: left side; R: right side; F: F scores.

Fig2: Patients with Discordant BOLD responses.

A (Patient 24): Patient with left temporal lobe epilepsy. The patient had signs of hippocampal sclerosis in the pre-operatory MRI and this was confirmed in the surgical specimens. Surgical outcome ILAE class 3 after a follow-up of 6 months. A1 shows the intra-MRI EEG with a left temporal spike (red arrow); A2 and A3 show the co-register of the BOLD response and the post-operatory MRI (no BOLD response observed in the surgical resection)*. B (Patient 27): Patient with left temporal lobe epilepsy. The patient had normal pre-operatory MRI and the surgical specimens revealed end folium sclerosis. Surgical outcome ILAE class 5 after a follow-up of 36 months. This patient had no spikes in the intra-MRI EEG. B1 and B2 show the co-register of the BOLD response and the post-operatory MRI (no BOLD response observed in the surgical resection)*.

* All results are shown with a statistical threshold of $p < 0.001$ (uncorrected for multiple comparisons).

BOLD: blood oxygen level-dependent; ILAE: International League Against Epilepsy; MRI: magnetic resonance imaging; L: left side; R: right side; F: F scores.