The impact of mapping interictal discharges using EEG-fMRI on the epilepsy presurgical clinical decision making process: a prospective study

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ABSTRACT

Purpose: We set out to establish the clinical utility of EEG-correlated fMRI as part of the presurgical evaluation, by measuring prospectively its effects on the clinical decision.

Methods: Patients with refractory extra-temporal focal epilepsy, referred for presurgical evaluation were recruited in a period of 18 months. The EEG-fMRI based localization was presented during a multi-disciplinary meeting after the team had defined the presumed epileptogenic zone, blinded to the EEG-fMRI findings. The impact of EEG-fMRI findings on the epilepsy surgery decision making process was recorded.

Results: Sixteen patients (six women), with a median age of 28 years, were recruited. Interpretable EEG-fMRI results were available in 13: interictal epileptic discharges (IEDs) were recorded in eleven patients and seizures were recorded in two patients. In three patients, no epileptic activity was captured during EEG-fMRI acquisition and in two of those an IED topographic map correlation was performed (between EEG recorded inside the scanner and long-term video EEG monitoring).

EEG-fMRI results presentation had no impact on the initial clinical decision in three patients (23%) of the thirteen and resulted in a modification of the initial surgical plan in ten patients (77%) of the thirteen finally presented in MDT; in eight patients the impact was on the planned placement of invasive electrodes and in two patients the EEG-fMRI led to additional non-invasive tests before proceeding further with surgery.

Conclusion: The study is a prospective observational cohort study specifically designed to assess the impact of EEG-fMRI on the clinical decision making process, suggesting a significant influence of EEG-fMRI on epilepsy surgery planning.

Key words: EEG-fMRI, epilepsy surgery, clinical management process, extra-temporal lobe epilepsy.

INTRODUCTION

Surgery is potentially curative for refractory focal epilepsy [1]. Rigorous presurgical evaluation is required for the selection of surgical candidates and for identifying the epileptogenic zone (EZ), since the precise localization of the epileptic focus is a prerequisite for good surgical outcome [2, 3].

In current clinical practice, the accurate identification of the EZ may be derived using a combination of tests, including a variety of non-invasive tests, such as scalp electroencephalography (EEG) video telemetry, structural magnetic resonance imaging (MRI), magnetoencephalography (MEG), positron emission tomography (PET), single photon emission computed tomography (SPECT) and electroencephalogram (EEG) recorded during functional magnetic resonance imaging (fMRI) (EEG-fMRI), sometimes followed by invasive investigations, such as intracranial EEG (icEEG). With the advance of technology, non-invasive multimodal neuroimaging may reduce the morbidity and costs involved in the preoperative evaluations of patients with refractory epilepsy, in three directions: better screening of candidates for selecting those with a reasonable likelihood of being amenable to surgical treatment, aiding noninvasive localization tests in such way that an increased proportion of patients may avoid intracranial electrodes and improving the yield and accuracy of invasive EEG [4, 5].

There is no agreement as to which tests should constitute the combination for evaluation of surgical candidates in every patient [6]. Validation of novel presurgical localization tests is commonly done against icEEG and/or location of the resected area combined with the surgical outcome. Although recognized as the best of the currently available methods, the limitations of this approach ('diagnostic accuracy studies') have been recently highlighted. Part of the problem is the combination of different tests in the localization process. Therefore it is useful to attempt to assess the impact of a particular test on the decision making process and management strategies [6]. This is possible by recording two sets of clinical decisions: one blinded to the results of the test of interest and a second one, following the presentation of the results of the test.

EEG-fMRI recording is a noninvasive tool to localize epileptic activity by mapping haemodynamic changes associated with epileptic discharges on EEG [7-10]. The technique has given important insights into generators and networks involved in epileptic activity and highlighted brain network abnormalities in different types of epilepsies [11-14] as it provides relatively quasi-uniform whole-brain coverage [15].

The hemodynamic changes associated with interictal and ictal epileptic discharges in EEG-fMRI [16, 17] can provide important localizing information in individuals with refractory focal epilepsies [18-23]. Although the value of EEG–fMRI in epilepsy presurgical evaluation and in long-term prognosis has been assessed in a number of retrospective studies [15, 18, 24-26], further evaluation is required.

In this study, we investigated the impact of EEG-fMRI on the epilepsy surgery decision-making process in patients with refractory extra-temporal epilepsy, during their presurgical evaluation, by presenting the EEG-fMRI results during a multidisciplinary team meeting. We assessed whether the EEG-fMRI findings altered initial clinical decisions made before the EEG-fMRI results presentation.

