Epilepsy & Behavior 143 (2023) 109229

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical added value of interictal automated electrical source imaging in the presurgical evaluation of MRI-negative epilepsy: A real-life experience in 29 consecutive patients

Roberto Santalucia [a,b,c,d,*], Evelina Carapancea [b], Simone Vespa [b], Enrique Germany Morrison [b], Amir Ghasemi Baroumand [e,f], Pascal Vrielynck [c,d], Alexane Fierain [c,d,g], Vincent Joris [b,d,h], Christian Raftopoulos [d,h], Thierry Duprez [d,i], Susana Ferrao Santos [b,d,g], Pieter van Mierlo [e,f], Riëm El Tahry [b,d,g,j]

[a] Cliniques Universitaires Saint-Luc, Paediatric Neurology Unit, Brussels, Belgium
[b] Institute of Neurosciences (IoNS/NEUR), Université Catholique de Louvain (UCL), Brussels, Belgium
[c] Centre Hospitalier Neurologique William Lennox (CHNWL), Clinical Neurophysiology, Ottignies, Belgium
[d] Cliniques Universitaires Saint-Luc, Reference Center for Refractory Epilepsy (CRE), Brussels, Belgium
[e] Medical Image and Signal Processing, Ghent University, Ghent, Belgium
[f] Epilog NV, Ghent, Belgium
[g] Cliniques Universitaires Saint-Luc, Neurology Unit, Brussels, Belgium
[h] Cliniques Universitaires Saint-Luc, Neurosurgery Unit, Brussels, Belgium
[i] Cliniques Universitaires Saint-Luc, Medical Imaging Department, Neuroradiology Unit, Belgium
[j] WELBIO Department, WEL Research Institute, Avenue Pasteur 6, 1300 Wavre, Belgium

ARTICLE INFO

Article history:
Received 6 February 2023
Revised 9 April 2023
Accepted 20 April 2023

Keywords:
Automated ESI
MRI-negative epilepsy
Presurgical evaluation

ABSTRACT

Objective: During the presurgical evaluation, manual electrical source imaging (ESI) provides clinically useful information in one-third of the patients but it is time-consuming and requires specific expertise. This prospective study aims to assess the clinical added value of a fully automated ESI analysis in a cohort of patients with MRI-negative epilepsy and describe its diagnostic performance, by evaluating sublobar concordance with stereo-electroencephalography (SEEG) results and surgical resection and outcome.
Methods: All consecutive patients referred to the Center for Refractory Epilepsy (CRE) of St-Luc University Hospital (Brussels, Belgium) for presurgical evaluation between 15/01/2019 and 31/12/2020 meeting the inclusion criteria, were recruited to the study. Interictal ESI was realized on low-density long-term EEG monitoring (LD-ESI) and, whenever available, high-density EEG (HD-ESI), using a fully automated analysis (Epilog PreOp, Epilog NV, Ghent, Belgium). The multidisciplinary team (MDT) was asked to formulate hypotheses about the epileptogenic zone (EZ) location at sublobar level and make a decision on further management for each patient at two distinct moments: i) blinded to ESI and ii) after the presentation and clinical interpretation of ESI. Results leading to a change in clinical management were considered contributive. Patients were followed up to assess whether these changes lead to concordant results on stereo-EEG (SEEG) or successful epilepsy surgery.
Results: Data from all included 29 patients were analyzed. ESI led to a change in the management plan in 12/29 patients (41%). In 9/12 (75%), modifications were related to a change in the plan of the invasive recording. In 8/9 patients, invasive recording was performed. In 6/8 (75%), the intracranial EEG recording confirmed the localization of the ESI at a sublobar level. So far, 5/12 patients, for whom the management plan was changed after ESI, were operated on and have at least one-year postoperative follow-up. In all cases, the EZ identified by ESI was included in the resection zone. Among these patients, 4/5 (80%) are seizure-free (ILAE 1) and one patient experienced a seizure reduction of more than 50% (ILAE 4).
Conclusions: In this single-center prospective study, we demonstrated the added value of automated ESI in the presurgical evaluation of MRI-negative cases, especially in helping to plan the implantation of depth electrodes for SEEG, provided that ESI results are integrated into the whole multimodal evaluation and clinically interpreted.

* Corresponding author at: Pediatric Neurology Unit, Cliniques Universitaires Saint-Luc, UCLouvain, Avenue Hippocrate, 10 1200 Brussels, Belgium.
E-mail address: roberto.santalucia@saintluc.uclouvain.be (R. Santalucia).

https://doi.org/10.1016/j.yebeh.2023.109229
1525-5050/

1. Introduction

Epilepsy surgery with the resection of the presumed epileptogenic focus is currently the treatment option with the highest efficacy for patients with drug-resistant focal epilepsy [1]. Crucial to the success of surgical treatment is a reliable delineation of the epileptogenic zone (EZ), defined as the area of the cortex that is indispensable for generating seizures [1,2]. Consequently, patients with refractory epilepsy undergo an extensive presurgical work-up, including a multimodal approach, in an effort to obtain different types of information and results (seizure semiology, electroencephalography, neuroimaging, neuropsychological evaluation, etc), converging on the same hypothesis about epileptic focus localization [3]. Undeniably, the presence of a clear MRI-detectable focal brain lesion can facilitate the surgical decision, provided that the lesion has an epileptogenic potential and does not cover an eloquent cortex. Unfortunately, the proportion of MRI-negative patients referred for presurgical work-up is relatively high and varies between 15% and 30% [4,5]. So far, there is no general consensus on how MRI-negative patients should be selected for presurgical evaluation, and which diagnostic tools should be used. As a consequence, these patients tend to be more challenging cases and often require multiple non-invasive and invasive explorations to localize the EZ more accurately, finally resulting in an underutilization of epilepsy surgery [6,7]. Thus, there is a need for additional non-invasive methods, using post-processing and signal analysis that help to localize the EZ, for MRI-negative patients. EEG source imaging (ESI) estimates the underlying brain activity from the measured EEG, using an electric conduction model built from the patient's own MRI. The value of ESI to localize the EZ with a moderate to high accuracy (57–88%) has already been shown in several studies [8–11]. In the presurgical evaluation, ESI performed by experts provides non-redundant information, leading to a clinically significant change in the management plan in one-third of the patients [12]. Other studies performing a subgroup analysis reported a higher rate of full concordance of ESI results with EZ in patients with negative versus positive MRI, suggesting that "non-lesional" cases (i.e., patients with non-detectable or occult lesion) might represent best candidates for ESI analysis [13,14]. Despite these promising results and the published compelling evidence on the accuracy and utility of ESI, its use has not gained wide diffusion in clinical practice and ESI is only used in a limited number of centers worldwide. A study from the E-pilepsy consortium showed that only 9/25 centers include ESI in their armamentarium of the presurgical evaluation for drug-resistant epilepsy [15]. This limited use can be explained by several factors: (i) the manual analysis that entails marking the spikes and constructing the head models from MRI is time-consuming, and (ii) it requires specific expertise in signal analysis that is not available in all centers. To overcome these obstacles and to contribute to the more widespread use of ESI in presurgical evaluation, fully and semi-automated analyses for identification and subsequent source localization of interictal epileptiform discharges (IEDs) and ictal activity from high-density (HD) and low-density (LD) EEG recordings have been recently developed (Epilog PreOp, Epilog NV, Ghent, Belgium) and validated in two separate blinded studies [16–19].

