EEG-fMRI Evaluation of Patients with Mesial Temporal Lobe Sclerosis

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Key words: focal drug resistant epilepsy, surgical treatment, EEG-fMRI

SUMMARY – *This preliminary study sought more information on blood oxygen level dependent (BOLD) activation, especially contralateral temporal/extratemporal spread, during continuous EEG-fMRI recordings in four patients with mesial temporal sclerosis (MTS). In two patients, EEG showed unilateral focal activity during the EEG-fMRI session concordant with the interictal focus previously identified with standard and video-poly EEG. In the other two patients EEG demonstrated a contralateral diffusion of the irritative focus. In the third patient (with the most drug-resistant form and also extratemporal clinical signs), there was an extratemporal diffusion over frontal regions, ipsilateral to the irritative focus. fMRI analysis confirmed a single activation in the mesial temporal region in two patients whose EEG showed unilateral focal activity, while it demonstrated a bilateral activation in the mesial temporal regions in the other two patients. In the third patient, fMRI demonstrated an activation in the supplementary motor area. This study confirms the most significant activation with a high firing rate of the irritative focus, but also suggests the importance of using new techniques (such as EEG-fMRI to examine cerebral blood flow) to identify the contralateral limbic activation, and any other extratemporal activations, possible causes of drug resistance in MTS that may require a more precise pre-surgical evaluation with invasive techniques.*

Introduction

Temporal lobe epilepsy (TLE) is the commonest location-related form of epilepsy accounting for more than 60-70% of all focal epilepsies¹. The major pathophysiologic mechanism underlying TLE is mesial temporal sclerosis (MTS), usually associated with hippocampal sclerosis. Traditional magnetic resonance imaging (MRI) detects this pathologic abnormality in only 65% of cases². In patients with MTS, traditional neuroimaging (MRI) usually shows (when present) highly diagnostic brain abnormalities such as hippocampal atrophy, usually associated with limbic T2-signal hyperintensity, whereas other features, such as ipsilateral ventricular enlargement and blurring at the grey-white matter boundary, are more variable³.

In the pre-surgical diagnostic work-up of patients with medically refractory focal epilepsy, the epileptogenic focus is usually identified by investigating the concordance of localizing information from neuroimaging studies, for example, functional MRI (fMRI) and non-invasive EEG recordings. In many cases, however, this information is inadequate to identify the seizure onset zone and patients have to undergo invasive EEG seizure recordings, using intracranial subdural, depth, or epidural electrodes⁴.

The major concern in patients with MTS who undergo surgery is the poor surgical outcome when the ictal onset zone involves the posterior hippocampal region⁵. Some patients with severe hippocampal sclerosis (sometimes called a “burned-out hippocampus”) nevertheless have atypical spread of ictal discharges, resulting in grossly discordant MRI findings and scalp EEG

Figure 1 Patient n. 3. Standard MRI (3T) on T2 condition: hyperintensity in the right mesial temporal region.

ictal recordings. These patients, many of whom are drug-resistant, nonetheless generally have excellent surgical outcomes⁶.

The presurgical evaluation to identify ictal onset zones in patients with MTS is necessarily a multimodality procedure. A multimodal study considering 90 patients with TLE found that the surgical outcome was significantly worse in patients with concordant MRI and non-lateralizing ictal EEG than in those with concordant MRI and ictal EEG findings ($p < 0.02$). Hence a concordant result from a combined MRI and ictal scalp EEG study is the finding most closely associated with surgical outcome in TLE⁷.

