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Case report

Ictal haemodynamic changes in a patient affected by "subtle" Epilepsia Partialis Continua

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ABSTRACT

We report on a 64 year-old woman presenting with Epilepsia Partialis Continua (EPC) affecting the left hand since the age of 24 without neurological deficit. Structural MRI showed a region of focal cortical dysplasia (FCD) over the right central gyrus and lesions in the mesial frontal and occipital cortex secondary to perinatal hypoxic injury. Ictal spike haemodynamic mapping using simultaneous EEG-fMRI revealed significant BOLD signal changes prominent in the region of FCD (larger cluster), occipital cortex (global statistical maximum), prefrontal cortex and cerebellum. The cluster over FCD was in good agreement with the result of EEG source analysis.

Our findings provide an interesting illustration of the ability of EEG-fMRI to reveal epileptogenic networks confirming the intrinsic epileptogenic properties of dysplastic neurons.

1. Introduction

Epilepsia Partialis Continua (EPC) is a rare form of partial status epilepticus, defined by continuous jerking of a focal body part that lasts for over hours, days or even years.[1,2] In adults, EPC is generally secondary to cerebrovascular diseases, tumours, infections and metabolic disorders.[2] Nevertheless, a considerable number of cases with Focal Cortical Dysplasia (FCD) presenting with EPC have been described.[3,4] Despite several studies, the anatomical and pathophysiological substrate of EPC is still subject of speculation. The favoured hypothesis is that of a cortical origin of the characteristic jerks[2] although subcortical mechanisms have also been proposed.[5]

Recently, simultaneous Electroencephalography (EEG) and fMRI recordings (EEG-fMRI) have been used to study the haemodynamic correlates of ictal and interictal EEG abnormalities in epileptic patients, with a primary aim of identifying the brain regions involved.[6] It has been demonstrated that this technique could provide information about the irritative and epileptogenic zone.[7,8]

The objective of the present study was to describe the clinical, imaging and EEG features of a patient with central sulcus FCD presenting as non progressive EPC and to map haemodynamic changes time-locked to scalp EEG abnormalities throughout the brain.

2. Methods

A 64 year-old woman (right handed) was referred to our Epilepsy Centre for evaluation in order to reduce anti-epileptic drug therapy. Seizures (onset age 25 years) were characterized by a prodromic sensation of brief paresthesias involving left hand fingers followed by loss of consciousness, left tonic deviation of the head and left harm extension. She has been taking Carbamazepine (1000 mg/day) from the age of 34 and has been seizure-free since. Her past medical history, including birth and development milestones, was unremarkable. Neurological examination was normal.

Polygraphic Video-EEG recording (18 EEG channels, 1 ECG channel and surface electromyograms (EMGs) of the left estensor digitorum muscle) was performed. It showed frequent spikes and polyspikes over the right fronto-central regions which corresponded to arrhythmic myoclonus, with positive and negative component, in the patient's left hand (see Fig. 1A). The patient