In this prospective study, we assessed the clinical added value of interictal automated ESI in 29 consecutive patients with drug-resistant MRI-negative focal epilepsy, by assessing how the epilepsy multidisciplinary team (MDT) decision varies in the light of the additional information given by ESI. In addition to the change in the management plan, we also determined the final concordance for a subset of patients that underwent SEEG and surgery, with resection zone (RZ) and 1-year postoperative outcome as ground truth whenever surgery was performed, or SEEG-seizure onset zone (SOZ) whenever surgery was not performed. Finally, we report two illustrative cases: one where ESI results were a key asset and another with discordant results, describing the practicalities of real-life ESI use in managing challenging epileptic patients.

2. Methods

2.1. Patients

We prospectively recruited all consecutive patients who were referred to the reference Center for Refractory Epilepsy (CRE) of St-Luc University Hospital (Brussels, Belgium) between 15/01/2019 and 31/12/2020. The study was approved by the local Ethics Committee (St-Luc University Hospital/UCLouvain EC - 2018/26SEP/355) and patients and/or their parents/legal guardians gave informed consent. Inclusion criteria were: i) patients aged between 0–65 years ii) with drug-resistant focal epilepsy undergoing a pre-surgical evaluation and iii) non-lesional 3.0 Tesla (3T)-brain MRI (as indicated in the radiology protocol) iv) for whom seizures could be recorded during a long-term LD-EEG or HD-EEG and v) for whom a maximum of 5 hypotheses (one primary and one to four secondary) about EZ location at sublobar level could be formulated by one of the 4 neurophysiologists/epileptologists (PV, AF, SFS, RET) of the CRE during the work-up. We excluded patients in whom a brain lesion was successively identified after the addition of optimized MRI sequences and voxel-based morphometry (VBM) analysis [20] and the second reading of an experienced neuro-radiologist (TD) at the time of the MDT meeting.

The presurgical work-up performed consists of epilepsy history and seizure semiology review, long-term video-EEG Monitoring (LTEM), 3T brain MRI with dedicated epilepsy protocol [21] and VBM analysis [22], 18F-fluorodeoxyglucose PET (FDG-PET), psychiatric and/or neuropsychological evaluation. When these first-step modalities are discordant or the MRI is unrevealing, other investigations are planned (HD-EEG, MEG, ictal SPECT) in function of each patient. When this leads to a main hypothesis and few alternative hypotheses, the implantation of intracranial electrodes is proposed. When there is no valid hypothesis or there are too many to be tested, the patients are rejected for surgery, and neuromodulation is considered.

2.2. EEG recordings and individual head models

LD-ESI was based on long-term (up to 11 days) EEG recordings with the standardized IFCN (International Federation of Clinical Neurophysiology) array of 25 electrodes, including the inferior temporal (F9/10, T9/10 and P9/10) chain [23]. LTEM was performed in all patients. HD-ESI was based on shorter recordings (up to 48 hours), using 76 manually glued scalp electrodes, according to the 10/10 international system. HD-EEG was realized in 9 patients, as clinically indicated. Indications to perform HD-EEG were: 1) lateralization of bilateral epileptiform discharges in two patients; 2) correct lateralization of midline (parasagittal) epileptic focus in three patients; 3) improved localization to guide invasive investigation near eloquent cortex in four patients. Additional HD-EEG was not proposed for children younger than 12 years and patients of any age with behavioral or psychiatric comorbidities, limiting the feasibility of the procedure. LTEM and HD-EEG were respectively performed at the Epilepsy Monitoring Unit (EMU) of St-Luc University Hospital (Department of Neurology) and Centre Hospitalier Neurologique William Lennox (CHNWL), Ottignies (Belgium). Electrode impedance was kept below 5 KΩ. EEG was recorded with a sampling frequency of 256 Hz, using the Deltamed Coherence® system (Natus). For each patient, the complete, avail-

able EEG recording was analyzed. Brain MRI was done at Neuroradiology Unit, St-Luc University Hospital, using a 3T Siemens scanner. When clinically indicated, the exam was performed under general anesthesia. T1-3D-MPR-sequence without contrast was used for constructing the individual head models for each patient from their own MRI, both for LD-ESI and HD-ESI.

2.3. Interictal Electrical Source Imaging (ESI)

De-identified long-term LD/HD-EEG and MRI data were analyzed using Epilog PreOp (Epilog NV, Ghent, Belgium). The analysis consists of automated spike detection, clustering of single detected spikes based on their morphology, and finally ESI analysis of the detected spikes at two time points: the half-rising time and the peak of the averaged spike waveforms. The whole analysis was performed blinded to all other clinical and paraclinical data. One person (SV, PhD student of the UCLouvain), not directly involved in the pre-surgical work-up and not being in the regular staff of the CRE, collected and anonymized the data and transferred them to a dedicated and secured platform, created by Epilog. Automated spike detection was performed using the Persyst Spike Detector P13 (Persyst, San Diego, CA, USA). Afterwards, the spikes were averaged for each of the detected clusters. Clusters with less than 15 single spikes were excluded from further analysis. Up to maximal four spike clusters, with the highest number of spikes, were further analyzed. For each patient, an individual head model with a $1 \times 1 \times 1$ mm resolution was constructed from the T1-weighted MR image. The head model consisted of six different tissues (scalp, skull, cerebrospinal fluid, grey matter, white matter and air). The source of each spike-cluster was localized at the half-rising time and the peak of the spikes using sLORETA as ESI inverse technique. For more technical details, we refer the readers to the article of Baroumand et al., 2018 [18].

