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Co-existence of idiopathic generalized and focal epilepsy suggested by simultaneous EEG-fMRI: a case report

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ABSTRACT – We present a rare patient clinically suspected to have mixed idiopathic generalized and focal epilepsy, which was supported by BOLD pattern based on EEG-fMRI. A 37-year-old female with three types of refractory seizures starting at age six - tonic with breathing difficulties and confusion, generalized tonic-clonic, and focal with brief impairment of awareness and versive head movement, initially thought to represent atypical absences - was evaluated by EEG-fMRI. She was also shown to have three types of interictal epileptic discharges: generalized spike or polyspikes and slow waves, and left fronto-temporal and right fronto-temporal discharges. We assessed BOLD activation and deactivation for each type. For generalized patterns, the BOLD activation and deactivation were typical of that seen in primary generalized epilepsy. Whereas maximum activation for left fronto-temporal EEG patterns was observed in the left superior frontal gyrus and posterior superior temporal gyrus, maximum activation for right fronto-temporal patterns was bilateral in the right posterior middle temporal gyrus and left posterior middle temporal gyrus. The EEG-fMRI results suggested that the patient had both refractory idiopathic generalized and focal epilepsy, and not a generalized epilepsy originating from a focus.

Key words: absence, focal epilepsy, EEG-fMRI, refractory idiopathic generalized epilepsy

The coexistence of idiopathic generalized epilepsy (IGE) and focal epilepsy in the same patient is rare, accounting for <1% of patients with epilepsy, although EEG focal abnormalities are found in 56% of patients with generalized epilepsy (Lombroso, 1997; Nicolson *et al.*, 2004; Jeha *et al.*, 2006;). In IGE, BOLD activation in both thalami and bilateral symmetrical cortical areas, and deactivation in the default mode network (posterior cingulate, precuneus, medial prefrontal cortex, and inferior parietal lobule) are typically observed during simultaneous EEG and functional MRI (EEG-fMRI) studies

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(Aghakhani *et al.,* 2004; Gotman *et al.,* 2005). In focal epilepsy, EEG-fMRI may reveal the seizure onset zone (SOZ) at the location corresponding to the maximum BOLD cluster (Khoo *et al.,* 2017). We report a rare patient who was initially assumed to have idiopathic generalized epilepsy with atypical absences, but was shown to have focal and generalized interictal epileptic discharges (IEDs), supported by an EEG-fMRI study showing BOLD patterns typical of IGE and focal epilepsy.

Case study

A 37-year-old female patient, who had relatively consistent refractory seizures from the age of six, was evaluated by EEG-fMRI. She described three types of seizures. Type 1: sleep-related tonic seizures with difficulty breathing and confusion; type 2: generalized tonic-clonic (GTC) seizures; and type 3: brief impairment of awareness with versive head turning, accompanied by discrete automatisms of the right upper limb with very inconsistent left arm dystonia lasting for seconds, without post-ictal confusion. She never described any aura or language impairment after these small seizures. For a while, this third type was considered to represent absences. The patient had no other antecedent and did not report a family history of epilepsy.

During the EEG-fMRI study, antiepileptic medications taken included brivaracetam (BRV) at 100 mg/day, topiramate (TPM) at 200 mg/day, and lamotrigine (LTG) at 500 mg/day. Her IEDs were classified as three types:

– generalized or bilateral spike or polyspikes and slow waves (SW or PSW) (s*upplementary figure 1*) ;
– left front-temporal spikes;
– and right front-temporal spikes.

The generalized SW occurred at 2-4 Hz and often lasted several seconds. The bilateral SW occurred in bilateral fronto-central and fronto-temporal areas. During a five-day period of video-EEG monitoring, no clinical seizure was captured although several generalized bursts of SW and PSW were recorded mostly during wakefulness, and frequent trains of bilateral or lateralized discharges from the left and right hemispheres were recorded particularly during sleep. Anatomical MRI showed no obvious lesion. We assessed the BOLD activation and deactivation for each type of EEG discharge.