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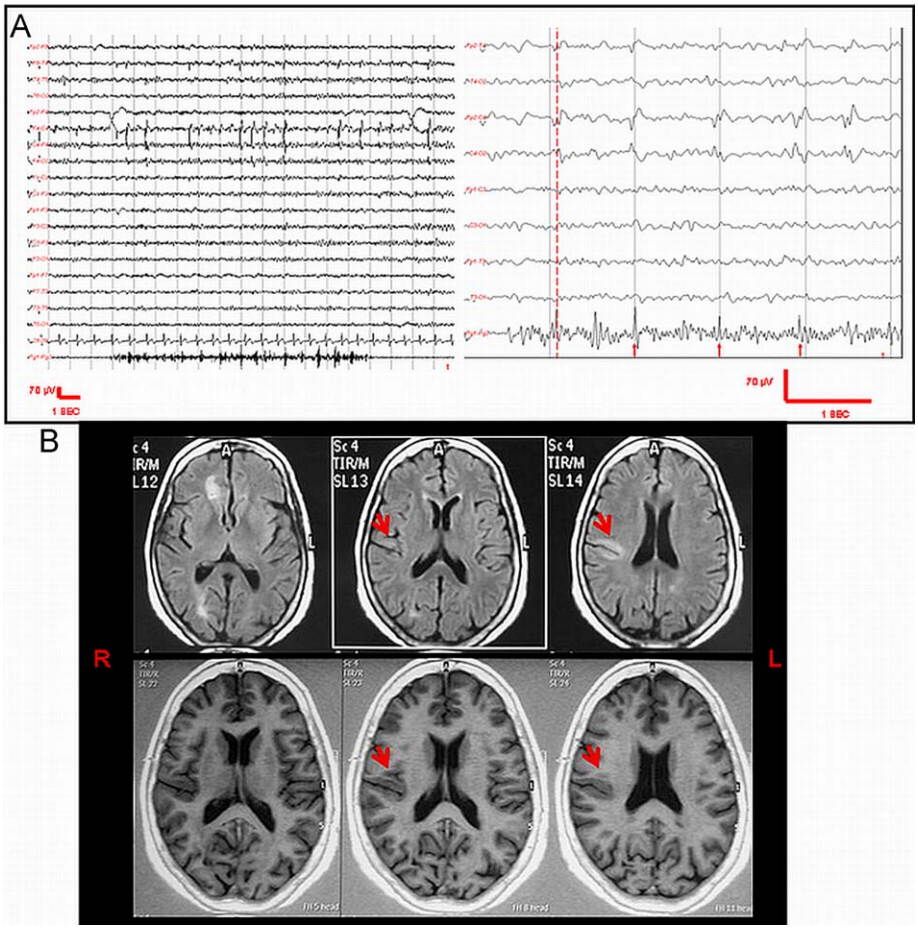

Fig. 1. Polygraphic Video-EEG recording and structural MRI scan. (A) Scalp polygraphic Video-EEG recording:18 EEG channels, 1 ECG channel (electrodes: 28–29) and surface electromyograms (EMGs) of the left estensor digitorum muscle (electrodes: Pg1–Pg2). EEG traces are displayed as bipolar montage (left image) and Jasper montage (right image). EEGs showed focal spikes and polyspikes located at fronto-central and fronto-temporal regions. The dotted red line (on the right image) shows the time-locked correspondence between focal spike and left hand myoclonus documented by EMG activity; the solid red arrows indicate the occurrence of myoclonic jerks on EMG electrode. Note the clear correspondence between myoclonus and spikes/polyspikes on EEG. (B) Top: T2-weighted fluid-attenuated inversion recovery (FLAIR) image, axial orientation. Bottom: T1-weighted inversion recovery (IR), axial orientation. The solid red arrow shows the FCD. R, right; L, left.

referred this movement to be "normal part of my life" and she does consider it to be a "seizure".

T1-weighted inversion recovery MR images (IR) revealed cortical thickening with reduced demarcation of gray-white boundary around the right central sulcus; T2-weighted fluid-attenuated inversion recovery (FLAIR) images showed a region of hyperintense signal in the subcortical white matter around the central sulcus and in the ipsilateral fronto-mesial and occipital regions (see Fig. 1B). The lesion in the central sulcus was identified by an expert (PP) as FCD, whereas the fronto-mesial and occipital lesions were described as secondary to hypoxic perinatal injury. The study was approved by the Ethics Committee of the University of Rome "La Sapienza" and written consent was obtained.

2.1. EEG-fMRI acquisition

Before and after fMRI session, the patient underwent Polygraphic Video-EEG recording to documented ictal pathological activity. fMRI data (EPI images, 20 axial slices, 5 mm thickness, TR/TE = 3000/50 ms, image matrix 64×64) were acquired using a clinical 1.5-T scanner (Philips Gyroscan).

EEG (18-channel cap, sampling rate 1024 Hz) was recorded simultaneously fMRI acquisition using a purpose-built digital recording system (Micromed, Italy). Two 10-min series of 200 scans each were acquired. The patient was asked to rest with eyes closed and to keep still. Additionally, two structural MRI scans were acquired for anatomical reference: T1-weighted SE images (TR/TE = 265/15 ms, 256×256 matrix, 24×24 cm^2 FOV, 20 slices) and T1-weighted Inversion Recovery scan (IR) (TR/TE = 2853/15 ms, 256×256 matrix, 24×24 cm^2 FOV, 20 slices).

2.2. fMRI data analysis

All fMRI data were preprocessed and analysed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/).