2.4. Clinical added value

Each patient was randomly discussed at one of the prefixed MDT meetings of the CRE. Principal and secondary hypotheses about the epileptogenic zone (EZ) location at a sublobar level (25 sublobes par hemisphere) were developed [24] and eventually modified from pre-surgical assessment after discussion and agreement between the members of CRE (each change requiring a relative majority of the participants). Then, the MDT formulated a clinical decision first blinded to the ESI results. The possible decisions for a single patient were: A) resective surgery of the presumed EZ; B) stereo-EEG (SEEG); C) rejected for surgery; D) necessity of other additional investigations (repeated LTEM, HD-EEG, MEG, ictal SPECT, fMRI, WADA test and all possible combinations of these). The formulated hypotheses and decisions were logged into a database during the meeting. Thereafter, interictal LD-ESI (for all patients) and HD-ESI (in 9 patients) results were presented by an external member (SV) at the same MDT meeting and interpreted in the context of the clinical scenario and other investigations. For this purpose, interictal ESI reports were presented to the physicians, who evaluated the automatically detected clusters (4 ordered clusters with the highest number of spikes), classifying them as epileptiform or non-epileptiform (artifacts or physiological activity). Thereafter, the clusters of clinical interest were selected (i.e., the identified clusters that best fit with the broad clinical context and weighed against all other data). Therefore, the clinicians could not consider at all an identified cluster of spikes (artifact or incongruent) or reclassify as principal an identified cluster with less abundant detected spikes. More details about ESI clinical interpretation can be found in the article of Baroumand et al., 2018 [18].

ESI results were considered contributive only if new and non-redundant information was obtained from ESI, leading to a re-evaluation of EZ hypotheses and a change in the clinical management decisions, accordingly to the new hypothesis. The following ESI-driven changes were possible: 1) a change in the first decision (moving from one to another option among A-B-C-D) or 2) confirmed option B but a change in the SEEG implantation plan. Therefore, after clinically oriented ESI interpretation, the results could be classed as 1) discordant with pre-ESI evaluation and non-contributive; 2) concordant with pre-ESI evaluation and non-contributive (no change in the management plan); 3) concordant with pre-ESI evaluation and contributive. The changes in patients with contributive ESI results were logged into the same database during the MDT meeting, including the type of change and which ESI method the change was based on (LD- and/or HD-ESI). Clinical added value was defined as the proportion of patients in whom the management plan was changed, based on the results of ESI. Patients, in whom ESI led to a change in clinical management, were followed up to assess the clinical relevance of these modifications. In patients undergoing SEEG, we assessed whether the location of the ESI was confirmed at sublobar level by the invasive recording. In patients undergoing epilepsy surgery, we determined whether the EZ localized by ESI at sublobar level was included in the resection zone on a post-operative MRI or not. For surgical outcome, we used the ILAE classification system and considered seizure-free only patients with ILAE class 1 at one-year post-operative follow-up. Concordance between ESI and SEEG or surgery was defined as total or partial depending on whether all clusters identified by ESI or only part of them were included in the SOZ and propagation zone (PZ) or the resected brain region.

On the other hand, we classified as discordant all the ESI results that were considered to be driven by a non-epileptic cluster or substantially diverged from the main localization(s) elaborated through the clinical reasoning, the whole presurgical work-up, and the MDT discussion of the case.

2.5. Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows 2.0 (IBM Corp., Armonk, USA). Data were collected from the electronic medical chart of each patient. Quantitative variables were expressed as mean ± SD or median (range), while qualitative variables were expressed as n (%). To compare the differences between subgroups, the Student t-test (or the Mann–Whitney U-test) was used for continuous variables, and the chi-square test (or Fisher's exact test) for categorical variables. The added clinical value was expressed as the percentage of patients in whom ESI changed the initial management plan.

3. Results

Thirty out of 132 (22%) consecutive patients that performed a presurgical evaluation in our CRE during the study period met the inclusion criteria and were eligible for the study (Fig. 1). One patient had a combination of focal seizures and PNES, which were the main events at the time of the evaluation, and therefore was excluded from the study. Data from all included 29 patients were analyzed (15 females; age: 3–54 years, median: 27 years). Ten patients (34.5%) were children (<18 years) at the time of inclusion. The mean age at epilepsy onset was 15 ± 13 years. The mean epilepsy duration was 11 ± 10 years and the patients had tried an average number of 5 ± 2 anti-seizure medications (ASMs) before the presurgical workup. One patient had a previous failed epilepsy surgery and received a vagus nerve stimulator (VNS) subsequently, with no significant improvement. 20/29 patients (69%) had extra-

