■ Clinical commentary

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Epileptic Disorders

Multimodal approach in the pre-surgical evaluation of focal epilepsy surgery candidates: how far are we from a non-invasive ESI-based "sourcectomy"?

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ABSTRACT – The management of drug-resistant patients with focal epilepsy is often challenging. Surgery is recognised as a useful and effective treatment option. The identification of the epileptogenic zone relies on the integration of clinical, neurophysiological, and neuroimaging findings. The role of non-invasive functional neuroimaging techniques has been reported to add diagnostic accuracy to first-line evaluations, avoiding invasive presurgical examinations in selected cases. In this view, we report the case of a 16-year-old male suffering from drug-resistant focal epilepsy with episodes rarely evolving to a bilateral tonic-clonic seizure. Conventional 1.5T and 3T MRI were considered uninformative. Based on electro-clinical data, focal cortical dysplasia was suspected. The epileptogenic zone was identified with the integration of further non-invasive functional neuroimaging techniques ([18F]-fluorodeoxyglucose positron emission tomography and arterial spin labelling), where electrical source imaging played the main role. All techniques pointed towards a cortical region, where a 7T brain MRI identified a signal alteration consistent with focal cortical dysplasia. A tailored resection of the lesion located in the inferior frontal sulcus was performed, guided by intraoperative electrocorticography (strip and depth electrodes). Postoperative seizure freedom was achieved. The histopathology confirmed the suspicion of focal cortical dysplasia type IIa. With this case report, we highlight the importance of a multimodal approach in the presurgical evaluation of candidates for epilepsy surgery, which, in selected cases, may allow invasive procedures, such as stereo-EEG, to be avoided in the investigation of the epileptogenic zone. Moreover, we underline the pivotal role of EEG source imaging, especially when focal cortical dysplasia is suspected.

Key words: ESI, FCD, focal epilepsy, epilepsy surgery, multimodal, HdEEG, arterial spin labelling

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The management of drug-resistant patients with focal epilepsy is often challenging. Surgery has proven to be superior to medical treatment of drug-resistant epilepsy in both adults [1] and children [2]. The eligibility of patients relies on a preoperative work-up aimed mainly at localizing the epileptogenic zone (EZ) to be resected/destroyed/disconnected, while preserving the eloquent cortex [3].

In most candidates, this is achieved by integrating clinical data and non-invasive neurophysiological and neuroimaging investigations [3]. Apart from conventional electro-clinical findings and structural MRI studies, the role of non-invasive functional neuroimaging techniques (NIFNTs), including [18F] fluorodeoxyglucose positron emission tomography (18F-FDG-PET), single photon-emission computed tomography (SPECT), magnetoencephalography (MEG), EEG - functional MRI (EEG-fMRI), high-density EEG - electrical source imaging (HdEEG - ESI) and arterial spin labelling (ASL), has been widely reported to add diagnostic accuracy to first-line evaluations [4-10].

Nonetheless, when the non-invasive evaluation provides not concordant results or structural MRI is uninformative, other studies become essential [3,7]. In particular, in patients with negative structural MRI, especially in those with extra-temporal lobe epilepsy, an invasive pre-surgical evaluation with stereotactically implanted intracranial depth electrodes (stereo-EEG), chronic subdural electrodes, or intraoperative electrocorticography (ECoG) may be required [3,6]. Nevertheless, additional evaluation with NIFNTs may represent a practical option for guiding or even avoiding extraoperative invasive EEG evaluations in selected cases [7-9].

Here, we report the case of a 16-year-old male suffering from extra-temporal, drug-resistant focal epilepsy, whose EZ was localized based mainly on an HdEEG source modelling technique (electrical source imaging [ESI]).