EEG ictal spikes were visually marked and served as onsets for a general linear model (event-related fMRI analysis including convolution with a haemodynamic response function (HRF) and its temporal (TD) and dispersion (DD) derivatives). Realignment parameters (motion) were modelled as confounds. A T contrast across the regressors of interest was specified to test for significant ictal spike-related BOLD signal changes; the computed SPM{T} was thresholded at $p < 0.05$ (corrected for multiple comparisons) and at $p < 0.001$ (uncorrected for multiple comparisons). The results were overlaid onto the structural MRI (IR image) for illustration.

2.3. EEG source analysis

EEG pre-processing was performed using the EEGLab software package (Delorme and Makeig 2004). After down-sampling

(250 Hz) and filtering (high-pass: 0.3 Hz; low-pass filtered 35 Hz) epochs starting from 100 ms prior to the ictal spikes to 100 ms following the end of the events were marked and averaged. Source reconstruction was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). A Boundary Element Model (BEM) consisting of a realistically shaped head was used for the forward model, which included the cortical mesh, brain, skull and scalp surfaces extracted by means of segmentation of the patient's normalised anatomical scan (IR image). Standard localization of the electrodes according to the 10-20 system was assumed to obtain electrodes coordinates. The Variational Bayes Equivalent Current Dipoles (VB-ECDs) model was used for the inverse solution.[9] The time window for reconstruction was accepted as the peak of the averaged EEG events (spikes and polyspikes) (0 ms); one dipole was assessed and no prior information regarding its location and moment was used. To demonstrate that our model (one dipole located on the right precentral cortex) is the best, irrespective of priors, we compared this model with a location prior in other regions: right occipital cortex, right prefrontal cortex. These other locations were decided based on the EEG/fMRI data analysis. We also included a model in which prior dipole location was on the left precentral cortex (i.e. on the wrong side of the head).

3. Results

Good quality EEG recordings were obtained which showed clear focal abnormalities over the right fronto-central region (see Fig. 2A). According to their shape, two clusters of events were identified: 105 spikes and 74 polyspikes.

EEG/fMRI data analysis have shown ictal events related BOLD signal increase in the right precentral gyrus (BA4), right postcentral gyrus (BA2), bilateral prefrontal cortex (BA10), right anterior cingulate cortex, right lingual gyrus (BA18) and left cerebellar pyramis (see Fig. 2B) ($p < 0.001$, uncorrected. No significant cluster was revealed at the corrected threshold level). The right precentral cluster was located over the anterior edge of the region of FCD and extended deeply along the central sulcus including posterior part of the insula; the right postcentral cluster was located on the posterior edge of the region of FCD. The region of BOLD increase in the right mesial frontal cortex and right occipital area overlaid partially to the abnormal signal in FLAIR and IR (see Fig. 2B). No significant clusters of BOLD signal decrease were observed.

2D topographic of spikes and polyspikes at the peak of the average spike did not shown significant differences between the two types with maximum changes over right temporal areas. For EEG source reconstruction we mapped a single dipole not considering the two different population of spikes.

EEG source reconstruction showed a dipole located over the central sulcus, covering the posterior edge of the region of FCD with an orientation perpendicular to the cortical surface (see Fig. 2C). Table 1 shows the log-evidences for 4 models computed for different priors location at the peak amplitude of averaged spike. Model comparison selects the veridical model: the model

Table 1
Model comparison results.

Models (one dipole, different location priors)	Model evidence (log-evidence)
Model 1: Right precentral cortex ($x = 48$, $y = -13$, $z = 16$)	−2.690e+001
Model 2: Right occipital cortex ($x = 15$, $y = -85$, $z = -11$)	−2.832e+001
Model 3: Right prefrontal cortex ($x = 39$, $y = 56$, $z = -2$)	−2.815e+001
Model 4: Left precentral cortex ($x = -48$, $y = -13$, $z = 16$)	−2.911e+001

Log-evidences for 4 different models (different informative priors location). The best model is highlighted in grey. See text for details.