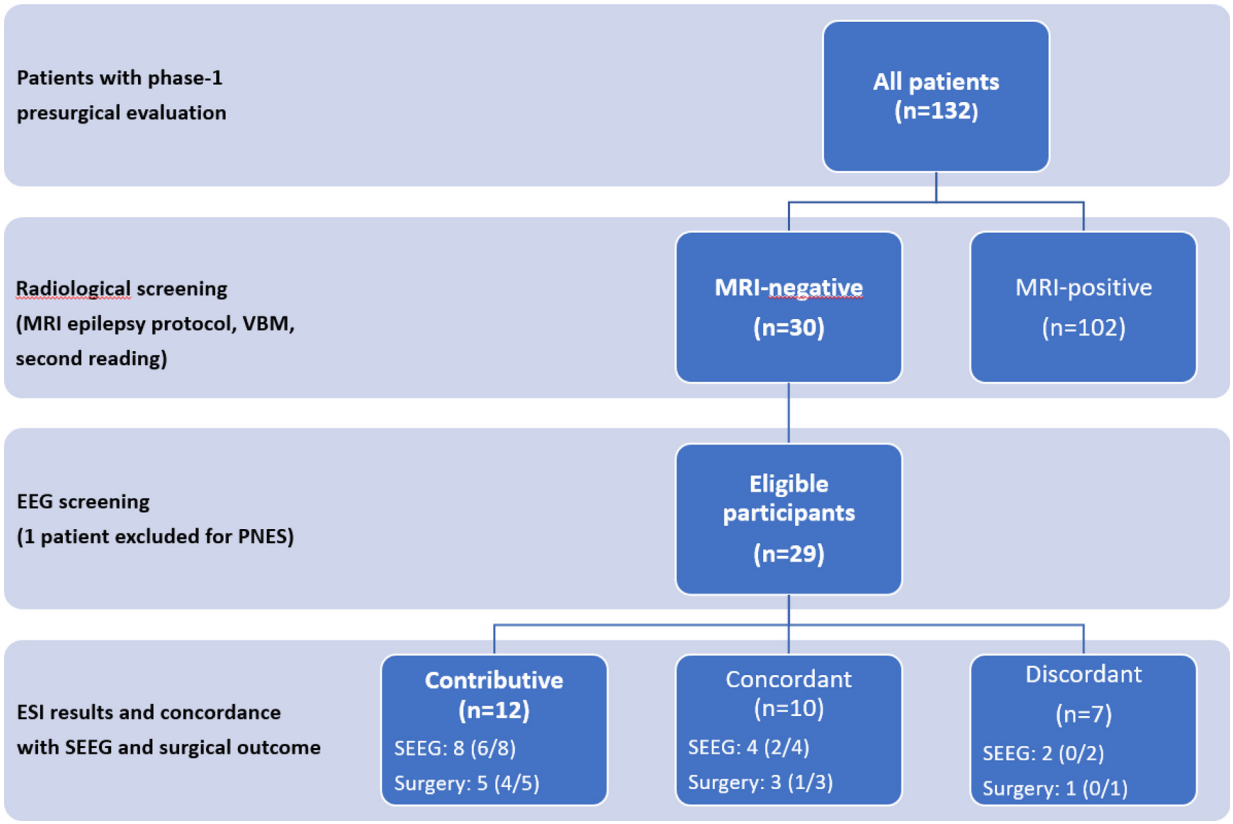

Fig. 1. Study flowchart. Brain MRI and electrophysiological data of all patients with available phase-1 presurgical evaluation in our center were reviewed during the study period to include only patients with definitive diagnosis of refractory MRI-negative focal epilepsy. Automated ESI followed by physician interpretation had a clinical added value in 12/29 patients (41%). Even if the numbers are low to assess diagnostic accuracy with sufficient evidence, there is a trend toward a higher concordance between ESI and SEEG SOZ and surgical outcome in those patients in whom ESI lead to a change in clinical management. ESI results were classed as *discordant* with pre-ESI evaluation and non-contributive; *concordant* with pre-ESI evaluation and non-contributive (no change in the management plan); *contributive* (change in the management plan).

temporal lobe epilepsy (ETLE) and 9/29 had temporal lobe epilepsy (TLE). The median seizure frequency was 12 (0.3–150) per month. The mean duration of LTEM and HD-EEG was 145 (±53) hours and 36 (±9) hours, respectively. The 3 subgroups (discordant results; concordant and not contributive results; concordant and contributive results) did not significantly differ in terms of demographic characteristics, epilepsy type, age at onset, epilepsy duration and severity. More details about the study population are presented in Table 1.

ESI led to a change in the management plan in 12/29 patients (41%). In 9/12 (75%) there was a substantial modification in the plan of invasive recording: additional depth electrodes were implanted in 6 patients (#4; #10; #11; #12; #15; #27), while in 3 patients (#13; #14; #17) the SEEG plan was changed (partial removal of previously planned electrodes and coverage of new brain areas pointed out by ESI). Other 3/12 patients had a change in the clinical management: for two patients (#23; #28), additional non-invasive procedures were recommended (1 MEG; 1 HD-EEG) instead of SEEG to further delineate the EZ before depth electrodes implantation; one patient (#8) initially rejected for surgery was proposed for invasive investigation with an SEEG plan including the principal ESI cluster. Until now, 8/9 patients (#10; #11; #12; #13; #14; #15; #17; #27) in whom ESI changed the plan of implanting intracranial electrodes, underwent invasive recordings. In 6/8 (all except for #11 and #13: 75%), the intracranial recordings confirmed the localization of the ESI at a sublobar level with partial or total concordance. So far, 5/12 patients (#10; #12; #14; #15 #17), in whom ESI changed the management plan, have been operated on and have at least one-year postoperative follow-up. In all cases, the EZ identified by ESI (at least one cluster) was included in the resection zone. Among these patients, four (80%) are seizure-free until now (ILAE 1) and one patient (#15) experienced a seizure reduction of more than 50% (ILAE 4).

ESI confirmed the initial MDT decision but did not lead to a change in clinical management in 10/29 patients (35%). Among these patients, 4/10 (#5; #21; #25; #29) underwent SEEG. In these patients, SEEG showed partial or total concordant results with ESI in half of them (#5; #29). So far, 3/10 patients have been operated on with resection of at least one ESI cluster: two (#26; #2) with outcome class ILAE 1 and ILAE 3, respectively, and one (#29) with less than one-year follow-up from surgery.

ESI results were discordant with MDT decision in 7/29 patients (24%). Discordant results were represented by non-epileptic clusters in two patients (physiological activity in #3 and artifact in #18) and ESI clusters localized contralaterally in three cases of presumed unilateral EZ (#6; #16; #20) or localized in a lobe when there was no additional electro-clinical or functional imaging correlate, corroborating this localization, in other 2 patients (#1; #22). Among these patients with discordant ESI, 2/7 (#1; #6) underwent SEEG with inconclusive results, and one patient (#3) has been operated on after additional non-invasive investigations (MEG and ictal SPECT) with a good one-year post-operative outcome (ILAE 2).

The results of the presurgical work-up, ESI interpretation, and confirmatory SEEG or surgical outcome are summarized in Table 2.

