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Successful epilepsy surgery in frontal lobe epilepsy with startle seizures: a SEEG study*

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ABSTRACT – Pre-surgical assessment and surgical management of frontal epilepsy with normal MRI is often challenging. We present a case of a 33-year-old, right-handed, educated male. During childhood, his seizures presented with mandibular myoclonus and no particular trigger. As a young adult, he developed seizures with a startle component, triggered by unexpected noises. During his ictal episodes, he felt fear and grimaced with sudden head flexion and tonic axial posturing. Similar seizures also occurred without startle. Neuropsychological assessment showed executive dysfunction and verbal memory deficit. The cerebral MRI was normal. Electro-clinical reasoning, investigations performed, the results obtained and follow-up are discussed in detail. [*Published with video sequence*]

Key words: startle epilepsy, mesial fronto-parietal network, SEEG, focal cortical dysplasia

Startle seizures are induced by a normal startle response, which in turn is elicited by an unexpected stimulus. This unexpected stimulus is often auditory but rarely it can also be visual or somatosensory (Bhidayasiri and Truong, 2011). The clinical manifestation is similar to the startle reflex, involving a shock-like movement with closed eyes, followed by asymmetric tonic posture and anterior head and trunk flexion (Bakker *et al.,* 2006). This type of epilepsy, associated with congenital brain conditions or brain lesions (due to early-life injuries),

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usually occurs during childhood, although it may appear in adulthood (Manford *et al*., 1996). There have been multiple attempts to characterize the neural mechanisms involved in this type of epilepsy and most of them have confirmed the involvement of mesial frontal structures with an important role of the supplementary motor area (SMA) (Job *et al*., 2014). We report a particular case of intractable startle seizures, explored by means of stereoelectroencephalography (SEEG), in which the patient became seizure-free after surgery.

Patient details

Patient and family history

Personal history was unremarkable, with no febrile convulsions, head trauma or central nervous system infection. Developmental milestones were normal. There was no family history of seizures or related pathologies. His seizures started when he was 3 years old, with a high frequency from the very beginning. The longest seizure-free period occurred seven years after the first anticonvulsant treatment was initiated. Seizures restarted afterwards and became intractable.

Clinical description of paroxysmal events

During childhood, seizures manifested with mandibular myoclonus. During video-EEG evaluation, he presented seizures with and without a startle component (unexpected noise), usually no aura (sometimes fear), grimacing ("chapeau de gendarme"), brief axial tonic contraction, anterior flexion with tonic contraction of upper limbs (primarily affected on the right side), and short loss of contact. Sometimes, he presented right head version. The seizures did not show any difference in frequency pattern between sleep and wakefulness, were usually short (a few seconds), and were not associated with secondary generalization. Postictally, he recovered immediately and was able to speak.

Surface video-EEG findings (interictal and ictal)

The surface EEG during wakefulness showed interictal bifrontal epileptiform discharges of spike-and-wave complexes and polyspikes over the midline, with left frontal dominance and phase reversal in F3. During sleep, EEG revealed short runs of rapid activity over the midline and left frontal regions, maximum in F3 *(figure 2)*. We recorded five seizures during long-term monitoring, with and without startle component. Ictal EEG showed an increase of interictal spikes over the midline and bifrontal regions before the clinical onset, followed by a large bifrontal baseline shift with superimposed fast activity and a diffuse electrodecrement that largely involved bifronto-parietal territories and dominated over the midline without clear-cut lateralization. In the postictal period, the scalp EEG showed diffuse flattening *(figure 3)*.

AED treatment history

The first effective AED combination was methsuximide and valproic acid, and the patient was seizure-free between the age of 3 and 10. Other anticonvulsants tried included carbamazepine, levetiracetam and topiramate in different combinations, but were discontinued because of suboptimal seizure control. During the non-invasive, as well as invasive recordings, he was taking valproic acid at 2000 mg/day, lamotrigine at 300 mg/day, and lacosamide at 200 mg/day.

