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Case report

EEG-fMRI as an useful tool to detect epileptic foci associated with secondary bilateral synchrony

Paolo Borelli [a,*], Mirko Avesani [a], Emanuela Formaggio [a], Silvia Francesca Storti [a], Tiziano Zanoni [b], Giuseppe Moretto [b], Antonio Fiaschi [a], Roberto Cerini [c], Paolo Manganotti [a]

[a] Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, P.le LA Scuro, 37134, Verona, Italy
[b] Division of Neurology, Borgo Trento Hospital, P.le A. Stefani 1, 37126, Verona, Italy
[c] Department of Pathology and Diagnostics, University of Verona, Italy P.le LA Scuro, 37134, Verona, Italy

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ABSTRACT

Introduction: Tailoring the epileptic cortex is the key issue in the pre-surgical work-up of patients with pharmacoresistant focal epilepsy. Not always, however, the conventional MRI and the scalp EEG are able to provide the information needed to address this issue since the imaging may be normal (criptogenetic epilepsy) and the EEG, even ictal, poorly localizing.
Patient and methods: We present a case of focal criptogenetic epilepsy with speech arrest seizures and bilateral synchronous spike and wave scalp EEG pattern (secondary bilateral synchrony). The patient underwent an EEG-fMRI continuous co-registration.
Results: The EEG-fMRI showed a clear cut activation of a BOLD signal during the epileptic discharge over the left Supplementary Motor Area (SMA) and, on lesser degree, over the homolateral motor strip.
Discussion: Knowledge and expertise about this technique has greatly increased over the last few years making it an useful tool for localizing purposes specially in patients with ambiguous scalp EEG and normal MRI just like the one we presented.

1. Introduction

Frontal lobe epilepsies (FLE) account for approximately 20–30% of all focal epilepsies.[1] The clinical features of seizures arising from the frontal cortex largely depend on the part of the frontal lobe involved by the epileptic activity and include bilateral tonic posturing, speech arrest, ictal incontinence, pseudo-absences, forced head and eyes deviation and hypermotor seizures.[1–4] The scalp electroencephalography (EEG) features of frontal lobe epilepsy both ictal and interictal are various and often ambiguous and include unilateral both ipsi- and contra-lateral spiking, bilateral asynchronous spiking, bilateral synchronous spike and wave discharges (secondary bilateral synchrony), vertex electrodes mild abnormalities or no abnormalities at all since the scalp EEG is poorly sensitive to deep generators located on the mesial surface of the frontal lobe.[4,5] In addition, given the often huge motor pattern of frontal lobe seizures, the ictal EEG may be obscured by artefacts.[5] Thereby, more investigations are often needed in the surgical work up for epilepsy to generate a localizing hypothesis and this task is even more difficult in conventional Magnetic Resonance Imaging (MRI) negative cases. In this regard many techniques have been developed over the last decades to address this issue including ictal Single Photon Emission Computed Tomography (SPECT) and interictal Positron Emission Tomography (PET).[6] However, these tools are expensive and not always broadly available. The continuous EEG- functional Magnetic Resonance Imaging (fMRI) is a relatively new technique capable to detect the epileptic focus on the basis of hemodynamic changes (Blood Oxigenation Level Dependent, BOLD) over the cortex responsible for the interictal epileptiform discharges (IED).[7–9]

We present the case of a young female patient with focal MRI negative epilepsy and generalized spike and wave discharges (secondary bilateral synchrony) on the interictal and ictal scalp EEG whose epileptic focus was identified by the continuous EEG-fMRI.

2. Patient

A 36 years old woman presented to our epilepsy outpatient clinic for seizures refractory to medical treatment since the age of 5. According to the detailed description of the patient herself and

* Corresponding author. Present address: Ospedale Unico Versilia, Via Aurelia 335, Lido di Camaiore (LU), 55049, Italy.
E-mail addresses: paoloborelli@hotmail.com, p.borelli@univr.it (P. Borelli).

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relatives who witnessed several times the seizures, her events took the form of sudden speech arrest episodes lasting from few seconds up to several minutes without any warning sensation.