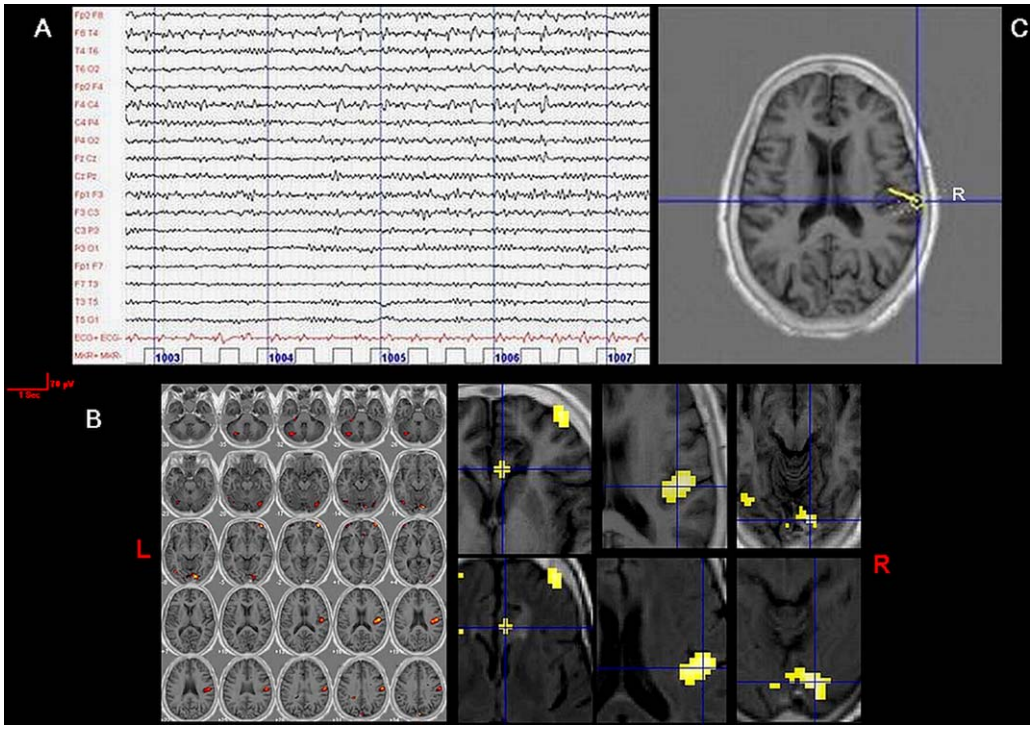

Fig. 2. EEG/fMRI results and EEG source imaging. (A) Scalp EEG recorded during scanning after off-line artifact subtraction. The blue vertical lines and related numbers corresponded to fMRI volume simultaneous acquisition. EEG trace is displayed as bipolar montage The EEG showed focal spikes and polyspikes located at fronto-central (F4-C4) and fronto-temporal regions (F8-T4). (B) Left panel: a colour-coded overlay of SPM{t} ($p < 0.001$ not corrected) onto the patient's IR slices overlay shows, BOLD signal increase in the right precentral gyrus (BA4), right postcentral gyrus (BA2), bilateral prefrontal cortex (BA10); right lingual gyrus (BA18), left cerebellar pyramis. Right panel: details of BOLD signal changes over lesional areas overlaid onto the patient's IR axial slices (upper line) and FLAIR axial slices (lower line). Clusters labelling done using the Talairach Daemon (http://ric.uthscsa.edu/project/talairachdaemon.html). BA, Brodmann area; R, right; L, left. (C) Variational Bayes Equivalent Current Dipoles (VB-ECDs) inverse solution. The dipole is displayed over the patient's anatomical MRI scan (IR). The ellipse shows the 95% confidence volume for dipole location. R, right.

with one dipole and informative prior location over right pericentral cortex is the best, i.e. the more likely, compared to the others.

4. Discussion

In this work, we described the fMRI correlates and EEG source localisation of ictal spikes in an adult patient affected by EPC.

The electroencephalographic features and structural MRI findings suggested a cortical origin of EPC in a region of FCD over the right central sulcus. The clinical history and the absence of neurological and cognitive deficits indicated a non progressive form of EPC, with very low impact on daily life. The patient, in fact, refused our offer to try different antiepileptic drugs and any surgical proposal. Other groups have previously described patients affected by EPC with mild presentation[3,4]; interestingly and similarly to our findings, in these reports, EPC was secondary to FCD in the perirolandic area.