Non-invasive investigations

MRI

MRI studies at 1.5 Tesla, with 1-mm slicing and 3D acquisition, showed no clear-cut lesion. However, there may have been a blurred grey-white matter junction over the left anterior cingulate gyrus *(figure 1)*.

Neuropsychology

Neuropsychological assessment showed deficit in executive functions and mild verbal dysfunction in terms of verbal fluency. Psychiatric evaluation revealed an organic anxiety disorder.

Invasive investigations

Based on non-invasive data, we decided that the patient was a suitable candidate for epilepsy surgery and an SEEG evaluation was judged to be necessary. The decision for the latter was taken under the premise that this was an MRI-negative case, the scalp EEG showed large discharges, and the mesial as well as lateral structures could be better sampled using depth electrodes. The hypothesis focused on a mesial frontal epilepsy with left dominance, and in order to identify the network involved, we also sampled the left parietal and right frontal lobe. A bifronto-parietal implantation was performed using 17 intracerebral electrodes (Dixi medical, Besancon France) of 0.8-mm diameter with 8-18 contacts, 2 mm in length, each situated 1.5 mm apart, inserted in a stereotactic approach, with both orthogonal and oblique trajectories *(figure 4)*.

SEEG recordings were conducted over 10 days in the Epilepsy Monitoring Unit at the University Emergency Hospital in Bucharest using a 64-contact Nicolet Wireless 64 Amplifier (Natus Medical Inc.). During the invasive evaluation procedure, the aim was to record activity and spontaneous habitual seizures during sleep and wakefulness. The interictal SEEG recordings during wakefulness revealed a widespread irritative zone, with epileptiform discharges consisting of spike and wave complexes, with bilateral involvement (with left dominance) of the cingulum, prefrontal cortex (mainly mesial), premotor cortex, SMA, and right orbitofrontal cortex. During sleep, SEEG showed fast activity resembling high-frequency oscillations, exclusively over the left mesial prefrontal cortex (electrodes P' and L'), anterior and middle cingulum (electrodes X' and Y'), and SMA (electrode M') *(figure 7)*.

We recorded 14 seizures, with and without startle component, that were considered to be typical seizures by the patient. Ictal SEEG revealed an increase of interictal spikes before the clinical onset. At the electrical onset, the SEEG showed a significant baseline shift, with low-voltage fast activity over the mesial prefrontal cortex, preSMA, and SMA, and a less tonic activation over the internal parietal and ictal discharge involving the same structures *(figure 6)*. The signal analysis of gamma activity showed prominent early activation involving dorsomesial prefrontal cortex and middle cingulum.

We performed functional stimulations using a clinical stimulator (Guideline LP+, FHC Inc, Bowdoin, ME) in order to determine the exact location of motor cortex. The SEEG recordings were very helpful in delineating the seizure onset zone involving the dorsomesial prefrontal cortex, anterior and middle cingulate, preSMA, and SMA. The epileptogenic network (*i.e.* areas involved in seizure generation and spreading that show ictal SEEG abnormalities) also included the dorsolateral prefrontal cortex, orbitofrontal cortex, and precuneus.

Action taken

Resection planning was based on data recorded during the non-invasive EEG and invasive phase. Three months after the SEEG investigation, the patient underwent a large resection of the left mesial prefrontal cortex, anterior and middle cingulate, pre-SMA, and superior frontal gyrus (F1). We did not include the SMA in our resection *(figure 5)*. Histopathological analysis confirmed type IB focal cortical dysplasia (ILAE classification, 2011), with tangential architectural abnormality and no dysmorphic cells, excluding type IIA focal cortical dysplasia *(figure 9)*.

Follow-up

The patient was seizure-free after one year of follow-up. Post-resection scalp EEG showed disorganized rhythm and sharp waves over the left parietal region. There were no epileptiform abnormalities over the right hemisphere *(figure 8)*. Neuropsychological assessment revealed executive function impairment, mostly with respect to working memory and attention, and verbal memory deficit. However, the patient is now socially integrated and back at his workplace. Anticonvulsant medication was not tapered.