Table 1
Patient characteristics. ETLE: extra-temporal lobe epilepsy; TLE: temporal lobe epilepsy; FAS: focal aware seizure; FIAS: focal impaired awareness seizure; FBTCS: focal to bilateral tonic-clonic seizure; +S/VNS: prior epilepsy surgery and VNS implantation; LTG: lamotrigine; LEV: levetiracetam; VPA: valproate; TPM: topiramate; RUF: rufinamide; FBM: felbamate; BRV: brivaracetam; LCM: lacosamide; CBZ: carbamazepine; PER: perampanel; OXC: oxcarbazepine; PRG: pregabaline; CLB: clobazam.

Patient	Age at inclusion (years)	Sex	Epilepsy duration (y)	Epilepsy type	Seizure type	Seizure frequency/month	tried ASMs (n)	current ASMs
#1	17	M	13	ETLE	FIAS (autonomic), FBTCS	0.3	4	LTG, LEV
#2	21	M	13	ETLE	FIAS (atonic-tonic), FBTCS	30	9 (+S/VNS)	VPA, TPM, RUF, FBM
#3	48	F	40	ETLE	FAS (sensory)	30	8	BRV, LCM
#4	19	M	5	TLE	FIAS (automatisms)	1.5	3	VPA, CBZ, LTG
#5	16	M	4	TLE	FIAS (automatisms)	16	3	LEV, LTG, PER
#6	54	M	4	TLE	FIAS (cognitive)	10	5	LTG, CBZ
#7	27	F	16	TLE	FIAS (sensory and clonic), FAS (cognitive)	8	3	LEV, LTG
#8	16	M	9	ETLE	FIAS (cognitive and tonic)	4	7	VPA, LTG
#9	24	M	2	ETLE	FIAS (cognitive and clonic)	12	5	OXC, VPA
#10	15	F	4	ETLE	FIAS (hyperkinetic, tonic, and behavior arrest)	4	8	CBZ, VPA, BRV, LCM
#11	31	F	15	ETLE	FIAS (hyperkinetic)	4	4	VPA, OXC, CLB
#12	7	F	5	ETLE	FAS (sensory)	30	4	CBZ, BRV
#13	13	F	6	ETLE	FIAS (cognitive)	1	3	TPM, CBZ, PER
#14	15	M	5	TLE	FBTCS	0.3	4	CBZ, BRV
#15	25	M	13	ETLE	FIAS (hyperkinetic)	1,5	8	CBZ, LCM, PER
#16	43	M	36	TLE	FIAS (cognitive)	30	8	LTG, PRG
#17	8	F	3	ETLE	FIAS (tonic)	90	5	VPA, BRV, LCM, CLB
#18	35	F	1	ETLE	FAS (sensory)	5	3	LTG, BRV, PER
#19	37	F	36	ETLE	FAS (clonic), FIAS (behavioral arrest)	25	7	CBZ, TPM, VPA
#20	36	F	12	ETLE	FAS (autonomic), FIAS (clonic)	150	5	LCM, CLB
#21	34	F	17	TLE	FIAS (emotional)	20	4	CBZ, VPA, LEV
#22	4	M	2	ETLE	FAS (sensory)	30	4	CBZ, TPM, BRV
#23	26	F	12	ETLE	FAS (sensory), FIAS (clonic)	2	5	OXC, LCM, PER
#24	4	F	1	ETLE	FAS (clonic)	4	4	CBZ, CLB
#25	27	M	10	ETLE	FBTCS	0,5	4	BRV, LCM
#26	54	F	2	TLE	FIAS (sensory and behavioral arrest)	7	5	LTG, TPM, BRV
#27	20	F	8	ETLE	FIAS (emotional)	150	5	LTG, LCM
#28	38	M	5	TLE	FIAS (behavioral arrest), FBTCS	0.3	4	CBZ, TPM, CLB
#29	27	M	12	ETLE	FIAS (autonomic), FBTCS	30	4	CBZ, LEV

3.1. Case study 1

The first case study (pat #10) describes a 16-year-old, right-handed, female patient with unrevealing personal and familial past history. Epilepsy started at the age of 11 years with a stormy onset of frequent and brief focal aware and unaware seizures with pleiotropic but stereotyped motor manifestations: asymmetric tonic posturing (extension of the right upper limb and left head deviation) and hyperkinetic non-lateralized movements with gelastic features. Seizures were mainly nocturnal leading to frequent awakenings but could occur also during the day. Rarely, the patient experienced focal to bilateral tonic-clonic seizures. Several antiseizure medications (ASMs) were tried (VPA, OXC, LEV, TPM, PER, LCM, BRV, CLB) with little improvement in seizure frequency and important side effects. At the time of presurgical evaluation, the patient reported on average 4 days of seizures/month while taking 5 different ASMs. LTEM showed interictal spikes and sharp waves on the left mesial fronto-central regions. Eighteen seizures were recorded with ictal onset in the same regions. An HD-EEG recording to exclude false lateralization on LD-EEG completed the non-invasive EEG monitoring. 3T-brain MRIs were repeatedly negative and VBM analysis was inconclusive. FDG-PET revealed a discrete hypometabolic cortical area on the left fronto-parietal region. The neuropsychological evaluation did not observe any lateralizing cognitive deficit, but the patient had a global slowing of mental performance in relation to ongoing seizures and current polytherapy.

Interictal ESI was realized on both LD- and HD-EEG recordings. Successively, the case was discussed in an epilepsy surgery meeting and the MDT formulated, blinded to ESI results, the following hypotheses: left frontal superior gyrus (first hypothesis), left dorsolateral frontal gyrus, and left anterior cingulate cortex (second hypotheses). An SEEG plan was defined accordingly using eight depth electrodes. In a second step, ESI results were presented at the same meeting and the MDT was asked to interpret them. Both LD and HD-ESI showed a principal cluster in the left middle/posterior cingulate cortex. Results are shown in Fig. 2A. The spike cluster was considered genuine and the corresponding EZ location at the middle/posterior part of cingulum highlighted by ESI was clinically plausible, taking into account the whole presurgical data. Therefore, the MDT retained an additional hypothesis about EZ location, and the SEEG plan was changed accordingly. Practically, a depth electrode was added for better coverage of the middle and posterior cingulate cortex intending to delimitate the posterior margin of the presumed EZ. The modified SEEG plan is shown in the Fig. 2B. Invasive EEG monitoring confirmed the EZ location suggested by ESI with concordant sublobar result in the left middle/-posterior cingulate cortex. An example of a seizure recorded during SEEG is shown in Fig. 2C. A revision of the brain MRI was performed focusing on the brain area found to be responsible for generating the ictal activity (SOZ) and a left middle/posterior cingular gyrus dysplasia was finally suspected. The patient underwent surgery with resection of the posterior cingular gyrus and part of the middle cingular gyrus. The margins of resection are depicted in Fig. 2D. Histopathology revealed a focal cortical dysplasia type IA (FCD IA). There were no perioperative complications and the patient is still seizure-free at the 24-month follow-up after surgery (ILAE class 1).