Other advanced strategies currently available for localizing epileptic foci include functional neuroimaging (positron emission tomography (PET); single photon emission computed tomography (SPECT); and fMRI) integrated by more invasive neurophysiological techniques (stereo-EEG; high-density EEG). Interictal fluorodeoxyglucose (FDG) PET and ictal-interictal SPECT rely on quantifying the metabolic activity in a neuronal population before and during seizures. Little is known on whether these molecular techniques can be used to study TLE, and in particular MTS. In particular PET, owing to the limitations linked to infusing a metabolite connected to a radioisotope, and SPECT, given the need for lengthy sampling, have proved unfeasible because both techniques entail study-

ing the patient during the ictal phase, sometimes an impossible task. Despite achieving good diagnostic specificity, both techniques have low sensitivity, localizing no more than half of the patients with ictal onset in the temporal zone and no more than a quarter of those with onset in the extratemporal zones⁸.

Magnetic source imaging (MSI) may detect interictal spikes from mesial temporal structures. A recent MSI study was performed on 22 patients with intractable MTS, candidates for surgical treatment. Sixty per cent of patients with non-localizing ictal scalp EEG had well-localized spikes on MSI ipsilateral to the side of surgery and 66.7% of patients with non-localizing MRI had well-localized spikes on MSI ipsilateral to the side of surgery. In conclusion, MSI may provide important localizing information in patients with MTS, especially when MRI and/or ictal scalp EEG are not localizing⁹.

Continuous EEG-fMRI is another simple recently developed neuroimaging tool that has already improved initial presurgical planning by helping to identify irritative foci that necessitate further study with more invasive techniques to identify the epileptogenic region. Notwithstanding these advantages, an early study reported that continuous EEG-fMRI yields low sensitivity in definitively identifying an irritative focus in the mesial temporal lobe¹⁰. Although this study made no distinction between patients whose EEG showed slow and high fir-

ing, a recent study by our group suggests that firing rates could have a major role in detecting brain haemodynamic activation related to interictal epileptiform discharges¹¹.

This preliminary study sought more information on blood oxygen level dependent (BOLD) activation, especially contralateral temporal/extratemporal spreading, during continuous EEG-fMRI recordings in MTS. We studied four patients with clinically, neurophysiologically and neuroradiologically (Figure 1) confirmed MTS, both drug-responsive and drug-resistant.

Because the surgical outcome may be different in MTS with and without contralateral diffusion, we also investigated whether EEG-fMRI might disclose contralateral/temporal spread of BOLD signal activation in patients with the drug-resistant form.

Our second endpoint was to investigate the link between firing rates in the irritative zone and fMRI-BOLD activation. To do so we selected for study a homogenous group of four patients all of whom had a high EEG firing rate (almost two interictal epileptic discharges (IEDs) a minute).

Materials and Methods

Patients

The first patient is a 73-year-old man who presented with right hemiparesis (predominantly involving the arm, shoulder and face). Although the hemiparesis disappeared within a few hours, a Jacksonian seizure developed in the right arm, shoulder and hemiface, and responded to diazepam. A computed tomographic (CT) brain scan identified no focal lesions. MRI of the brain disclosed decreased volume, with ME and enhancement in T2, of the left hippocampal region (compatible with MTS). Neuropsychological assessment disclosed no language, memory or attention deficits. Standard ictal and interictal EEG recordings showed an irritative focus (characterized by high amplitude slow-spiked waves) in the left frontotemporal region. This EEG seizure activity remained unchanged during eye opening. EEGs showed no evidence of contralateral ictal spread. After diazepam infusion the patient manifested no other epileptic syndromes, although the irritative focus persisted. After returning home he remained seizure-free.

The second patient is a 23-year-old girl, admitted to our ward after a traffic accident and following concussion with loss of consciousness.