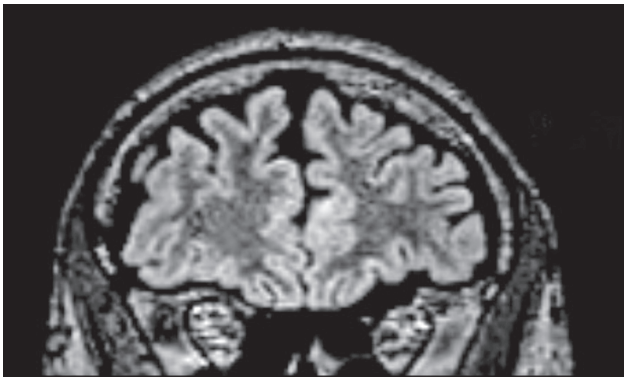

Figure 1. Pre-resection 1.5 T MRI, FLAIR sequence; coronal section at the level of the anterior cingulate cortex.

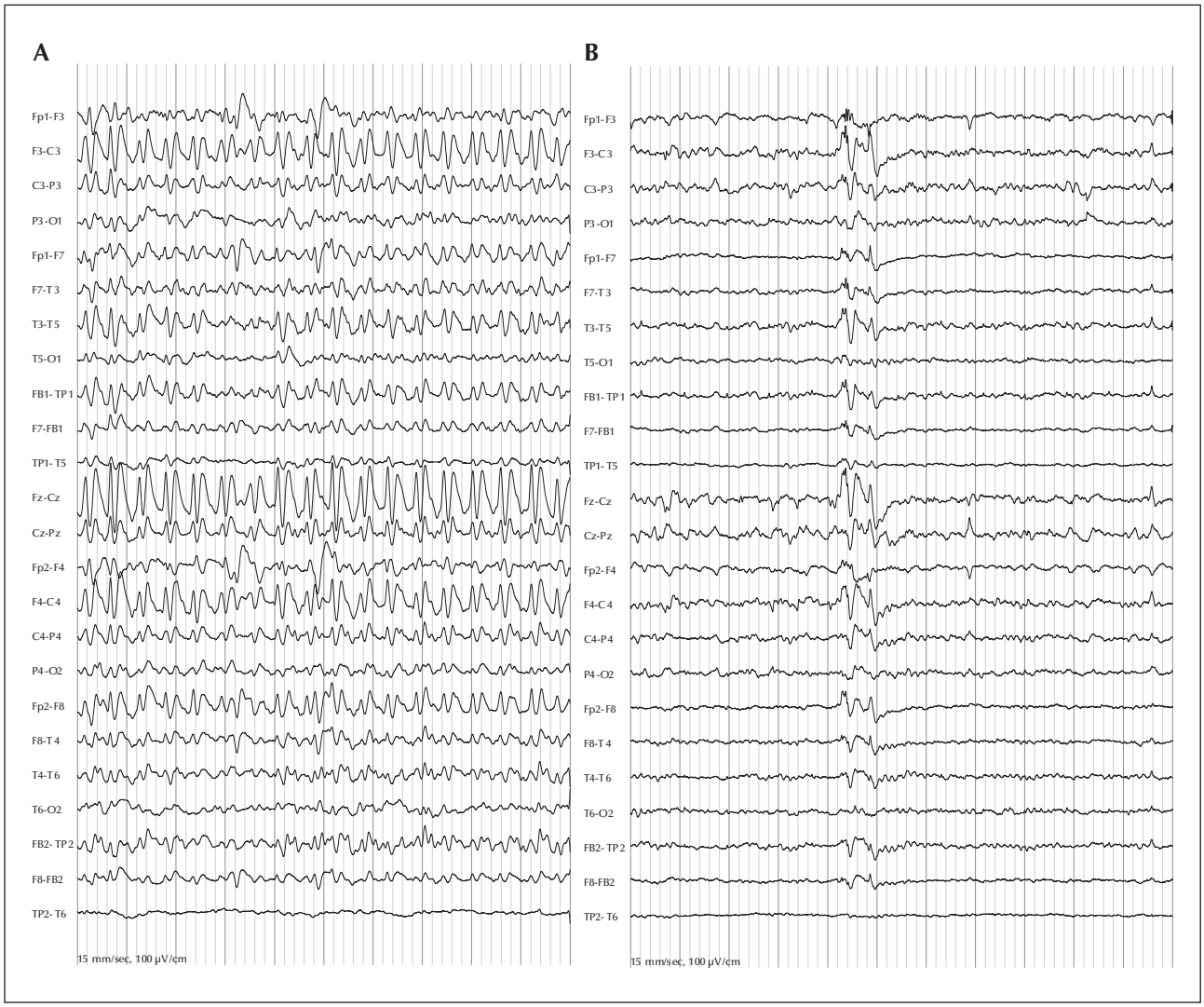

Figure 2. Interictal scalp EEG during wakefulness (A) and sleep (B) showing epileptiform discharges over