METHODS

Adults with refractory focal epilepsy referred for pre-surgical evaluation underwent EEG-fMRI at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK. During the recruitment period, patients with extra-temporal lobe epilepsy and particularly all cases with difficult to localize epilepsy, for which EEG-fMRI was performed at the request of the clinical team, were recruited into the project.

The EEG-fMRI results were presented during a multidisciplinary team (MDT) meeting. All patients had EEG video-telemetry and structural MRI, in accordance to our standard epilepsy protocol [3]. Additionally, ictal SPECT, PET and/or MEG were performed in some of the cases. During the MDT clinical, electroencephalographic, neuroimaging and neurophysiological findings were presented and recorded. The possible lateralization, localization and the presumed EZ were defined and the continuation of the patient's clinical management was discussed and decided. The possible outcomes of the decision process were as below:

- Surgical candidacy or no further proceeding with epilepsy surgery

- Requirement for further non-invasive tests (MEG, PET and/or ictal SPECT, if not already performed, and/or EEG video-telemetry re-performance) before proceeding with invasive EEG (placement of intracranial electrodes) or before surgical resection;

- Requirement for intracranial EEG including electrode placement plan.

All the aforementioned findings and outcomes of the decision process were recorded on a form (Figure 1), while the MDT was blinded to EEG-fMRI results. Subsequently, EEG-fMRI results were presented. Following the EEG-fMRI data presentation, the possible lateralization, localization and the presumed EZ were re-defined and any change was recorded and documented on the form, mainly based on the localisation revealed in the IED-related blood oxygenation level dependent

(BOLD) maps in relation to the initially presumed epileptogenic zone. BOLD increases and decreases were considered equally, since it has been demonstrated that both can be observed in the EZ [7]. The degree of concordance of BOLD map with the initially presumed epileptogenic zone was classified as described previously [27, 28], in decreasing order of degree of concordance: Entirely Concordant ('EC'; all BOLD clusters in the same lobe as and within 2 cm of the presumed seizure onset zone), Concordant Plus ('C+'; the global-maximum cluster was in the same lobe as and within 2 cm of the presumed EZ, and other clusters were remote from the presumed EZ), Some Concordance ('SC'; the global-maximum cluster was remote from the presumed EZ, and one of the other clusters was in the same lobe as and within 2 cm of the presumed EZ) and Discordant ('D', all clusters were remote (different lobe or opposite hemisphere) from the presumed EZ).

The possible outcomes were re-evaluated and recorded: surgical candidacy, requirement for further non-invasive investigations, requirement for invasive EEG recordings and when indicated, the intracranial EEG electrode placement plan (Fig 1). In each case, the potential changes in possible outcomes were synthesized into one of the four following categories:

1) Change on the decision for surgery candidacy

2) Request for additional non-invasive localization tests

3) Change or no change on the initial decision for intracranial EEG electrode placement necessity

4) Modification of the intracranial EEG electrode placement strategy (additional or redefined invasive electrodes).

It was considered that the EEG-fMRI results led to modification of the original clinical plan if any change in any category was reported; otherwise it was considered that there was no change on the initial decision of the MDT.

The study was approved by the joint research ethics committee of the NHNN (UCLH NHS Foundation Trust) and UCL Institute of Neurology, Queen Square, London, UK.

EEG-fMRI acquisition

EEG-fMRI was performed with the aim of mapping hemodynamic changes associated with interictal epileptiform discharges. Images were acquired using either a 3T GE Signa® Excite-HDX-Echospeed or 3T Siemens Trio MRI scanner with a standard transmit/receive head coil. Two 20 minute echo-planar-imaging sessions were acquired with the following parameters: GE Signa: echo-time = 30 ms, flip angle = 90º, slices = 44, slice thickness = 2.4 mm with 0.6 mm gap, field-of-view = 24x24 cm2, matrix = 64x64; Siemens Trio: echo-time = 30 ms, flip angle = 90º, slices = 48, slice thickness = 2 mm with 1 mm gap, field-of-view = 192x192 mm2, matrix = 64x64. T1-weighted MRI scans were also acquired at the same time.