In the ictal phase the patient reports to be able to move, understand and write properly (in some cases She wrote down her inability to speak to her husband). No clonic movements nor orofacial automatisms are experienced by the patient in this early stage. In most cases the event does not progress any further and patient has a full recollection of the episode. Sometimes this was followed by clonic jerking over the right part of the face and arm and just occasionally the patient experienced generalized tonic clonic seizures.

The sequence and the characteristics of the ictal events were consistently reported in the same way over the several outpatients clinic consultations even by different witnesses and to two different neurologists (PB and TZ) who agreed about the semiology described. The seizures frequency was on a weekly base despite polytherapy (Valproate 1500 mg/day; Levetiracetam 2000 mg/day and clonazepam 2 mg/day). The 3 T MRI was normal. She reported no febrile seizures nor significant head injuries. Pregnancy, delivery and developmental milestones were unremarkable as well as the rest of previous medical history.

Interictal scalp EEG showed frequent high amplitude 2 to 3 Hz generalized spike and wave discharges (see Fig. 1). There was an inconstant mild amplitude prevalence over the left hemisphere electrodes. In one case, during a conventional scalp EEG recording, the patient complained a brief episode of speech arrest associated with the usual EEG pattern (Fig. 2). This event was witnessed by a neurologist (TZ) aware about the clinical history and He described a brief inability to speak (matter of few seconds) during which the patient waved the hand to attract the doctor attention. There were no clonic movements and once the patient regained the speech She accurately described the event. An attempt to carry out a 3 h video-EEG monitoring was made in a day of seizures clustering but no usual events happened. On the basis of these elements, the diagnosis of generalized epilepsy was also made in another hospital.

3. Methods

During the MRI scanning, the EEG was acquired using a MR compatible EEG amplifier (SD MRI 32, Micromed, Treviso, Italy) and a cap providing 32 Ag/AgCl electrodes positioned according to a 10/20 system. 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.

Then the patient underwent a 6-min fMRI recording session in the resting state condition after giving informed consent.

The EEG artifact induced by the magnetic field gradient was digitally removed off-line using an adaptive filter[10] while the EEG artifact associated with pulsatile blood flow, the ballistocardiogram (BCG), was removed using an averaging procedure[11] both implemented in the SystemPlus software (Micromed).

Then a single electroencephalographer visually reviewed the filtered EEG and marked the time of onset and duration of each IED.

Images were obtained with a 1.5 T MR scanner (Symphony, Siemens, Erlangen, Germany). T1 anatomical images were obtained at the beginning of the study (192 slices; field of view = 256 × 256, scanning matrix 512 × 512, slice thickness 1 mm, sagittal slice orientation, echo time (TE) = 3ms, repetition time (TR) = 1990 ms.

fMRI data were acquired, using a standard gradient-echo (echo planar imaging: EPI) sequence, on the axial orientation (voxel size 3 × 3 × 3 mm; 36 slices; matrix 64 × 64; TE = 50 ms, TR = 3.7 s; slice thickness = 3 mm). BrainVoyager software (QX 1.9, Brain Innovation, Maastricht, Netherlands) was used for image processing and statistical analysis of the fMRI time series data. The MR images were realigned to reduce the effect of head motion (three-dimensional motion correction with trilinear interpolation). To correct for the different acquisition times, a slice scan time correction was used with ascending, interleaved scanning order with linear interpolation in time. Data were then pre-processed with linear trend removal, to remove all drifts, and with a temporal