the midline and frontal region with left dominance.

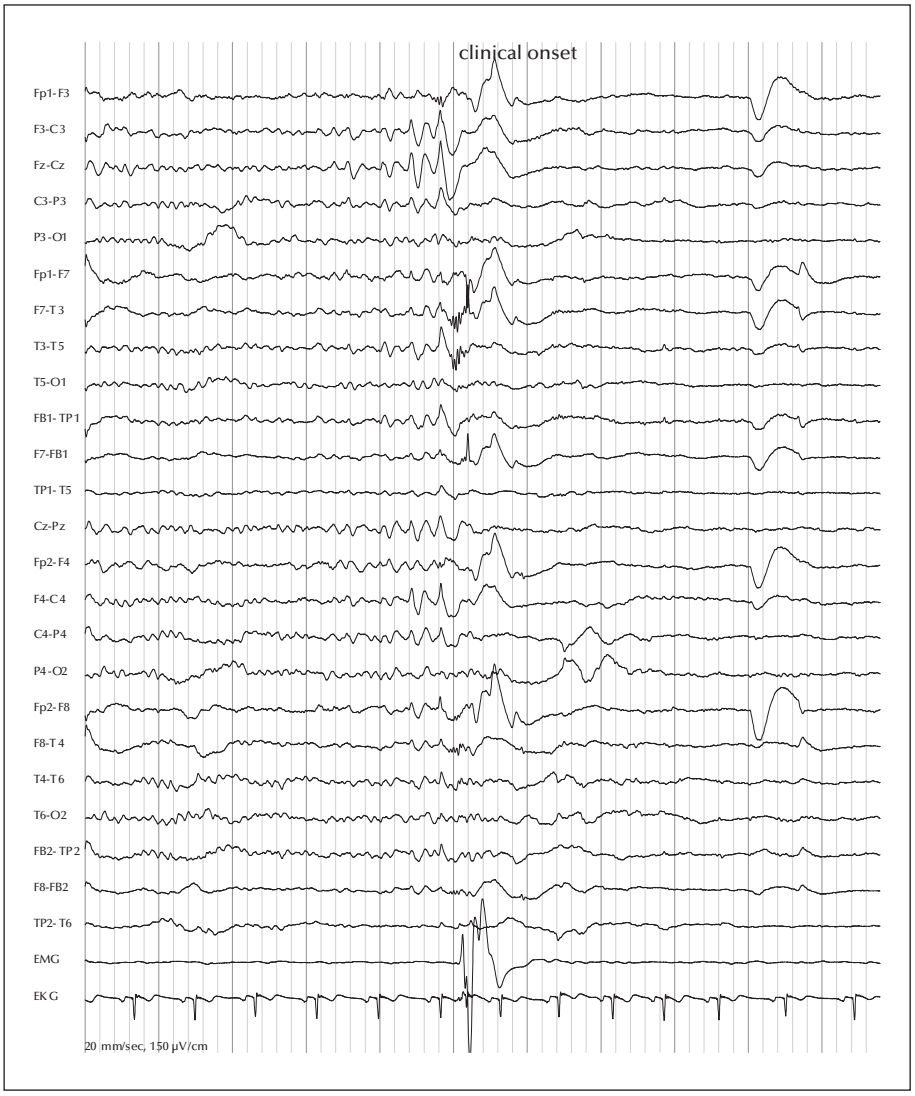

Figure 3. Ictal scalp EEG of a startle-induced seizure revealing baseline shift and fast activity over the bifronto-parietal region with left dominance. EMG shows a myoclonic startle component at seizure onset.