Patients were fitted with a 64-channel EEG cap (BrainCap MR, Germany), ear plugs, and their head was immobilized using a vacuum cushion and they were asked to remain still during scanning. Scalp EEG and video (two cameras: one of the patient's entire body and one of the face) were recorded synchronously during functional MRI scanning (see [28] for details of the setup).

EEG-fMRI processing

Scalp EEG recording during fMRI was corrected offline for scanner and cardiac pulse-related artifacts [29, 30] using Brain Vision Analyzer 2 (Brain Products, Germany). The EEG was then reviewed to identify, mark and categorize epileptic discharges, taking into account the patient's EEG recorded during clinical long-term video-EEG monitoring. In patients who had seizures during the EEG-fMRI acquisition, each seizure was identified and labelled according to our previous work [27]. In addition, for two patients in whom no epileptiform event was identified during the scalp EEG-fMRI acquisition (cases #6 and 7), we performed a topographic map-based correlation analysis [31].

In summary, IED were identified and marked on a representative sample of scalp EEG from clinical long-term video-EEG monitoring, averaged and a voltage topographic map calculated at the peak of the global field power. We then calculated

the strength of a surrogate of the epileptic activity as a function of fMRI scan time in the form of the correlation between the averaged spike map and the topography of the ongoing scalp EEG. The time-course of the square of the correlation coefficient quantifying the presence of the epileptic map (topographical correlation coefficient) was used for further fMRI analysis.

In all cases the following phenomena were also identified on the intra-MRI video and EEG, and marked as confounding events and each represented as a series of zero-duration stick functions or variable duration blocks depending upon the duration of event: eye blinks and eye movements, swallowing, jaw clenching, small head jerk, facial twitches, brief hand and foot movements [28].

EEG-fMRI modelling

The fMRI data were analyzed within the general linear model framework to map epileptic activity-related BOLD changes. In summary, individual IED were represented as stick functions (single zero-duration event onsets) and runs of IED, as variable duration blocks. In cases with multiple IED types, each type was modelled as a separate effect of interest (series of event onsets). In the patients in whom no IED was recorded during EEG-fMRI the topographical map correlation coefficient (calculated as above) was included in the design matrix as the effect of interest. In cases with seizures, these were partitioned into up to three phases and represented as blocks, as described previously [27, 32]. All vectors of onsets for the effects of interest (i.e., IED, topographical map correlation coefficient, ictal phases) and physiological activities were convolved with the canonical hemodynamic response function and its derivatives.

In addition, the regressors for the above-mentioned physiological activities [28] were included in the design matrix as confounds, along with bulk head motion-related regressors [33] and heart beat-related regressors [32, 34].

For patients with IED on intra-MRI EEG, a F-contrast was evaluated across all IED regressors on intra-MRI EEG; for those with no IED on intra-MRI EEG, F-contrast was evaluated for the topographic correlation repressors. F-contrasts were estimated at conventional statistical threshold of $p<0.05$ (family wise error (FWE) corrected). In addition, in cases when FWE corrected conventional statistical threshold resulted in

null (empty) maps, the data was further explored by applying a less conservative statistical threshold of $p<0.001$ (uncorrected for multiple comparisons), in line with previous similar studies [27].

RESULTS

Sixteen patients, (6 women), fulfilled the selection criteria. The median age at the time of the MDT meeting was 28 years (range: 21-60 years) and the median age at seizure onset was 10.5 years (range: 1.5-25 years). Seven patients had frontal lobe epilepsy, two had fronto-parietal lobe epilepsy, two had parietal lobe epilepsy, one had temporo-parietal, two had parieto-occipital lobe epilepsy, one had temporo-occipital lobe epilepsy and one had right hemisphere epilepsy.

The detailed clinical data of patients, the electroencephalographic and the neuroimaging findings are summarized in Table 1.

Of the sixteen patients, interpretable EEG-fMRI results were available in 13 patients and presented to the MDT. In eleven patients there were IEDs during EEG-fMRI and two patients had seizures during EEG-fMRI. In the three remaining patients the reasons for the lack of interpretable results were: absence of significant BOLD clusters after application topographic map-based correlation analysis (case #6 and 7) while in the other case (#4) there was absence of epileptic discharges during EEG-fMRI and the IED recorded in the clinical EEG monitoring was non localising, thereby precluding the use of the topographic map-based correlation analysis.