Case study

A 16-year-old, right-handed male with normal neurological development, a full-scale Intelligence Quotient (IQ) of 98 (Wechsler Intelligence Scale for Children-IV), and no family history for epilepsy, presented his first focal to bilateral tonic-clonic seizure at the age of 13. The seizure semiology was characterized (in order of appearance) by head version to the right side, speech impairment (apparently dysphasia), and sustained rhythmic jerking rapidly involving the right side of the body followed by a bilateral tonic-clonic seizure. Brain computed tomography and 1.5T MRI were considered uninformative. Interictal EEG showed a peculiar pattern characterized by focal left fronto-central rhythmic spikes and especially polyspikes, intermingled with background activity, enhanced during drowsiness and sleep. Although clobazam was started, he developed focal episodes (two to three episodes/week) characterized by bilateral eyelid myoclonic jerks associated with transient confusion without loss of consciousness or memory impairment. After the sequential introduction of levetiracetam and valproate, he continued to have focal episodes with the same semiology, reduced to a monthly frequency, rarely evolving to bilateral tonic-clonic manifestations.

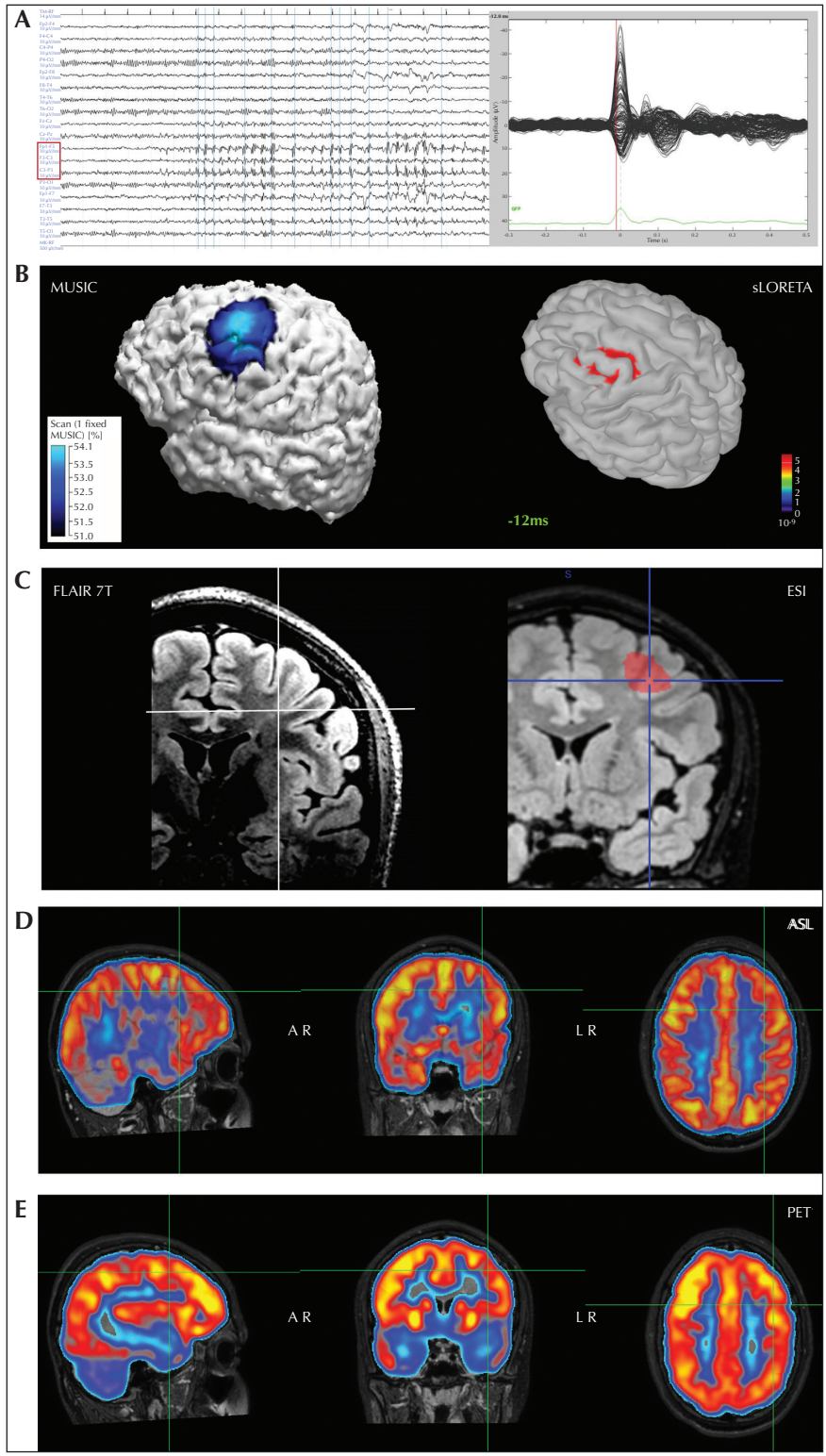
Therefore, the patient was sent to our centre for a pre-surgical evaluation.