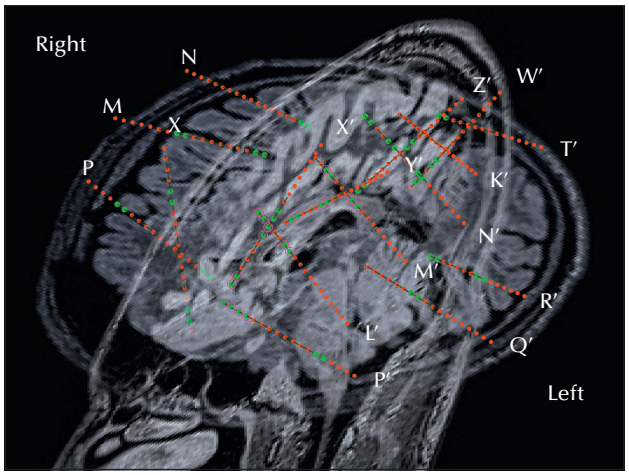

Figure 4. 3D map of depth-electrode placement following a mesial left frontal hypothesis, also targeting the right frontal and left parietal structures.

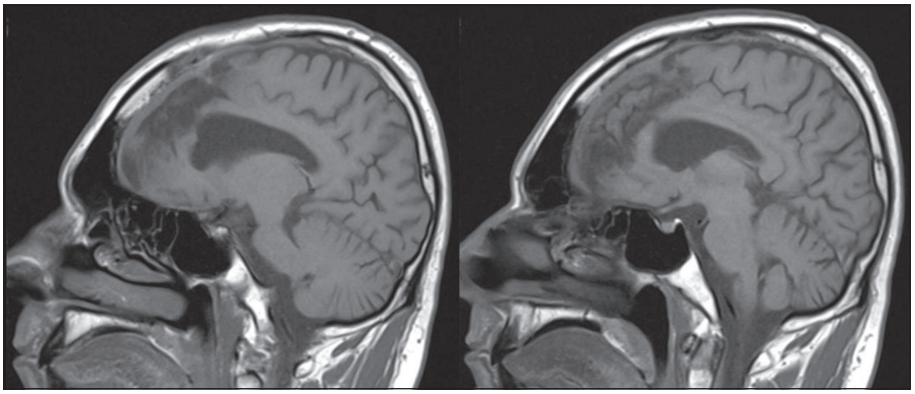

Figure 5. Post-resection MRI in T1 sequence; resection of the mesial prefrontal cortex and anterior and middle cingulum, with the SMA as the posterior limit.