EEG-fMRI results presentation had no impact on the initial clinical decision in three patients (23%) of the thirteen and resulted in a modification of the initial surgical plan in ten patients (77%) of the thirteen finally presented in MDT and in 62.5% of the sixteen recruited into the study; the changes included request for additional localization tests and modification of the invasive electrode placement strategy. More precisely, additional non-invasive tests before any further proceeding with epilepsy surgery were requested in two patients and modification of the invasive electrode placement strategy was documented in eight patients (additional or relocated electrodes) (Table 2).

For the three patients in whom EEG-fMRI had no impact on the clinical decision, the BOLD changes were discordant with the presumed EZ in two patients. In the third patient the team considered the EEG-fMRI results did not add any further information

for the presumed EZ (the BOLD map was classified as Concordant Plus, indicating the most significant cluster overlapped or was in close proximity with the presumed EZ, but there were additional clusters, remote from the EZ) and were not taken into account.

In the two patients in whom EEG-fMRI lead to requests for additional localization tests before proceeding further with epilepsy surgery, EEG-fMRI results showed a wide distribution of BOLD changes including some overlapping or in close proximity with the presumed EZ. In six patients, in whom EEG-fMRI lead to modification of the invasive electrode placement strategy, the EEG-fMRI results were classified as EC in one patient, C+ in six patients and SC in one patient (Table 2). Consequently, additional electrodes were placed or electrodes placement was redefined to cover the areas of BOLD changes. Five patients proceeded further with intracranial EEG electrode placement. Electrode positioning was recorded to match the BOLD maximum clusters more closely as follows: to cover areas more inferiorly to the presumed EZ (two patients; cases #1,11), on the lateral edge of the presumed EZ (one patient; case #10) and deeper in the presumed EZ with depth electrodes (two patients: cases #5,13). In three patients the BOLD cluster was included in the EZ (cases #1,5,11) and in one patient the BOLD cluster represented an area with very rapid involvement (case #13). In the fifth case (case #10) no involvement was noted in the electrodes placed near the BOLD cluster.

Surgical outcome

Post-surgical outcome was defined according to ILAE outcome classification [35]. For the two patients, in whom EEG-fMRI showed a wide distribution of BOLD changes and led to requests for additional localisation tests, no final decision on proceeding to surgery has been made in the first case; in the second case the post-operative outcome at 30 months is ILAE Class III.

Of the remaining patients, in whom EEG-fMRI findings had an impact on the intracranial EEG electrode placement plan, four are awaiting surgery (three of them have not undergone invasive electrodes placement), two refused surgery and two

subsequently underwent epilepsy surgery; in both the outcome was good (ILAE class I and II after 34 and 12 months of follow up, accordingly). In the first patient (case #1) one of the ECoG grids was placed to cover the EEG-fMRI global maximum cluster over the left inferior frontal gyrus, located more inferiorly than the presumed epileptogenic zone. One of the contacts of this grid was found to overlap with the seizure onset zone.

In the second patient (case #5) two additional depth electrodes were placed to target the area of the EEG-fMRI global maximum cluster. It was found that ictal onset discharges frequently involved contacts in these electrodes.

DISCUSSION

This is a prospective observational cohort study of the effects of disclosure of EEG-fMRI data on clinical decision making in patients with refractory extra-temporal lobe epilepsy. The EEG-fMRI results were taken into account by the team and led to modification of the original clinical plan in more than half of the patients included in the study. In summary, the effects on the decision ranged from not proceeding further with surgical treatment before more non-invasive methods were performed to modifying and/or increasing the invasive EEG electrode coverage.

The conventional non-invasive presurgical workup can often provide sufficient information on lateralization and localization to allow surgery to proceed [36]. However, in some cases, confidence in the localization may be lacking [6], since continuous video-EEG using surface electrodes and imaging investigations may fail to localize the EZ or may localize it inaccurately and more advanced and/ or invasive localization tests are often required before further proceeding. All currently available localization methods have limitations [6, 37] for the localization of the presumed EZ, as this is inferred by surgical outcome [38]. Regarding invasive localization tests, depth electrodes have a limited volume of sensitivity while grid and strip electrodes also suffer from limited coverage, which must include the EZ in order to provide accurate localization [6, 37, 39] otherwise may be non-localizing [40]. Additionally there is a high potential for complications [41] and the ability to repeat the test is limited [42] More generally, its use as a reference standard conducted in selected cases can lead to biased estimates of test performance [43].