EEG-fMRI acquisition, processing, and analysis were identical to that performed in previous studies (Khoo *et al.,* 2017; Yamazoe *et al.,* 2019). EEG was recorded when the patient was positioned inside a 3 Tesla MRI scanner (Siemens Trio) with 25 MR compatible electrodes placed on the scalp using 10-20 (reference FCz) and 10-10 (F9, T9, P9, F10, T10 and P10) electrode systems. Functional images were collected in 6-minute runs for a total scan of 70 minutes with the patient at rest, using the following T2*-weighted echo planar imaging (EPI) sequences: repetition time (TR)=1.9 seconds; echo time (TE)=25 mseconds; 64×64 matrix; 33 slices; voxel=3.7×3.7×3.7 mm; flip angle=90 degrees. Very active interictal generalized and more focal IEDs were observed on her EEG during the scan. Background was estimated for around 60% of her whole EEG recording. Data were analysed based on an event-related design using fMRIstat, using a single model involving the different types of event. The timing and duration of each IED were convolved with four haemodynamic response functions (HRFs) peaking at 3, 5, 7, and 9 seconds, resulting in four regressors. A combined t map was created by taking, at each voxel, the most significant t value from the four t maps created with the four HRFs. Two levels of statistical significance were used. The first level of significance, uncorrected, was defined as a response with five contiguous voxels with t value >= 3.1 or <= -3.1, corresponding to uncorrected $p < 0.001$ for the analysis of each HRF, equivalent to uncorrected $p < 0.005$ for the combined analysis using the four HRFs. The second level of significance (corrected for multiple cluster comparisons) was defined by t values greater than the threshold corresponding to the corrected whole-brain topological false discovery rate (FDR) of 0.05. The cluster defining threshold in the FDR computation was selected as t >= 3.1 or <= -3.1. We refer to clusters that reach the corrected significance level as "above FDR", and clusters that reach uncorrected but not the corrected significance level as "below FDR".

For type 1 IEDs, BOLD activation was present in bilateral symmetrical temporal areas and BOLD deactivation was present symmetrically in areas of the default mode network (*figure 1*). These are typical patterns of activation and deactivation, as seen in IGE. On the other hand, for left fronto-temporal IEDs, maximum BOLD activation was observed in the left superior frontal gyrus and posterior superior temporal gyrus (*figure 2*), and for right fronto-temporal IEDs, maximum BOLD activation was observed bilaterally in the right and left posterior middle temporal gyri. These BOLD responses are not typically seen in IGE and were assumed to be triggered by independent right and left focal generators. We concluded that the patient had epileptic activity typical of IGE and independent focal/regional responses typical of focal epilepsy, on both sides.

After the assessment and the addition of valproic acid (VPA), her GTC seizures stopped, however, her focal seizures increased. Medication was again modified after withdrawal of VPA due to intolerance, and GTC seizures returned. Ethosuximide was tried twice, but also discontinued because of intolerance.