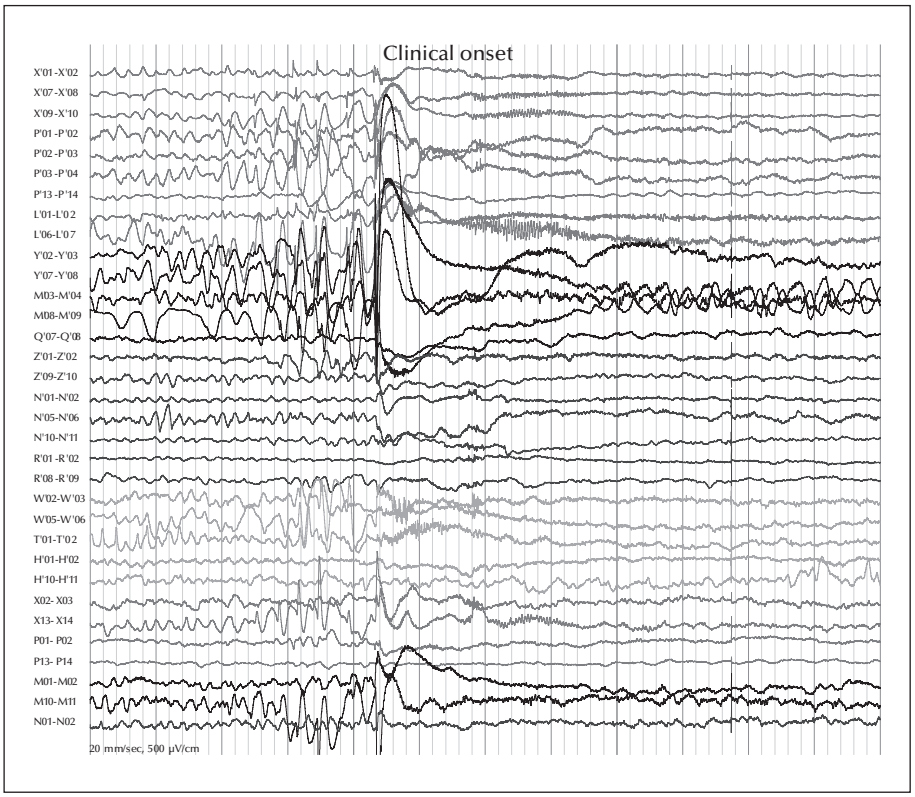

Figure 6. Ictal SEEG showing the seizure onset zone and epileptogenic zone over the mesial prefrontal cortex, anterior and middle cingulum, preSMA, SMA, and precuneus.

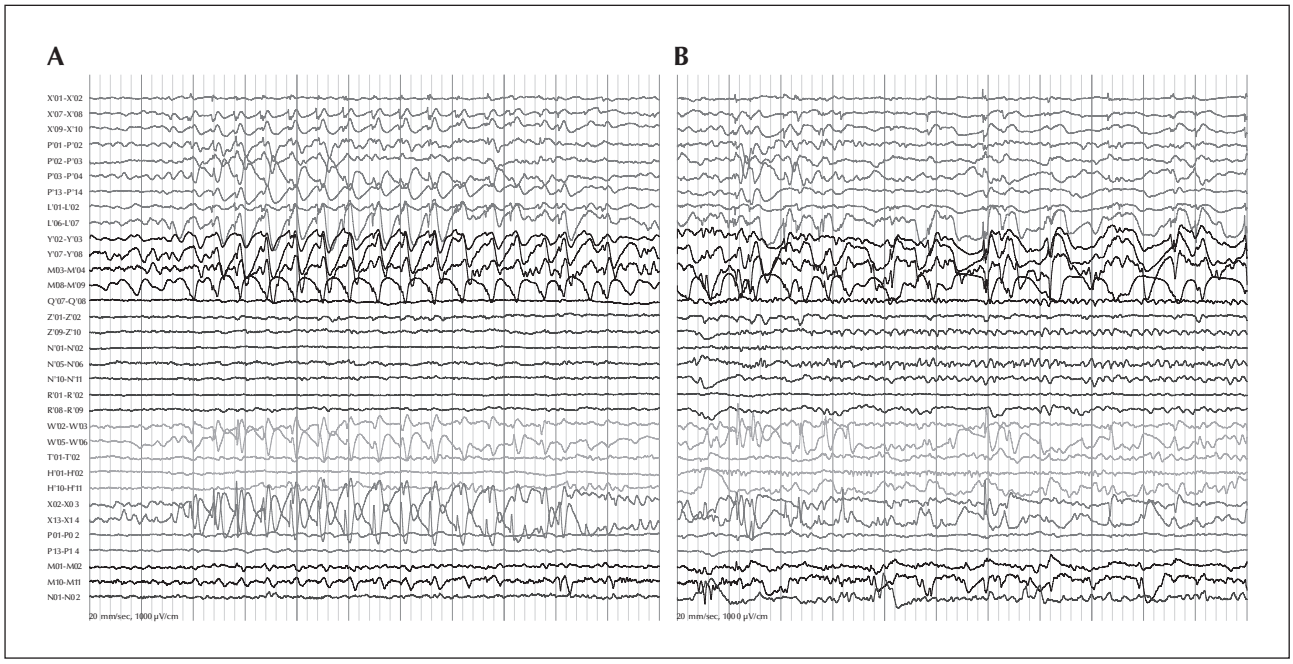

Figure 7. Interictal SEEG during wakefulness (A) and sleep (B) revealing the large irritative zone spreading over the left mesial frontal and parietal areas. Spontaneous high-frequency oscillations only occurred over the left prefrontal cortex and anterior and middle cingulum.