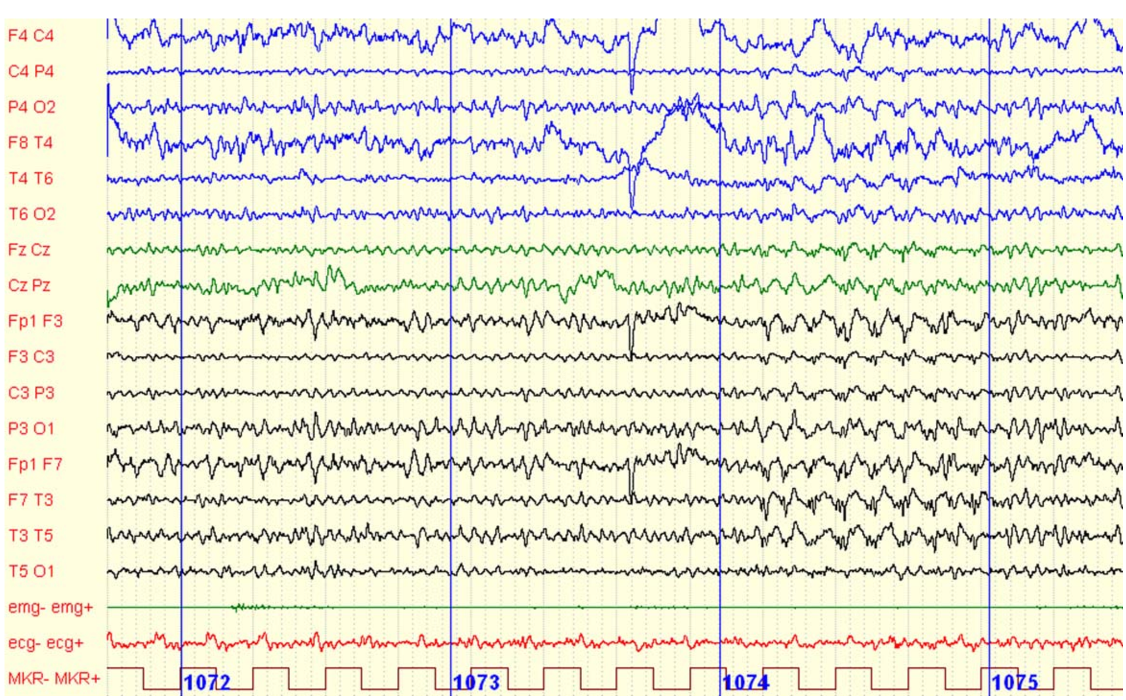

Fig. 1. EEG recorded during the fMRI acquisition showing generalized spike and wave discharges.