A neuropsychological evaluation was administered using some subtests of the Italian NEPSY-II version (the revised edition of the NEPSY, Developmental Neuropsychological Assessment) [11], which also

▼ **Table 1.** Presurgical and postsurgical scores based on the Italian NEPSY-II version [11].

	Presurgical score	Postsurgical score
Attention and Executive Functioning		
Visual Attention	5	14
Inhibition		
Naming condition	11	8
Inhibition condition	8	13
Switching condition	10	11
Language		
Word Generation		
Semantic category	5	8
Phonological category	4	8
Visuo-spatial processing		
Design Copying	11 (global score)	11 (global score)

Normative data (scaled scores): 1-3=well below average; 4-5= below average; 6-7=borderline; 8-12=average; 13-19=above average [11].

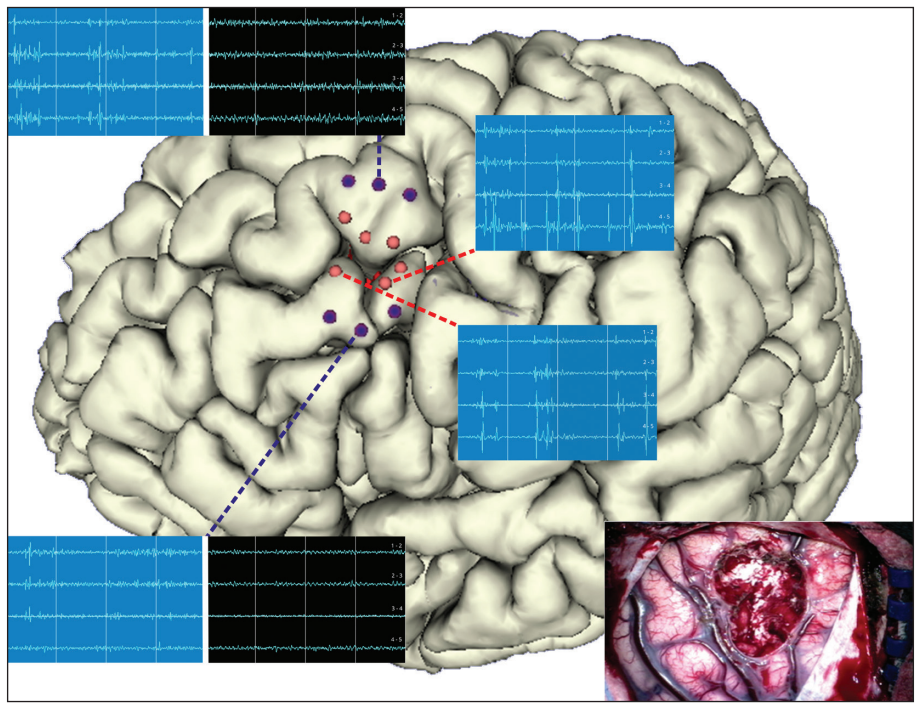


■ **Figure 1.** The multimodal approach. (A) Left panel: interictal EEG during wakefulness showing left fronto-central interictal epileptiform discharges (reduced montage with 256-channel recording, 20 seconds/page, sensitivity of 10 µv/mm, high-frequency filter of 70 Hz, low-frequency filter of 0.1 seconds); right panel: arithmetic spike average of the 256-channel EEG traces with a duration of 0.8 seconds. (B) Left panel: 3D cortical representation of EEG source imaging, inverse problem solution used: MUSIC (grey matter 3D reconstruction from individual