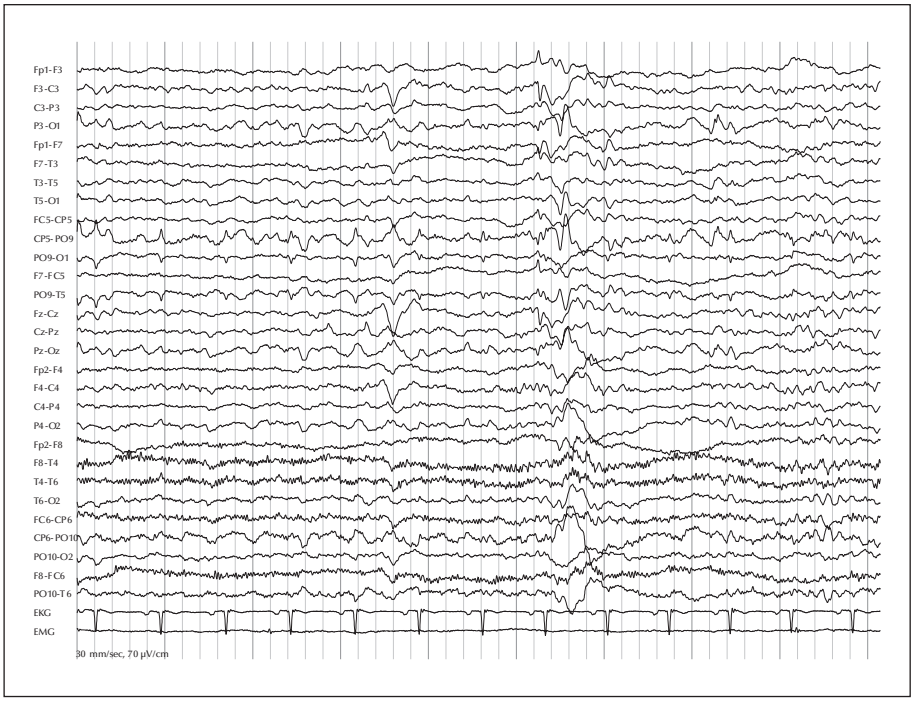

Figure 8. Scalp EEG after one year of follow-up shows rare epileptiform discharges, mostly over the left parietal region.