New methods of brain imaging have been implemented, and older methods have undergone additional refinement [44]. However, diagnostic accuracy studies report clinical outcomes following surgery [45] and surgical outcome can be affected by known and unknown variables, unrelated to the accuracy of localizing test [42] such as operative complications, incomplete resection of the seizure focus, excision of adjacent tissue and post-surgical management issues. Secondly, the outcome prediction studies are based only on patients who have undergone surgery and therefore do not provide information for the proportion of patients who are assessed and for whom the decision not to undertake surgery is made [46].

The present study shows that EEG-fMRI may have an impact on the clinical decision making and patient management process, with a substantial rate of modification of the original clinical decision.

We have to stress the point that the patients, included in the study, were complicated difficult cases from the point of view of localization. The implementation of an expert panel, in order to make a consensus decision, helped address the concerns regarding subjective interpretation of test results and inter-observer variation [47]. The study design used, with the initial treatment plan being delineated before presentation of the EEG-fMRI results, and allowance of changes of the original plan after EEG-fMRI results presentation, increases the impact of our finding.

Two studies of magnetic source imaging (MSI), based on a similar design, have also reported additional value of MSI. In the first study of 77 patients, decisions were made whether to proceed with intracranial EEG and where to place electrodes, before and after presenting MSI results, indicating additional electrode coverage in 23% of the case [4] while MSI provided non-redundant information in 33% of the patients in the second study of 69 participants [48].

For EEG-fMRI, previous studies have examined, retrospectively, the accuracy of scalp EEG-fMRI to predict surgical outcome in small groups of heterogeneous drug-resistant patients [7, 18, 25, 49] or in patients with FCD and heterotopias [19, 20, 50-52] but only few cohorts of patients, with more than 20 recruited patients, have been reported [14, 21, 26]. Even fewer have evaluated the use of EEG-fMRI as a potential pre-surgical tool. In a series of 29 adult surgical candidates with an unclear focus and/or presumed multifocality on the basis of EEG, EEG-fMRI was shown to have a concrete impact on a small proportion of the patients [24]. The lower impact, compared to the present study, may be explained by the selection criteria of Zijlmans et al study, where the cases recruited in the study were patients initially rejected for epilepsy surgery. EEG-fMRI, presentation led to improved source localization or corroborated the negative decision regarding surgical candidacy in 37% of patients [24]. In a quite recent study, EEG-fMRI was used to noninvasively identify cortical areas involved in the interictal epileptiform activity generation zone in 21 patients with extra-temporal refractory epilepsy, against localization of hypo-metabolism depicted by the FDG-PET [14].

EEG- fMRI studies have demonstrated concordance with the presumed EZ in 50 to 70% of patients with epilepsy, investigating either IED-related BOLD signal changes [15, 19, 21, 26, 53] or ictal-related BOLD signal [32]. In the present study, we used a measure of concordance of the BOLD maps with the presumed EZ, using a method in line with previous studies by our group and others [15, 19, 27, 54] as a way of summarising the often complex patterns and to help synthesise the relationship between the BOLD maps and surgical outcome [55, 56]. In this regard, this study provides some evidence of the predictive value of the EEG-fMRI maps for surgical outcome in line with previous retrospective studies [15].

There are certain limitations in the study. The first limitation is present in most studies recruiting patients during presurgical evaluation. The fact that patients with unifocal abnormalities are more likely to persist with surgical work up compared to patients with multifocal findings infers possible selection bias with more complex cases being selected for EEG-fMRI. Other limitations of the study include the small number of patients recruited and the lack of control group.

Despite the limitations, the findings are indicative of the significant potential clinical impact of EEG-fMRI on the pre-surgical decision making process. This technique should therefore be considered in surgical candidates who do not have satisfactory indication for epilepsy foci from seizure semiology, electroencephalogram, magnetic resonance imaging and other non-invasive techniques. Regarding the post-surgery outcome, the aforementioned limitations of our study do not allow us to determine the impact of EEG-fMRI on surgery outcome.

Our findings support the evolving consensus that a combination of techniques can yield complementary information and their concordance is crucial and specific for every surgery candidate [57, 58], to help in tackling the decision problems faced by clinicians.

In summary, the mapping of epileptic activity using EEG−fMRI appears to be a promising tool in epilepsy presurgical evaluation. With the advance of technology [59], this non-invasive approach may become more predictive. EEG−fMRI, together with other non-invasive neuroimaging approaches has the potential to play a greater role in epilepsy presurgical evaluation.