3.2. Case study 2

The second case study (pat #3) describes a 48-year-old, right-handed, female patient with a personal past history of preterm birth and developmental delay. Epilepsy started at the age of

Table 2
ESI interpretation and added value. R: right; L: left; Bil (R > L): bilateral with right predominance; Bil (L > R): bilateral with left predominance; F: frontal; C: central; P: parietal; T: temporal; O: occipital; HypoM: hypometabolism; FP: frontopolar; FSM: frontal superior mesial; DLFS: dorsolateral frontal superior; DLFI: dorsolateral frontal inferior; ObF: orbitofrontal; PSM: parietal superior mesial; PIM: parietal inferior mesial; PSL: parietal superior lateral; PIL: parietal inferior lateral; TM: temporomesial; TL: temporolateral; TB: temporobasal; TP: temporopolar; OM: occipital mesial; OL: occipital lateral; FOp: frontal opercular; POp: parietal opercular; TOp: temporal opercular; InsA: anterior insular; InsP: posterior insular; TOJ: temporo-occipital junction; TPJ: temporo-parietal junction; CingA: anterior cingular; CingM: middle cingular; CingP: posterior cingular; Hipp: hippocampus; FS: frontal superior; FM: frontal middle; TS: temporal superior; ATL: anterior temporal lobectomy; AH: amygdalohippocampectomy; EcoG: electrocorticography; FCD: focal cortical dysplasia; HS: hippocampal sclerosis; N/A: not applicable; (+) addition of; (-): removal of. First decision: A (surgery); B (SEEG); C (surgery rejected; neuromodulation proposed); D (need for additional non-invasive investigations). ESI added value: 1 (Discordant); 2 (Concordant, Not Contributive); 3 (Contributive).

Patient	LTEM	HD-EEG (Y/N)	FDG- PET	EZ hypotheses	1st decision	ESI clusters	ESI added value	Changes /Additional investigations	SEEG - SOZ + PZ	Surgery - RZ	Anatomo-pathology	ILAE outcome
#1	R CP	N	Normal	R PSM, R + L CingP, R CingM, R PIM	B	R + L TM	1	No (ESI clusters not included in SEEG plan)	L Hemisphere (inadequate coverage)	N/A	N/A	N/A
#2	R F	N	R F HypoM (surgical cavity)	R FSM, R InsA	A	R FSM; R InsA	2	No (confirmed option A)	N/A	R F Disconnection	No definite FCD	3
#3	R FP	**Y**	R TM HypoM	R FSM, R DLFS	D	Physiological	1	MEG and ictal SPECT support R F hypothesis	N/A	R FS and FM cortectomy (EcoG-guided)	FCD IIa	2
#4	L T	N	Normal	L TL, L FP, L FSM, L FOp, L TOp	B	L TM; L InsP	3	SEEG plan: (+) 1 electrode in L InsP	N/A	N/A	N/A	N/A
#5	Bil T (R > L)	**Y**	Normal	R PSM, R TM, R TB, R TPJ, L PSM	B	R TM; L TM	2	No (confirmed SEEG plan)	Bitemporal: R TB and L TM	N/A	N/A	N/A
#6	R T	N	Normal	R InsA, R ObF, R TM, R TL, R TB	B	L TM	1	No (ESI clusters not included in SEEG plan)	Interictal: R Hipp and TB; No seizure recorded	N/A	N/A	N/A
#7	Bil T (L > R)	N	L T HypoM	L TM, L TB, R TM, R TB	C	L TM; R TM	2	No (confirmed option C: VNS/ DBS)	N/A	N/A	N/A	N/A
#8	Bil FT (R > L)	N	R F HypoM	R TP, L TP, R TM, L TM	C	R ObF; R InsA	3	C –> B (SEEG plan including ESI clusters)	N/A	N/A	N/A	N/A
#9	L FT	N	Normal	L FP, L ObF, L TP	D	L ObF; L InsA	2	No (confirmed extra-T hypothesis and need for repeated LTEM)	N/A	N/A	N/A	N/A
#10	L FT and F midline	**Y**	L FP HypoM	L FSM, L DLFS, L CingA, L CingM	B	L CingP; L CingM	3	SEEG plan: (+) 1 electrode in L CingP	L CingP + CingM (1/2 post)	L CingP and partial CingM cortectomy	FCD Ia	1
#11	L TPO	N	Normal	L PSM, L PIM, L insP, L TOJ, L TPJ	B	L TM; L TB	3	SEEG plan: (+) 1 electrode in L TB (fusiform gyrus)	Multifocal: L PSL, L Hipp, L TB	N/A	N/A	N/A
#12	Bil F (R > L)	N	R F posterior HypoM	R FOp, R InsA, R Cing A	B	R FOp	3	SEEG plan: (+) 1 electrode in R FOp (anterior limit)	R Pre-C gyrus and FOp	R F cortectomy (EcoG-guided)	FCD IIa	1
#13	R TO	N	Normal	R OM, R TL, R TOJ	B	R PSM	3	SEEG plan: (-) 1 T electrode; (+) 1 electrode in R PSM (precuneus)	Multifocal: R TB, R Hipp, R cuneus and TOJ	N/A	N/A	N/A
#14	L TPO	N	L FTP HypoM	L TM, L TL, L TB, L TOJ, L TPJ	B	L TP; L InsA	3	SEEG plan: (-) 1 O electrode; (+) 1 electrode in L InsA	L TP + L Hipp	L ATL + AH	HS	1
#15	Bil F (R > L)	N	Normal	R FP, R FSM, R ObF, R FOp, R insA	B	R InsP; R POp	3	SEEG plan: (+) 1 electrode in R InsP and POp	R InsP + InsA + FP Op	R Insula + POp cortectomy	FCD Ia	4
#16	Bil TPO (R > L)	N	Normal	R PIM, R PIL, R TOJ, R TPJ, R TM	B	L TB	1	No (ESI clusters not included in SEEG plan)	N/A	N/A	N/A	N/A
#17	L PT	N	L FT and Bil ObF HypoM	L PIL, L TM, L TB, L TPJ, L InsP	B	L ObF	3	SEEG plan: (-) 1 T and 3 P; (+) 3 F electrodes	L ObF + CingA	L ObF, mesial pre-F and partial CingA cortectomy	Gliosis	1
#18	Bil FP (L > R)	N	L FP and T lateral HypoM	L FOp, L InsA	D	Artefact	1	Repeated LTEM	N/A	N/A	N/A	N/A
#19	Bil FPT (R > L)	N	L T anterior HypoM	R PSL, R + L TM, R + L InsA	D	R + L TM; R + L InsA	2	No (confirmed possible Ins involvement and option D)	N/A	N/A	N/A	N/A
#20	Bil FT (L > R)	N	R FT HypoM	L InsA, L InsP, L ObF, L CingA, L CingM	D	R > L TM	1	MEG: clusters at R T; ictal SPECT: R InsA	N/A	N/A	N/A	N/A