There was no history of neurological disorders or epilepsy in her family. She was second born at term after a normal pregnancy, eutocic and spontaneous birth. Growth and psychomotor development were normal. At one year of age, on awaking and during fever, she presented a sudden generalized stiffness with myoclonus at the arms and legs and loss of consciousness, lasting ten minutes and interrupted by diazepam. At three years of age, during fever, she manifested sudden pallor, loss of consciousness, foaming at the mouth, lasting two minutes and interrupted by diazepam. At 12 years of age she manifested weekly episodes of sudden fear and pavor without loss of consciousness, lasting 30 seconds. Sometimes, but not always, she presented with pallor. If asked, she answered automatically and did not remember what she had been asked after questioning. An EEG (1995) resulted normal, but the episodes increased in frequency in the following months (one to two per day) so she was admitted to the child neuropsychiatry ward. Standard EEG demonstrated interictal epileptiform discharges (theta angular waves of low amplitude, with rare slow-spiked waves) on right frontotemporal regions. An MRI (1995) disclosed right mesial temporal lobe sclerosis, concordant with EEG and clinical data. She was diagnosed with partial symptomatic temporal lobe epilepsy and had been on polytherapy (carbamazepine, and levetiracetam) ever since without a complete resolution of the seizures. On admission to our ward she was responsive and the neurological examination excluded focal deficits and cognitive impairment. During the first days of stay in hospital she manifested two ictal episodes characterized by psychic phenomenology. She now represents a case of drug-resistant MTS.

The third patient is a 31-year-old man born at term after a normal pregnancy, eutocic and spontaneous birth. He had had frequent febrile seizures since the age of two. The first seizures occurred at the age of six, characterized by gastric aura followed by partial complex seizures with areactivity and oral-manual automatisms, and subsequently leg and arm automatic movements (pedalling) lasting between 30 seconds and one minute (suggesting an involvement of the supplementary motor cortex). He recovers the ability to speak and answer a few seconds after the seizure. He never developed generalized seizures. The rate of the seizures increased with time and they now appear in clusters of 10-15 seizures every one to two months. Auras appear every two weeks. Standard and

Table 1

	Years	MRI findings	Drug response	Irritative pattern on EEG	Irritative focus	Contralateral diffusion
Pt. 1	73	L-MTS	Responsive	h.a.s.w.// h.a.sp.s.w.	T3-T5	NO
Pt. 2	23	R-MTS	Resistant	s.w.	T4-T6	YES
Pt. 3	31	R-MTS	Resistant	h.a.sp.s.w.	T6-T8	YES
Pt. 4	62	L-MTS	Responsive	s.w.//sp.s.w.	F7-T3	NO

L/R-MST: left/right-mesial temporal sclerosis; h.a.s.w: high amplitude slow wave; h.a.sp.s.w:high amplitude spiked slow wave; s.w: slow wave; sp.s.w: spiked slow wave.

prolonged video-EEG demonstrated an irritative focus (high amplitude spiked slow wave activity) on T6-T8, concordant with MRI, with a tendency to diffusion over the contralateral temporal regions and also over the right frontal regions (F8). MRI disclosed severe right hippocampal sclerosis (Figure 1). He was first treated only with phenobarbitone, and subsequently with levetiracetam and carbamazepine (without positive response), now he is treated with phenytoin, phenobarbitone and topiramate, without a positive response. In conclusion, he represents a case of drug-resistant MTS.

The fourth patient is a 62-year-old man with complex seizures since adolescence. Seizures are characterized by a gastric aura followed by areactivity, pallor, oral/manual automatisms with psychic phenomena (anxiety and pavor). The seizures occur at an inconstant rate (between one every two weeks and two a day). Treated with clobazam and phenobarbital, he manifested a satisfactory response to therapy. Standard and videopoly-EEG identifies an irritative focus (slow wave, spiked slow wave) in the left frontotemporal regions (F7-T3).

EEG Recordings and Analysis

The EEG was acquired using a MR compatible EEG amplifier (SD MRI 32, Micromed, Treviso, Italy) and a cap providing 18 Ag/AgCl electrodes positioned according to a 10/20 system (impedance was kept below 10 k Ω). To remove pulse and movement artifacts during scanning, two of these electrodes were used to record the electrocardiogram (ECG) and electromyogram (EMG). The EMG electrode was placed on the right abductor pollicis brevis (APB) muscle and the other (ECG) on the precordial area.