CONCLUSION

The study is a prospective observational cohort study showing a significant potential clinical impact of EEG-fMRI on the pre-surgical decision making process. EEG-fMRI yields complementary information in surgical candidates and should be considered in presurgical evaluation.

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Figure 1: The form used at MDT meetings

Effect of EEG-fMRI data presentation on surgical decision-making and icEEG electrode implantation

VTM Date: 26/07/12
Patient: DSC   40439241
Consultants:

Previous Investigations	performed		conclusion
Long-term video EEG monitoring:	**YES**	NO	
MRI	**YES**	NO	
Language fMRI	**YES**	NO	
PET	YES	**NO**	
Ictal SPECT	YES	**NO**	
MEG	YES	**NO**	
Neuropsychological assessment	**YES**	NO	

Pre EEG-fMRI data presentation

Possible lateralization		
Possible localization (presumed epileptogenic zone)		
Surgical candidate	YES	NO*
Further non-invasive investigations	YES * *	NO
icEEG	YES	NO
IcEEG plan		

* Please clarify and select one of the following three:
1. Not satisfactorily localized for surgical resection
2. Existing functional imaging data insufficient to support a reasonable epilepsy localization hypothesis

3. High likelihood that eloquent cortex overlapped with suspected epileptogenic tissue

** Further non-invasive investigations: please clarify

Post EEG-fMRI data presentation

Possible lateralization		
Possible localization (presumed epileptogenic zone)		
Surgical candidate	YES	NO*
Further non-invasive investigations	YES **	NO
icEEG	YES	NO
IcEEG plan		

* Please clarify and select one of the following three:
1. Not satisfactorily localized for surgical resection
2. Existing functional imaging data insufficient to support a reasonable epilepsy localization hypothesis
3. High likelihood that eloquent cortex overlapped with suspected epileptogenic tissue

** Further non-invasive investigations: please clarify

Questions
1. *Did the opinion of being a possible surgery candidate or not change after the f-MRI data presentation?*

2. *Did the suggestion for further non-invesive investigations change after the f-MRI data presentation?*

3. *Did the suggestion for invasive electrodes placement change after the f-MRI data presentation?*

4. *Did the plan of invasive electrodes placement change after the f-MRI data presentation?*

Patient ID	Epileptic activity on EEG during fMRI	BOLD									Concordance with presumed EZ	Impact on clinical decision process
		RF	RT	RP	RO	LF	LT	LP	LO	Others		
1	IED: LF					IFG MSFG					C+	Additional or redefined electrodes
2	IED: RP		*TO*				*TO*				D	No
3*	IED: LF					***MFG/IFG,*** *Orbitofrontal*	*TP*			*MedF*	C+	No
	Seizure: Onset phase	SFG, IFG	TP-ANG G	Superior		SFG/MFG				**MedF,** Basal ganglia	C+	
	Seizure: Established phase	**SFG/MFG**	TP			SFG/MFG				MedSFG, CG, SMA, Pc	SC	
	Seizure: Late ictal phase	**Motor cortex, premotor cortex**				SFG	TP			MedF, SMA	SC	
4	None										NA	No
5*	IED: RP			**SMG**							C+	Additional or redefined electrodes
	Seizure : Onset phase	**MFG**		**SMG**						MedF		
	Seizure : stablished phase	MFG		SMG Superior		MFG		Superior		MedF		
6	None										NA	No
7	None										NA	No
8	IED: BF									***R MedF***	D	More non-invasive tests
9	IED: LF							***Parieto-temporal junction***			D	No
10	IED: LF,BF	MFG				MFG				**MedF, SMA**	C+	Additional or redefined electrodes

11	IED: LP,RP			Superior				Superior		IFG	Additional or redefined electrodes
12	IED: LF	IFG, MFG, FPole	STG	Superior		IFG, MFG	FP	STG	Superior	PC, cuneus, MedF	SC	More non-invasive tests
13	IED: RT	MFG	Temporal PC								C+	Additional or redefined electrodes
14	IED: LF, frontal MFG	FPole, MFG	Posterior, TO	Superior		FP MFG	Posterior, TO	Superior	PC, MedF	C+	Additional or redefined electrodes
15	IED: L PC, R FT	Fusiform gyrus Anterior STG			MedF					C+	Additional or redefined electrodes
16	IED: LT			Parieto-Occipital			Occipital			SC	Additional or redefined electrodes