Table 2 (*continued*)

Patient	LTEM	HD-EEG (Y/N)	FDG- PET	EZ hypotheses	1st decision	ESI clusters	ESI added value	Changes /Additional investigations	SEEG - SOZ + PZ	Surgery - RZ	Anatomo-pathology	ILAE outcome
#21	L FT	N	L T mesial HypoM	L CingA, L InsA, L ObF, L TM, L TB	B	L TM	2	No (confirmed SEEG plan)	L InsA	N/A	N/A	N/A
#22	L PT	N	L T lateral HypoM	L PSL, L PIL	D	L DLFS	1	MEG: cluster located at L FPOp	N/A	N/A	N/A	N/A
#23	L CPT and C midline	**Y**	Normal	L FOp, L TOp, L ObF, L InsA, L InsP	B	L TM; L CingA	3	B –> D (MEG: clusters located at L Ins)	N/A	N/A	N/A	N/A
#24	Bil CPT (R > L)	N	Normal	R DLFI, R PIL, R FOp, R POp	D	R FOp	2	No (confirmed R FOp hypothesis and option D)	N/A	N/A	N/A	N/A
#25	R CPT	**Y**	R F HypoM	R DLFS, R DLFI, R FSM	B	R FSM	2	No (confirmed SEEG plan)	R InsA	N/A	N/A	N/A
#26	R FT and F midline	**Y**	R T mesial HypoM	R TL, R TM, R TB	A	R TB; R TM	2	No (confirmed option A)	N/A	R ATL + AH	HS	1
#27	R FT	**Y**	Normal	R FOp, R TOp, R ObF, R TL, R TB	B	R InsP, R TB	3	SEEG plan: (+) 1 electrode in R InsP	R TS gyrus + R InsP	N/A	N/A	N/A
#28	R FCT and L T	**Y**	Normal	R TM, R TB, R TL, R TOp, R FOp	B	L CingA, R TB	3	B –> D (HD-EEG: L CingA cluster, included in the modified SEEG plan	N/A	N/A	N/A	N/A
#29	L FT	**Y**	L FPT HypoM	L FP, L FSM, L DLFS, L ObF, L CingA	B	L CingA	2	No (confirmed SEEG plan)	L CingA + L FM gyrus	L CingA + partial FM gyrus cortectomy	No definite FCD	N/A (<1 year)

8 years with the onset of daily focal seizures characterized by a forced left head and eye deviation with preserved alertness, followed by an ipsilateral painful sensation in the neck. Several ASMs were tried (VPA, CBZ, TPM, LEV, CLN, PER, LCM, BRV), failing to achieve adequate seizure control. At the time of the presurgical work-up, the patient reported a mean frequency of one focal seizure per day while taking two ASMs at the maximum tolerated doses. She also complained of very frequent cephalic auras, such as dizziness and headache. Evolution from focal into bilateral tonic-clonic seizures was exceptional and the last episode was in young adulthood. Neurological examination was normal. The neuropsychological evaluation revealed below-average intellectual functioning with impaired attention and episodic memory and poor performances in verbal fluency tasks, all indicating a frontal lobe dysfunction. LTEM showed a slower background activity in the right fronto-parietal region. Nine seizures were recorded with non-localizing ictal EEG onset and bilateral spread of rhythmic epileptiform discharges in the frontal and centro-parietal areas during seizure progression. HD-EEG was performed with the aim of lateralizing rapidly bilateral ictal discharges but the patient did not present any seizure during a 24-hours recording. 3T-brain MRI and VBM analysis did not reveal any convincing structural abnormality. FDG-PET showed a discrete hypometabolic area on the right mesial temporal region. The patient was included in the study and automated interictal ESI was performed both on LD-LTEM and HD-EEG recording. Successively, during an epilepsy surgery meeting, the case was discussed by the MDT, blinded to ESI results. The following hypotheses about EZ location were formulated: right superior frontal gyrus (1st hypothesis) and right dorsolateral superior frontal gyrus (2nd hypothesis). After a first discussion without ESI results, it was proposed to complete the work-up with additional investigations, including functional MRI (fMRI), MEG and ictal SPECT to map the eloquent cortex and better localize the SOZ. Thereafter, ESI results were presented at the same meeting and the MDT was asked to interpret them and reformulate hypotheses about EZ location and management decision, integrating at this time ESI data with the overall clinical reasoning.

ESI results showed one major cluster pointing in the right thalamus with bilateral mesial cortex involvement (Fig. 3A). This localization was considered to represent a non-epileptic cluster of physiological sleep activity (K-complexes) and the results were classed as discordant with the presurgical evaluation. Therefore, in this case, ESI neither corroborated the EZ location hypotheses nor changed the further clinical management.