The reference was placed anterior to Fz, and the ground posterior to Fz as in other studies¹¹⁻¹⁴ using the same system. To ensure subjects' safety, the wires were carefully arranged to avoid loops and physical contact with the sub-

ject. To minimize the variability in the EEG artifacts due to the MR sequence and avoid wire movement caused by mechanical vibration, the wires rested on foam pads.

EEG data were acquired at the rate of 1024 Hz using the software package SystemPlus (Micromed, Treviso, Italy). To avoid saturation, the EEG amplifier had a resolution of 22 bits with a range of ± 25.6 mV. An anti-aliasing hardware band-pass filter was applied with a bandwidth between 0.15 and 269.5 Hz. Details of the EEG recording method are given in Bénar et al.¹⁵. The EEG artifact induced by the gradient magnetic field was digitally removed off-line by an adaptive filter (Micromed). EEG artifacts associated with pulsatile blood flow were digitally removed off-line using a simple averaging procedure^{16,17}. Subsequently a single electroencephalographer visually reviewed the filtered EEGs, and marked the time of onset and duration of each IED.

fMRI Acquisition and Analysis

Images were acquired on a 1.5 T MR scanner (Symphony, Siemens, Erlangen, Germany) equipped with EPI capability and a standard transient/receive (TR) head coil. At the start of each study, a T1-weighted anatomical MRI was acquired (192 slices; FOV = 256 $\times$ 256; scanning matrix 512 $\times$ 512; slice thickness 1 mm; sagittal slice orientation; echo time (TE) = 3 ms; repetition time (TR) = 1990 ms).

All patients then underwent an eight-minute fMRI recording session, after giving informed consent. BOLD fMRI data were acquired using a standard gradient-echo (EPI) sequence on the axial orientation, in one run lasting eight minutes with the patient in the resting state, as described by Kobayashi et al.¹⁸ (voxel dimension 3 $\times$ 3 $\times$ 3 mm; 36 slices; matrix 64 $\times$ 64; TE = 50 ms, TR = 3.7 s; and slice thickness = 3 mm). At the onset of each fMRI acquisition, the scanner provided a trigger signal that was

Figure 2 Patient n. 1. EEG during a scanning session. Focal IEDs (h.a.s.w./h.a.sp.s.w.) without diffusion.

Figure 3 Patient n. 3. EEG recording during a scanning session (monopolar montage).

Table 2 Number of IEDs revealed on EEG during the recording session and BOLD activation in 2D-fMRI, with number of contiguous activated slices.

Pt. 1	61	2.54	Left mesial temporal lobe	2	No
Pt. 2	58	2.41	Right mesial temporal lobe	2	Yes
Pt. 3	57	2.38	Right mesial temporal lobe	3	Yes
Pt. 4	57	2.38	Left mesial temporal lobe	3	No
Mean	58.25	2.43			
s.d.	1.9	0.07			
	(IEDs/24')	(IEDs/min)	(BOLD activation in 2D reconstruction)	contiguous activated slices)	Contralateral activation

recorded by the EEG system and used as a volume marker.

For image processing and statistical analysis of the fMRI time series data we used Brain-Voyager QX 1.9 software (*Brain Innovation, Maastricht, Netherlands*) running in a windows Vista environment. Pre-processing of the functional MRI included three-dimensional motion correction, slice scan time correction (linear interpolation), linear trend removal by temporal high-pass filtering (three cycles in time course) and transformation into the Talairach coordinate space. Neither spatial nor temporal smoothing were used.

In each subject, activated voxels were identified with a single-subject general linear model approach for time series data¹⁹. To account for the haemodynamic delay, the boxcar waveform representing the rest and task conditions was convolved with an empirical haemodynamic response function²⁰.