\# Seizures during EEG-fMRI; Blood oxygen level dependent (BOLD) changes are described at P<0.005 (FWE: family-wise error corrected) and italici... BOLD changes seen at less conservative statistical threshold P<0.001 uncorrected. The most statistically significant cluster (global maximum) shown in bo... right; NA: not applicable; SFG: superior frontal gyrus; F: frontal; P: parietal; T; temporal; O: Occipital; BF: bi-frontal; FP: fronto-parietal; TP: temporo-pa... temporo-occipital; PC: Parieto-central; MSFG: middle superior frontal gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus,; STG: superior temp... MFG: middle temporal gyrus; medF: medial frontal; SMA: supplementary motor area

Table 2: BOLD changes and impact on clinical decision process

Table 1: Clinical data, electroencephalographic and neuroimaging findings

Patient ID	Gender	Age	Age of seizure onset (years)	Epilepsy types	Presumed EZ	Scalp EEG	MRI	PET/FDG-SPECT /MEG
1	M	29	16	Frontal	L lateral frontal	Regional L frontal	L frontal craniotomy and mature postoperative changes in L frontal lobe with ex-vacuo dilation of the left frontal horn	NA/ NA/ L frontal lobe superior to the area of damage from the surgery. Propagation to Broca's area
2	F	31	1.5	Parietal	R parietal lobe	Regional R centroparietal	FCD in right parietal lobe	NA/ NA/ NA
3	F	60	25	Frontal	L frontal lobe	Regional L frontal or L temporal	FCD in L middle frontal gyrus	NA/ NA/ No spikes
4	F	29	23	Fronto-parietal	L parietal lobe (R leg sensory region)	NLAT, NLOC	Cyst-like area in L parietal lobe: likely low grade glioma	NA/NA/ NA
5	M	28	7	Parietal	R parietal lobe	Regional R frontocentroparietal	FCD in R supramarginal region	NA/ NA/ NA
6	M	28	10	Frontal	L frontal lobe	Regional L frontocentral	L frontal FCD (middle frontal gyrus)	NLAT/ NA/ NA
7	F	26	3	Frontal	L mesial frontal region	Regional L frontal (FC and FCT)	L frontal lobe (FC and FCT)	L superior frontal/ L frontal or insular focus/ No spikes
8	F	26	4	Frontal	L inferior frontal gyrus	NLAT, NLOC	Non-lesional	L inferior frontal gyrus/ NA / L inferior frontal gyrus
9	M	22	11	Parieto-occipital	L parietoccipital region	Regional L fronto-temporal and L temporo-ooccipital	Gliosis in L parietoccipital region	NA/ NA/ NA

10	M	21	2	Frontal	R precentral frontal region	Regional R fronto-central	R cavity in R middle frontal gyrus, residual FCD at margins with posterior extension to anterior bank of precentral gyrus and to ventricular surface	NA/NA/spikes round cavity with propagation from posterior to anterior
11	M	25	6	Fronto-parietal	L central region, in proximity to hand sensory and motor areas	Regional L central	FCD in L postcentral gyrus	NA/ NA/ spikes in the vicinity of the abnormality, extending into left intraparietal sulcus
12	M	23	11	Frontal	L anterior FL (orbitofrontal cortex)	Regional L frontocentral	Non-lesional	L medial and inferior frontal gyrus / NA/ NA
13	M	28	8	Right hemisphere epilepsy	R front. centro-temporal region (opercula/insular)	Regional R temporal and R FCT	Polymicrogyria in R superior middle and inferior temporal gyri, and R parietal	NA/ NA/ No spikes
14	M	24	13	Temporo-occipital	L temporo-occipital region	Regional L post/basal temporal with rapid propagation to both hemispheres	FCD in L isthmus/anterior calcarine sulcus	L temporal and R temporal/ R caudate, putamen/NA
15	F	35	1.5	Left parietal-occipital	L Parieto-occipital and RT	Regional L Parieto-occipital and RT	L Occipital craniotomy and cavity at L occipital lobe and posterior L medial temporal lobe	NA/NA/NA
16	M	38	17	R tempo-parietal	R TPO junction	Regional R TPO junction	Non-lesional	L temporal/ R Temporal/ R posterior inferior temporal region

M: male; F: female; L: left; R: right; FC: frontocentral; FCT: frontocentrotemporal; NLAT: non lateralising; NLOC: non localizing. FCD: focal cortical dysplasia; NA: not applicable, TPO: Temporal-parietal-occipital

Conflict of interest

Declaration of interest: None