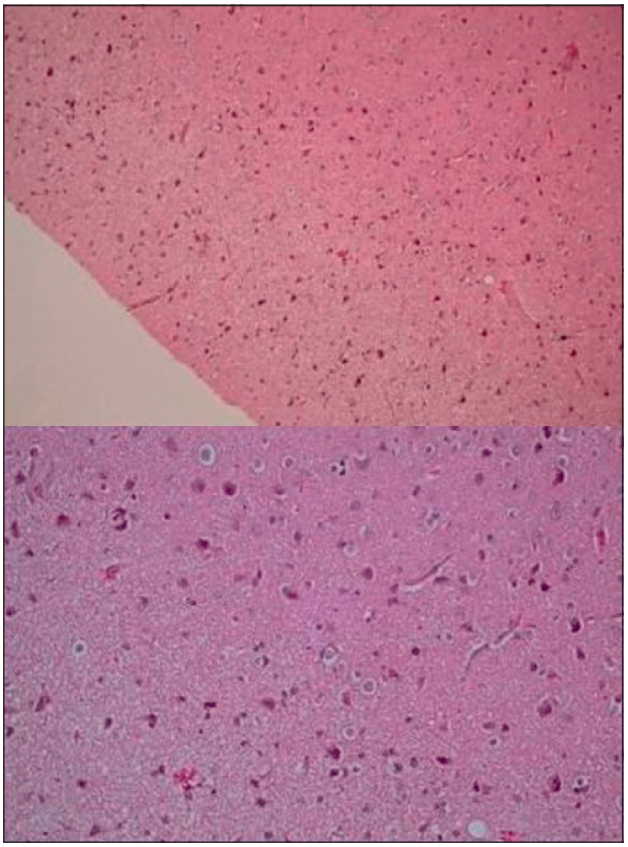

Figure 9. Architectural abnormalities and no dysmorphic cells at histological analysis.

Discussion and conclusion

We present a case of intractable epilepsy, classified as a startle syndrome with typical clinical presentation; the startle component induced by auditory stimuli elicited an asymmetric tonic posture (Bhidayasiri and Truong, 2011). Seizures without a startle component also occurred. However, our patient presented only mild cognitive impairment (mostly regarding executive dysfunction), normal development, and no perinatal injuries, in contrast to other cases stated in the literature (Klinkenberg *et al.,* 2014). Our patient did not have any visible lesion on MRI.

The important role of the anterior cingulate region in this network was apparent from the very beginning, in accordance with specific clinical features. Grimacing with the corners of the mouth turned down ("chapeau de gendarme") is described in the literature to have a cingulate cortex origin (Souirti *et al.,* 2014). Fear, on the other hand, could be generated by the rostroventral part of the anterior cingulate cortex, as part of the limbic circuit.

Startle reflex is mediated at the subcortical level in the caudal brainstem with a secondary activation of the reticular formation (Dreissen and Tijssen, 2012). Several previous reports have described startle seizures with involvement of the mesial fronto-parietal network, affecting the SMA, perirolandic premotor cortex, and precuneus (Fernández *et al.,* 2011; Job *et al.,* 2014). Furthermore, novel fMRI studies show that fear-potentiated startle response to threatening stimuli enhance the neural activity in the anterior cingulate (Lindner *et al.*, 2015). We may therefore hypothesise that in our case the network between the anterior cingulate and SMA could activate other larger cortical and subcortical networks, inducing a cortical-triggered startle response.

Intracranial recordings, in our case, revealed a dominant activation of the preSMA, SMA and precuneus, but also early involvement of the mesial prefrontal cortex and anterior and middle cingulum at seizure onset. However, even though a large mesial frontal resection was performed, the SMA was not included. We decided to spare the SMA due to the extension of the resection and also due to the fact that semiology pointed to a very early involvement of the anterior cingulate cortex (grimacing and fear). In the event of new seizures, we plan to enlarge the resection to include the SMA.

Our patient was categorised as Engel class I, one year after the resective surgery. Histopathological analysis revealed a type IB focal cortical dysplasia, in contrast to other studies where the underlying cause was congenital, due to perinatal brain injuries or tumours (Manford *et al.*, 1996), or associated with unremarkable histology (Job *et al.*, 2014). This type of dysplasia could explain the negative imaging studies.

One limitation of this case report concerns the non-invasive imaging; we were unable to perform interictal PET or ictal SPECT/SISCOM, which may have been of benefit in planning invasive SEEG.

In conclusion, although startle seizures in frontal epilepsy are rare, these should be suspected and identified even in normal cognitive patients. A good outcome can be expected with frontal mesial resection, tailored using accurate SEEG investigation.

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.

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None of the authors have any conflict of interest to disclosure.

Legend for video sequence

Seizure with startle component. The seizure starts with a brief, myoclonic movement of the right upper limb, followed by tonic anterior flexion of the head and trunk, to a slight right-side version.

Key words for video research on www.epilepticdisorders.com

Syndrome: startle epilepsy
Aetiology: focal cortical dysplasia
Phenomenology: startle; grimace; tonic asymmetric
Localization: mesial frontal

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TEST YOURSELF

(1) Did the patient have startle seizures?

(2) Why were depth electrodes used and not strips or grids?

(3) Why was the SMA not included in the resection?

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".