A *t* statistic was used to determine significance on a voxel-by-voxel basis and correlation values were transformed into a normal distribu-

tion (*Z* statistic). The results were displayed on parametric statistical maps in which the pixel *Z* value is expressed on a colorimetric scale. We identified the single region of condition-associated BOLD signal changes with a statistical threshold based on the amplitude ($p < 0.05$) and extent of the regions of activation. The location of voxels with maximal signal increase was expressed in terms of *x*, *y*, and *z* in the Talairach space, and activation volumes were expressed in terms of number of activated voxels. Positive BOLD-fMRI responses were defined as activations. Significant responses were defined as almost five contiguous voxels with $p < 0.05$ over at least two contiguous slices²¹⁻²³ in 2D reconstruction. The anatomic localization of BOLD responses was determined by co-registration of the anatomic data and statistical *t* maps.

We analyzed the extent and maximum fMRI response for each study, considering all areas with significant activations. We also determined the locations of maximum activation based on the maximum peak response (maximum *t* value).

Figure 4 Patient n. 1. BOLD activation related to focal IEDs.

Results

Clinical Data

Although sharing a common condition (high firing rate of interictal focus), the four MTS presented here differed considering response to therapy: two (n. 1 and n. 4) proved drug-responsive, and two (n. 2 and n. 3) were drug-resistant (Table 1).

EEG Data during fMRI Scanning Session

No clinical or EEG manifestations of ictal events developed during scanning sessions (all patients persisting in interictal condition). None of the patients reported discomfort or other side-events related to the EEG recording procedure.

In two patients (first and fourth, *the drug-responsive MTS*), EEG showed unilateral focal activity during the EEG-fMRI session concord-

Figure 5 Patient n. 3.

ant with the interictal focus previously identified with standard and video-poly EEG (Figure 2). In the other two patients (n. 2 and n. 3, *the drug-resistant MTS*), EEG demonstrated a contralateral diffusion of the irritative focus. In the third patient (with the most drug-resistant form, and also extratemporal clinical signs), there was an extratemporal diffusion over the frontal regions (F8), ipsilateral to the irritative focus (Figure 3).

IEDs recorded inside the scanner had a localization, amplitude and morphology similar to those in previous routine EEG recordings (Table 1). IEDs recorded inside scanner occurred at a rate of almost two a minute (Table 2).

EEG-fMRI Bold Responses: Sites of Activation

In all patients, fMRI analysis showed a significant focal BOLD activation in the sclerotic

Figure 6 Patient n. 3. Extratemporal activation (right supplementary motor cortex).

mesial temporal region, concordant with the EEG irritative focus previously identified and triggered as “active state” in fMRI protocol analysis. The activation is presented in Table 2 (fMRI-2D reconstruction).

Table 3 (fMRI-3D reconstruction) shows the coordinates (x,y,z) of regions of interest and the corresponding brain areas. We observed a large number of activated voxels. In the first patient we noted an activation only in the sclerotic left mesial temporal lobe. In the second patient we also detected a contralateral activation (right and left mesial temporal lobe activation). In the third patient we noted an activation in the right sclerotic mesial temporal region but also in the left mesial temporal region and right supplementary motor area, concordant with clinical data (automatic movements at the arms and legs after partial complex seizures) and EEG findings (diffusion on F8 and in contralateral temporal regions). In the fourth patient we noted an activation only in the sclerotic left mesial temporal lobe.

Discussion

EEG-fMRI has recently been applied to the study of MTS¹⁰. The first results (considering five MTS patients) were not encouraging: only three out of five patients demonstrated a significant BOLD activation related to the irritative focus on EEG.

The new element considered in this study was the high firing rates (almost two IEDs/minute), considered the hallmark of this particular group of patients. The different condition among this sample is the follow-up: the first and the fourth patients are drug responsive, while the other two are drug-resistant, and (in particular) the third is now a candidate for neurosurgical treatment (evaluated by Niguarda Hospital in Milan).

The main purpose was to investigate the area of BOLD activation in MTS, to verify the correlation between neuroradiological and neurophysiological data (in particular we compared the BOLD activation linked to irritative focus with the known lesional area) to analyze the linkage, suggested by the literature, between irritative, epileptogenic and lesional areas²⁴.