MRI, Curry); right panel: EEG source imaging at 50% rising phase of the peak, Current Density results (threshold, 90%) constrained to the cortex, inverse problem solution used: sLORETA (grey matter 3D reconstruction from individual MRI, Freesurfer). (C) Left panel: coronal 7T brain MRI, FLAIR sequence (area of hyperintensity and a possible "tapering" toward the ventricle at the intersection of the two white lines); right panel: ESI (in red, threshold: 90%) overlaid over 3T coronal MRI FLAIR sequences (using FMRIB Software Library, FSL). (D) Sagittal, coronal, and axial (from left to right) arterial spin labelling (ASL) sequences co-registered to T1-sequences (using FMRIB Software Library, FSL) with ESI localization (at the intersection of lines); the region localized by ESI is included within an area of hypoperfusion detected by ASL. (E) Sagittal, coronal, and axial (from left to right) 18F-FDG-PET sequences co-registered to T1 sequences (using FMRIB Software Library, FSL) with ESI localization (at the intersection of lines); the region localized by ESI is included within an area of hypometabolism detected by 18F-FDG-PET.

includes the "Visual Attention" subtest. The "Visual attention" ("Attention and Executive Functioning" domain) and "Word generation" ("Language" domain) subtests revealed scores below the expected level, compared to normative data (*table 1*) [11].

Since the available clinical data and interictal EEG (*figure 1A; left panel*), strongly suggested focal cortical dysplasia (FCD), other examinations were carried out. A 3T MRI study was considered uninformative, while both 18F-FDG-PET and ASL revealed regions of hypometabolism and hypoperfusion in the left fronto-lateral dorsal cortex, respectively. On long-term scalp Video-EEG monitoring, no seizures were recorded. Non-invasive source localization (256 electrodes



■ **Figure 2.** Intraoperative electrocorticography (ECoG). 3D grey matter reconstruction based on individual brain MRI scans showing 12 spots (six in red around the sulcus and six in blue distal to the sulcus), tested using hand-placed depth electrodes (five recording levels). The six distal to the sulcus were tested before (light blue ECoG traces) and after (black ECoG traces) the resection; the six around the sulcus were only tested before, as within the resection (light blue ECoG traces). For the ECoG traces of two spots around the sulcus and two distal to the sulcus, bipolar montage was set at: 300 μV/division, 30 mm/sec, four seconds each. Concerning spots distal to the sulcus, visual analysis of post-resectional ECoG traces showed improved background rhythm and pathological epileptiform activity.

HdEEG) was applied to the left interictal fronto-central spikes, using two different software packages, Curry (Compumedics, Abbotsford, Australia) and Brainstorm[1]. The analysis with Brainstorm was performed to both confirm the localization and generate 3D source maps, to be overlaid over other neuroimaging sequences (FLAIR, 18F-FDG-PET, ASL), based on an internal presurgical protocol.

The forward problem was solved by creating a realistic head model of the brain using T1-weighted individual sequences; the boundary element method (BEM). Two different inverse solutions were used: multiple-signal classification algorithm (MUSIC) and standardized low-resolution brain electromagnetic tomography (sLORETA) [13]. Both ESI analyses placed the rising phase of the activity (in terms of increase in current density) into the bottom of the left inferior frontal sulcus (*figure 1A, B*). On the basis of ESI results, 7T brain MRI was performed, allowing the identification of a subtle, small area of hyperintensity at the bottom of the sulcus, highlighted by ESI and a possible "tapering" toward the ventricle on FLAIR sequences (*figure 1C*). The region localized by ESI was included within the area of hypometabolism and hypoperfusion detected by 18F-FDG-PET and ASL, respectively (*figure 1D, E*).