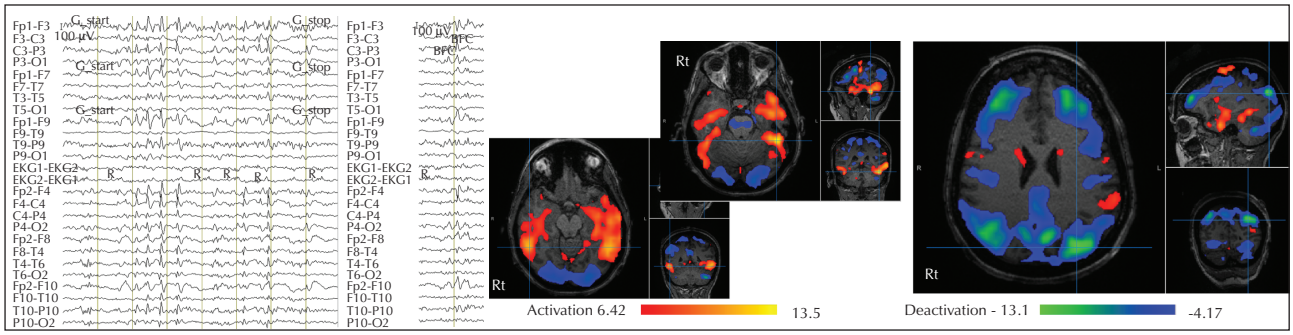

Figure 1. BOLD clusters in the analysis of generalized and bilateral IEDs (*n*=277). These clusters were thresholded at the FDR (activation: +4.22; deactivation: -4.17). BOLD activations were present in bilateral symmetrical temporal areas, with maximum activation in the left fusiform gyrus (t value: 12.74) and second maximum activation in the right posterior middle temporal gyrus (t-value: 10.60). BOLD deactivations were present in the areas of the default mode network, bilateral precuneus and prefrontal cortex, and minimum deactivation was seen in the left precuneus (t value: -13.18).