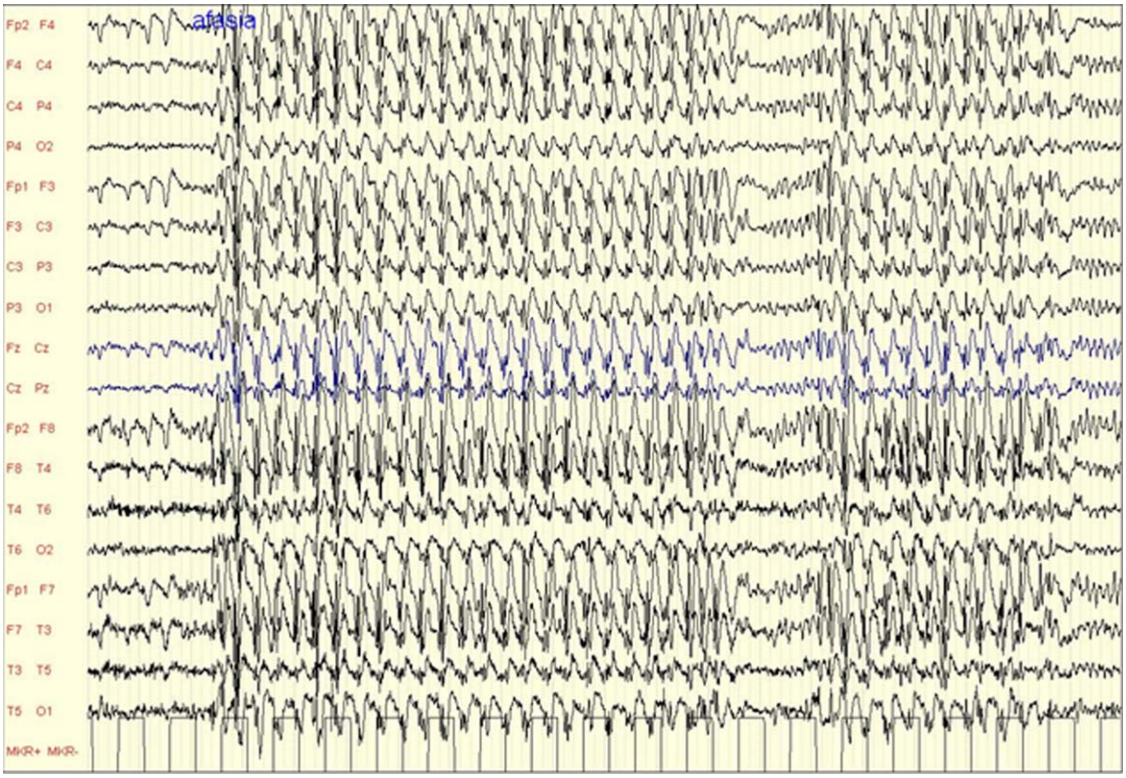

Fig. 2. Ictal EEG during a brief speech arrest episode (“Afasia” marks the beginning of the speech impairment).

high-pass filter (3 cycles in time course) to reduce the influence of breathing and physiological noises. The anatomical and functional data were kept in the subject’s native space. Activated voxels were identified with a single-subject general linear model approach for time series data. To account for the hemodynamic delay, a spike protocol based on the onset of IEDs in the EEG was convolved with a canonical hemodynamic response function: two gamma function. A t statistic was used to determine significance on a

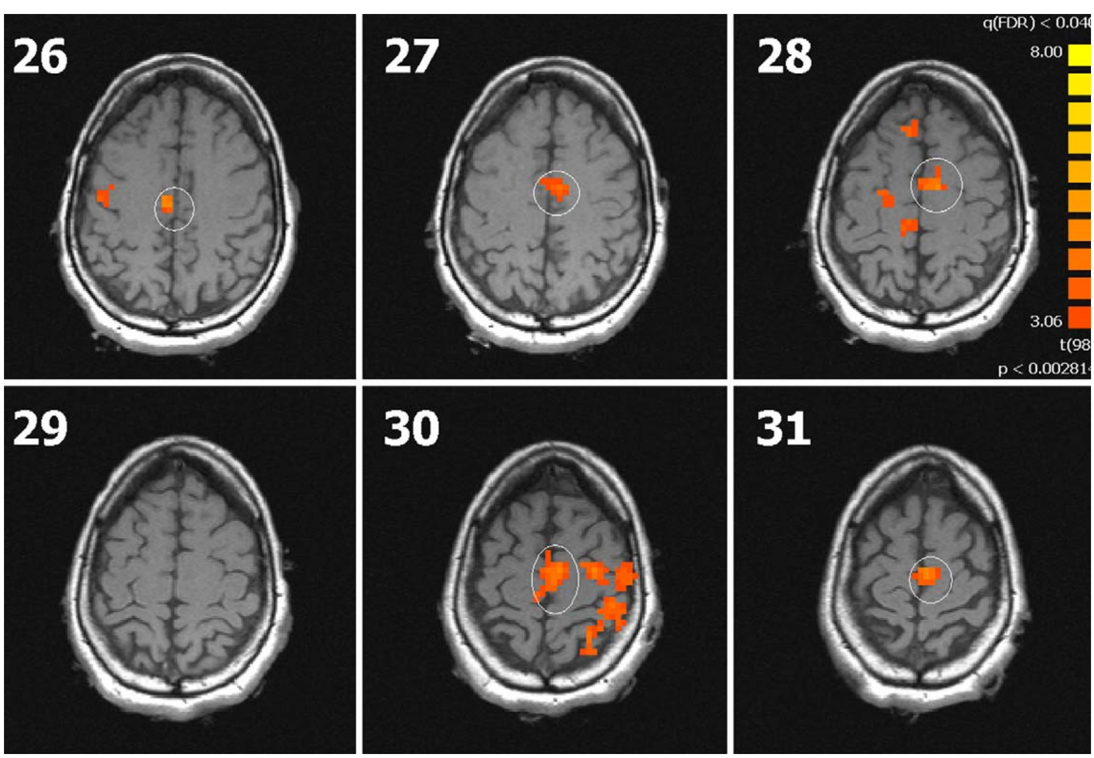

Fig. 3. The EEG-fMRI during the generalized spike and wave discharge shows a clear-cut activation of the left (radiological convention) Supplementary Motor Area (SMA) and on the contralateral SMA on a lesser degree. Spread over the left motor strip is also evident.

voxel-by-voxel basis and correlation values were transformed into a normal distribution (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 ($P < .05$, corrected for multiple comparisons: False Discovery Rate FDR) and extent of the regions of activation.