Based on these co-localizing anatomo-electro-clinical data, the patient was considered eligible for surgery, and a lesionectomy was planned.

A tailored resection guided by neuronavigation (incorporating anatomical, functional, and ESI data) and visual analysis of the intraoperative ECoG, with both a multi-contact strip and depth electrodes placed by hand, was performed (*figure 2*).

Postoperatively, the patient presented with transient mild right hemiparesis and expressive aphasia, which completely cleared within a couple of weeks. After one year of follow-up, the patient was seizure-free, anti-seizure drugs (valproate and clobazam) were tapered, and postoperative brain 3T MRI revealed that the resection fully matched the targeted area. Moreover, the postoperative neuropsychological assessment (one year after surgery) showed an improvement in both "Visual attention" and "Word Generation" subtests on the Italian NEPSY-II version, which resulted above average and average, respectively (*table 1*) [11]. The histopathology revealed FCD type IIa.

Discussion

MRI-negative patients suffering from focal epilepsy, especially with a presumed extratemporal origin, represent the most challenging cases and have sub-optimal surgical outcomes [3,7]. Therefore, in these cases, the addition of various NIFNTs, including HdEEG-ESI, to conventional first-line investigations has been advocated for improving the accuracy in identifying the surgical target [4,5,7-10]. In our patient, ESI played the central role in localizing a possible epileptogenic lesion and allowed for a more accurate interpretation of ASL, 18F-FDG-PET, and MRI findings. The area localized by ESI was included within the region of hypoperfusion and hypometabolism detected by ASL and 18F-FDG-PET, supporting the suspicion of a possible small area of FCD. Indeed, a small area of FCD may be missed on MRI, although this may be recognized on histology based on resected specimens of patients with MRI-negative focal epilepsy [14]. The clinical features of our patient (normal IQ, drug-resistance, and high seizure frequency), as well as the interictal EEG features, characterized by focal continuous and rhythmic interictal epileptiform discharges (IEDs) [15], strongly suggested the presence of type II FCD. This was also supported by 7T brain MRI with an accurate focus on the area identified by ESI, applied to IEDs. Surgery was performed without ictal recordings which was planned on the basis of a suspected, subtle MRI lesion, concordant with clinical, interictal EEG, ASL, and 18F-FDG-PET findings [16]. We performed intraoperative cortical mapping with ECoG with both strip and depth electrodes, which allowed tailoring the resection of the lesion through a visual estimation of pre- and post-resectional spike activity, as described in other studies [17,18]. In conclusion, with this case report, we confirm the relevant contribution of a multimodal approach in the work-up for candidates of epilepsy surgery. We highlight the importance of the convergence of findings from several, discrete, functional neuroimaging techniques to identify the EZ, rather than based on such findings alone. In this view, in selected cases, the multimodal approach may allow invasive EEG monitoring, such as stereo-EEG, to be avoided. Moreover, we underline the pivotal role of the EEG source imaging technique, especially when FCD is suspected. Further studies are needed to identify those patients for which an ESI-based "sourcectomy" might be a reliable surgical approach. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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None of the authors report any conflicts of interest.

[1]Freely available for download online under the GNU general public license (http://neuroimage.usc.edu/brainstorm) [12].

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TEST YOURSELF

(1) Epilepsy surgery: What is the main role of presurgical investigations?

(2) List at least three non-invasive functional neuroimaging techniques (NIFNTs) which provide further diagnostic accuracy to first-line evaluations during presurgical assessment.

(3) Describe the interictal scalp EEG pattern frequently found in FCD type II?

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".