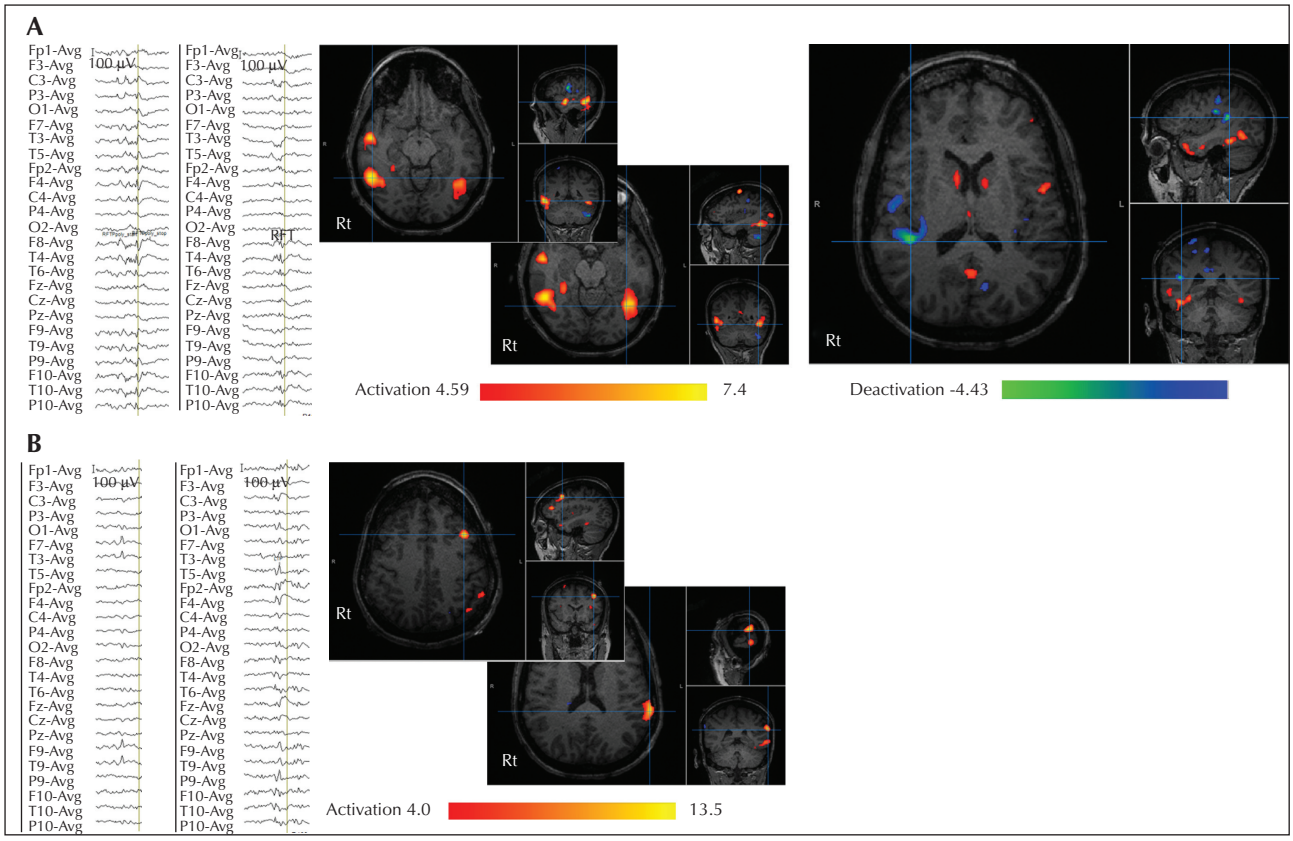

Figure 2. BOLD clusters in the analysis of right and left fronto-temporal IEDs. (A) For the right fronto-temporal patterns (*n*=200), thresholded at FDR (activation: +4.59, deactivation: -4.43), maximum activation was seen in the right posterior middle temporal gyrus (t-value: 7.40), and the second maximum activation was observed in the left posterior middle temporal gyrus (t value: 6.97). Deactivation was seen in the right posterior superior temporal gyrus (t value: -6.12). (B) For the left fronto-temporal patterns (*n*=111), thresholded at FDR (activation: +5.03, deactivation: -4.28), the maximum activation was seen in the left superior frontal gyrus (t value: 6.13), and the second maximum activation was seen in the left posterior superior temporal gyrus (t value: 6.01). Deactivation was not observed below the FDR.

Discussion

Absence epilepsy is considered as a disorder of the thalamocortical network (Huguenard, 2019). However, several studies propose that the origin of generalized spike-and-wave discharges is frontal and cortical -the "cortical focus theory"- such that absence seizures may be initiated by widespread cortical areas and sustained by the driving between the cortex and thalamus (Meeren *et al*., 2005; Seneviratne *et al*., 2014). Supporting this hypothesis, EEG-fMRI studies in patients with typical absence seizures have shown BOLD activity in the frontal cortex before thalamic activation based on dynamic time course analysis (Bai *et al*., 2010; Szaflarski *et al*., 2010). Patient-specific focal cortical BOLD activations associated with absences were also seen at the onset of absences (Moeller *et al*., 2010).

Initially, our patient was thought to have a generalized epilepsy. The possibility of the coexistence of IGE and focal epilepsy versus a generalized epilepsy disorder, but with focal onset or accentuation of generalized seizures, was then raised. Although all her habitual seizures were not confirmed on video-EEG monitoring, many IEDs exhibited the typical generalized pattern associated with absences, lasting for several seconds. Other seizures exhibited focal EEG changes or accentuation and were associated with a semiology that, for a while, was assumed to represent atypical absence seizures. The EEG-fMRI analysis for each IED pattern helped to clarify the situation and revealed different BOLD changes, some observed in IGE and others typical of focal epilepsy. The results make it more likely that the widespread discharges were those of IGE and not resulting from propagation from a focus. In the EEG-fMRI studies of patients with IGE, a prominent feature of BOLD changes is a symmetrical distribution over the cerebral hemisphere, but not always involving the thalamus (Aghakhani *et al*., 2004). By contrast, based on the analysis of bilateral synchronous IEDs in patients with focal epilepsy, local accentuations of BOLD signal were observed, although BOLD changes in the thalamus were also sometimes seen (Aghakhani *et al*., 2006). We reported a similar case in which the EEG-fMRI study revealed the coexistence of focal motor and absence seizures and distinct BOLD responses; one following a pattern of generalized epilepsy and the other focal and closely related to focal cortical dysplasia of the left central sulcus (Chassagnon *et al*., 2009). EEG-fMRI illustrates the epileptic network associated with IEDs, and hence may reveal IGE or focal epilepsy in the same patient, when other non-invasive methods remain inconclusive. EEG-fMRI may therefore support such clinical decisions for diagnosis as well as the choice of the most appropriate anti-seizure medication. □

Supplementary data.
Supplementary figure is available on the www.epilepticdisorders.com website.

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None of authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Describe the BOLD patterns based on EEG-fMRI associated with IEDs in primary generalized epilepsy.

(2) What areas of the brain contribute to the default mode network?

(3) What are the typical characteristics of absence seizures?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".