Using EEG-fMRI we investigated the haemodynamic brain network involved during ictal spikes recorded on scalp EEG. FMRI data analysis showed BOLD signal increase related to those events over the right occipital cortex, right frontal cortex, cerebellum, and right central gyrus, the latter overlaid the FCD. Although limited by the small number of EEG channels available, the result of EEG source analysis is in agreement with the fMRI results, showing a dipole in the region of FCD, corroborating our previous electro-clinical suggestions. Nevertheless, the single equivalent dipole analysis fitted to the average spike at the peak is too limited for the identification of the seizure onset zone and it might reflect propagation of the epileptiform activity.[10] Further EEG source reconstruction analysis with advanced tool and increase number of channels will allow a better identification of the epileptogenic zone.

Our findings confirm the intrinsic epileptogenic property of dysplastic cortex and its crucial role in generating epileptic phenomena.[11] Recently, Espay et al.[12] described EEG-fMRI findings in a case affected by EPC manifesting as hemifacial spasms. As in our case, those authors provided evidence of a good correlation between electro-clinical data and fMRI findings. To our knowledge no other studies have investigated the ictal haemodynamic changes in EPC patients. In addition to the pericentral BOLD increases, our analysis has shown BOLD signal changes over other cortical regions: bilateral prefrontal cortex (BA10), right anterior cingulate cortex, right occipital cortex (BA18). This is suggestive of a possible widespread network involvement in the maintaining of epileptic activity as has previously been noted in EEG-fMRI studies in patients with focal and generalized epilepsy[13] and cortical dysplasia.[14]BOLD signal changes in the thalamus during seizures have been well documented, mainly when they are accompanied with loss of consciousness (such as absences for example).[15] In our patient we did not observe consciousness impairment during ictal spikes both inside and outside the scanner. This might explain the lack of thalamus involvement. We note that Espay and colleagues[12] did not reveal thalamus haemodynamic changes (using EEG/fMRI) during hemifacial chronic spasms without any other neurological sign in a case of EPC.

The role of the thalamus, and in general subcortical structures, in EPC pathogenesis is still controversial although cortico-thalamic loops has been documented to be involved.[16] Although lack of significant fMRI change is not a demonstration of lack of neural involvement, our failure to reveal thalamic BOLD changes is consistent with the concept of our patient's ictal activity being akin to cortical reflex myoclonus with the main activity located in the motor cortex. Thalamus haemodynamic involvement might play a role in the intra-hemispheric spread of pathological activity and hence transition between the focal cortical activity to a "full" seizure with loss of consciousness.

An intriguing aspect of our study is the significant BOLD signal increase in the controlateral (to epileptic focus) cerebellum hemisphere. A positive BOLD signal, likely to reflect an increase in neuronal activity, in the cerebellum during ictal events could have several interpretations. Firstly, more intuitively, cerebellar activation could be secondary to sensory-motor integration processes. In other words, sensorial inputs elicited by continuous myoclonia coming from the (ipsilateral) periphery are integrated with motor output coming from controlateral frontal cortex (via cortico-ponto-cerebellar pathways) in the cerebellum.

This neuronal circuitry can explain the frequent cerebellum BOLD signal increase observation in healthy subjects during neuroimaging studies which involve activation of motor cortex.[17] A recent simultaneous Electromyogram (EMG) and fMRI recordings in patients with cortical myoclonus and cerebellar degeneration (FCMTE – Familiar Cortical Myoclonic Tremor with Epilepsy) failed to identify controlateral cerebellum involvement during a motor task, which is in line with the known cortico-ponto-cerebellar circuitry dysfunction.[18]

Cerebellum involvement as part of the motor network is not the only explanation for the BOLD signal increase linked to ictal spikes in our patient. We speculate that it could be directly linked to epileptic activity generation. It has been known that cerebellum has an inhibitory effect on epileptic activity by means of the release of the inhibitory transmitter gamma amino butyric acid (GABA) from the Purkinje cells.[19,20] Therefore, cerebellar activation could be due to an increased demand for inhibition, in order to compensate the abnormal excitability of the controlateral frontal cortex. Similar evidence has been found in cases of status epilepticus[13] and tonic–clonic seizures.[21] Very recently, Mohamed and colleagues[22] demonstrated controlateral magnetoencephalography (MEG) cerebellum activation during motor partial seizures. Interestingly cerebellar activation was found to increase in magnitude over the time during seizures which might support the hypothesis on the cerebellum role in seizure inhibition and termination. A further study on a larger cohort of patients is required to confirm this finding.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2011.09.003.

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