4. Results

During the MRI scan, 6 spike and wave discharges were recorded (mean duration 3.25 s). Those were used as activation phases. Then we used 3 normal EEG sequences as rest phases since the rest condition was clear enough. These 2 EEG patterns were eventually compared. Then We tried to use all the 6 normal sequences before the spike and wave discharges recorded and the result, in the comparison with discharges, was the same.

The EEG -fMRI analysis showed a prominent BOLD activation over the left supplementary motor area (SMA) during the spike and wave discharge compared to the rest state (see Fig. 3). This activation pattern is reproducible according to the Duncan criteria since it was present in 2 contiguous slices.[12] The statistical significance value of this activation was $p < 0.0028$ even after FDR correction. More activations were found in the contralateral SMA and homolateral motor strip as well. No significant deactivation areas nor thalamic involvement (activation or deactivation) were found.

On the basis of this result the patient was referred to level 2 epilepsy surgery center for pre-surgical work up protocol including long term video-EEG monitoring but eventually She refused the option.

5. Discussion

The speech arrest is an epileptic feature usually related to the involvement of the supplementary motor cortex either over the dominant or non dominant hemisphere. Often that is associated with other motor features such as bilateral tonic posturing, facial grimacing and ictal incontinence. Occasionally it may occur isolated. As shown by an elegant polygraphic case study by Meletti et al.[13], this phenomenon might be the result of motor inhibition involving the phonatory muscles.

The bilateral spike and wave discharges pattern (secondary bilateral synchrony) is often detected in FLE specially if the generator is deep for instance over the mesial surface of the frontal lobe.[4,5] In the presurgical work up for epilepsy surgery, such a scalp EEG pattern certainly raises questions about the origin of the focal epilepsy specially when the conventional MRI is negative. In the latter case, usually more investigations are obtained at least to guide the placement of depth electrodes for invasive EEG. Ictal SPECT and interictal PET are commonly used for this purpose but they are expensive, difficult to interpret and usually provide regional rather then local data. In addition, if the ictal event is brief, SPECT might be falsely negative due to incorrect timing of the tracer injection.[6,14] Safety issue is also raised by the use of radioactive substances.

The EEG-fMRI is relatively new tool able to provide localizing data on the basis of the EEG changes.[7,8] That is safe for the patient, relatively cheap and the increasing knowledge about this technique is rendering it more and more effective in the study of focal also non lesional epilepsies even in a presurgical work-up perspective as shown by Moeller et al and Zijlmans et al. in two important studies.[14,15]

Literature about EEG-fMRI in patients with secondary bilateral synchrony is quite poor except a paper by Aghakhani et al.[16] in which 11 patients with such an EEG pattern were studied with a variable activation-deactivation pattern including thalamic involvement in 6 out of 11 (55%). The clinical seizure pattern and the MRI findings were variable.

In our case, the EEG-fMRI managed to reveal the origin of the epileptiform discharges including the spread over the homolateral motor strip which is highly consistent with the patients clinical feature (speech arrest followed by clonic jerks over right half of face and right arm) whilst 3T MRI and conventional interictal scalp EEG were helpless in this regard. Some involvement of the contralateral SMA was also detected and its significance is less clear. In fact it may be the result of a transcallosal spread from the left SMA or simply of an imperfect spatial resolution of the technique used.

Moreover in our case no thalamic changes were seen as frequently, but not constantly (6/11 pts), reported by Aghakhani et al.[17]

Unfortunately our localizing hypothesis could not be proven by invasive EEG and post-surgical outcome since the patient gave up surgery option.

However, this case suggests that in the presurgical work up for epilepsy the EEG-fMRI is an useful tool in order to generate a localizing hypothesis to be tested with invasive recording in patients affected by focal epilepsy with bilateral spike and wave discharge EEG (secondary bilateral synchrony) and negative MRI.

Conflict of interest

None declared.

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