The statistically significant increase in deoxyhaemoglobin in all sclerotic limbic lobes is the most interesting result.

Another endpoint of our study was the identification of the diffusion of irritative activity (both in the contralateral mesiotemporal lobe and in extratemporal regions) among the first (drug-responsive) and the second (drug-resistant) group. Our aim was to verify if, in parallel with the tendency of contralateral/ipsilateral diffusion of interictal activity (on EEG), there was a specular activation of BOLD.

The diffusion of interictal activity is reported in the literature²⁵ as one of the negative prognostic factors in terms of drug resistance and

Table 3 Number of activated voxels, Coordinates (mean and s.d.) and corresponding Talairach system localization of activated regions in 3D reconstruction.

	Mean "X"	Mean "Y"	Mean "Z"	N. Voxels	CORRESPONDING AREA
Pat. 1	-18 ± 1.7	-7 ± 1.8	-19 ± 1.3	177	Left Cerebrum, limbic lobe, parahippocampal gyrus, Brodman area 34
					Contralateral activation: no
Pat. 2	17 ± 3	-14 ± 1.5	-15 ± 1.2	175	Right cerebrum, limbic lobe, parahippocampal gyrus, Brodman area 28
					Contralateral activation: Left Cerebrum, limbic lobe, parahippocampal gyrus, Brodman area 34
Pat. 3	4.2 ± 3	51 ± 1.9	-0.49 ± 2.5	368	Right cerebrum occipital lobe, superior temporal gyrus, Brodman area 38
					Contralateral activation: Left Cerebrum, limbic lobe, parahippocampal gyrus, Brodman area 34
					Frontal region activation: Right cerebrum, frontal lobe, medial frontal gyrus Brodman area 10
Pat. 4	-31 ± 1	-40 ± 2.5	-14 ± 0.8	350	Left cerebrum, temporal lobe, fusiform gyrus, Brodman area 20
					Contralateral activation: no

hence an inclusion criterion for surgical treatment with a good outcome⁶.

The first and the fourth MTS patients (drug responsive) did not manifest a contralateral diffusion and fMRI did not manifest contralateral BOLD activation (Table 3). The other two MTS patients (drug-resistant) manifested a constant diffusion of the irritative focus, both on the contralateral mesiotemporal region (n. 2 and n. 3) and on the ipsilateral supplementary motor cortex (n. 3). In this patient, diffusion to the supplementary motor cortex, suggesting loss of an intratemporal seizure-inhibitory network, is concordant with the clinical findings (areactivity and leg automatisms).

Even though we examined a small sample, and need to confirm the conclusions with a large number of MTS patients, we obtained a significant activation in all sclerotic limbic regions, and not only in half, as reported in previous studies. The possible explanation is the firing rate. In addition, the morphology and amplitude of IEDs may have a role in detecting this activation but a large number of patients is needed to confirm this hypothesis.

This study confirms a highly significant activation with a high firing rate of the irritative focus, but also suggests the importance of using new techniques (such as EEG-fMRI

to examine cerebral blood flow) to identify the contralateral limbic activation, and any other extratemporal activations, possible causes of drug resistance in MTS that may require a more precise presurgical evaluation with invasive techniques.

This finding may also confirm the pathophysiology of seizure diffusion in the contralateral temporal region or in extratemporal regions. The current hypothesis considers the loss of an intratemporal network limiting the irritative focus when its stimulus causes a seizure by activation of the epileptogenic region²⁶. Our results (four out of four activations in patients with a high firing rate; association between interictal activity diffusion on EEG and drug resistance; correlation between interictal activity diffusion on EEG and haemodynamic diffusion of BOLD activation) seem to confirm this hypothesis.

A further development of this study, to be improved with a larger sample to confirm the results, will be the temporal definition of haemodynamic diffusion of BOLD activation related to EEG diffusion of interictal activity, in order to establish whether this phenomenon occurs along distinct tract fibers, no longer inhibited by an intratemporal network and hence insufficient.

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