In a second step, the patient underwent additional investigations as requested by the MDT. MEG and ictal SPECT provided strong arguments for a right frontal origin with a SOZ identified in the right superior frontal gyrus (SFG). Surgery guided with intraoperative electrocorticography (ECoG) was performed. The invasive EEG showed near-continuous polyspikes interrupted by low-voltage fast rhythmic activity in the posterior part of the right SFG propagating to the ipsilateral middle frontal gyrus (MFG) and sparing the precentral gyrus. The EEG pattern was highly suggestive of focal cortical dysplasia (Fig. 3B). Partial (posterior) resection of the right SFG and MFG disconnection were realized, leading to an attenuation of the epileptic activity on the intraoperative ECoG recording (Fig. 3C). Postoperatively, no motor complications were observed despite the proximity of the resection cavity to the primary motor cortex. The postoperative brain MRI is shown in Fig. 3D. The patient experienced a transient, spontaneously remitting, episode of non-epileptic complex visual hallucinations (Charles Bonnet syndrome). Histopathology confirmed the presence of an FCD type IIa. At the last postoperative follow-up (3 years and a half), the patient has no more focal seizures since surgery but auras are still present even if significantly less frequent (ILAE class II).

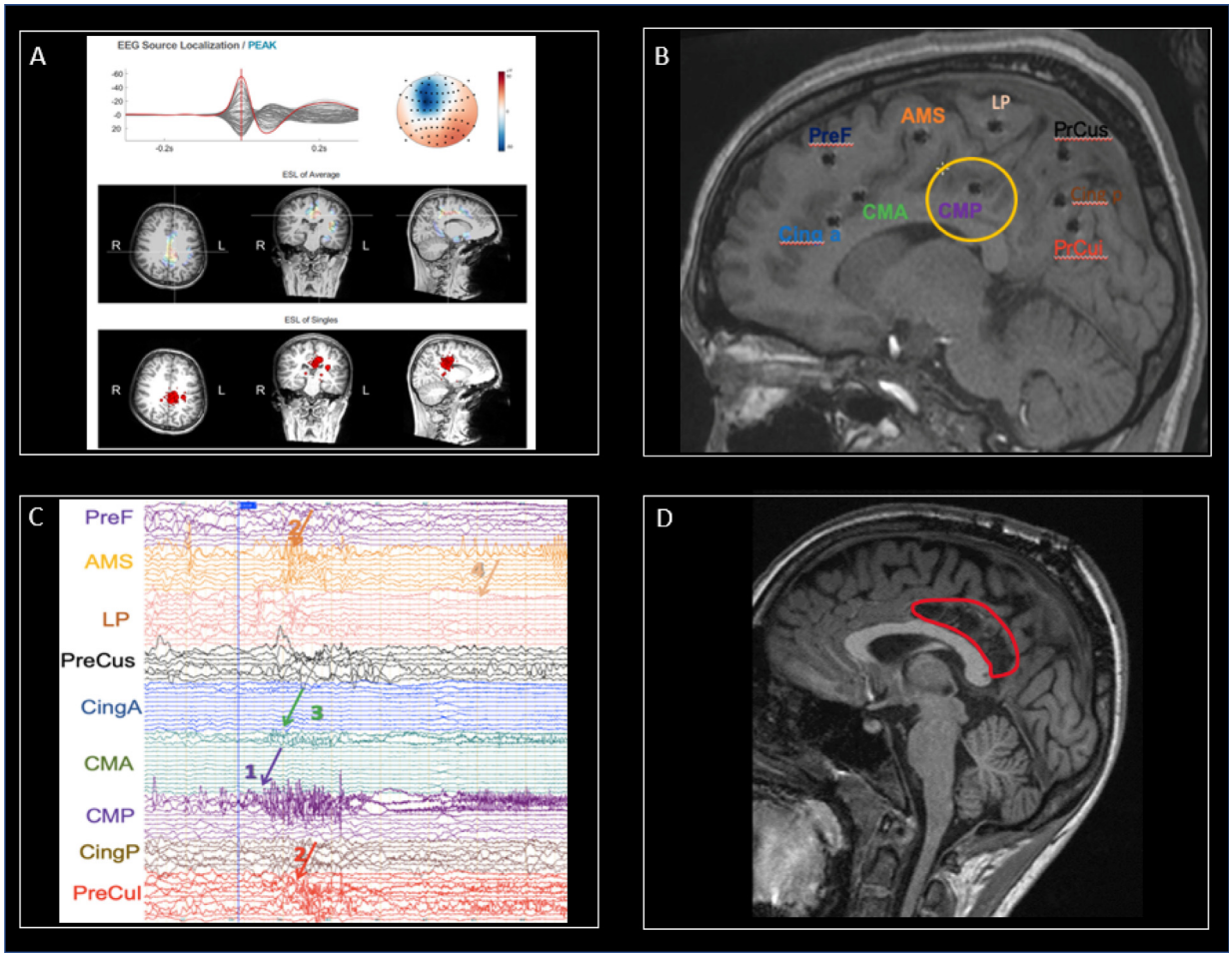

Fig. 2. Case-study 1. A: Results of automated ESI of the first (in red) cluster, at the peak of the averaged waveform (maximum localized at the crosshair), and of the individual spikes in the cluster. Note that both the maximum of the averaged waveform, and the majority of the individual spikes (red circle) indicate a source in the left middle/posterior cingulate cortex, which is in concordance with the SEEG-SOZ and the resection site. ESI results of the other clusters and at half-rise time are similar and are not shown there; **B:** Modified SEEG plan suggested by ESI results, including an additional depth electrode (CMP), to cover the middle/posterior cingulate cortex (yellow circle); **C:** SEEG recording showing a seizure with clear onset of ictal discharges in the CMP electrode (violet arrow), followed by rapid and multidirectional propagation to AMS (dark yellow arrow), Precui (red arrow) and CMA (green arrow); **D:** Postoperative MRI showing a limited posterior cingulate cortectomy and sparing of the front half. Margins of resection are bordered in red. ESI cluster is included in the resection zone. The patient is seizure-free (ILAE class I) at 2-year postoperative follow-up. CingA: anterior cingular cortex; CMA: anterior/middle cingular cortex; CMP: middle/posterior cingular cortex; CingP: posterior cingular cortex; PreF: prefrontal; AMS: supplementary motor cortex; LP: paracentral lobule; PrCus: precuneus (superior part); PrCui: precuneus (inferior part).

4. Discussion

In this prospective study, we addressed the diagnostic added value of automated ESI in the presurgical evaluation of MRI-negative patients, which represent the most challenging cases. We found that an automated ESI analysis (Epilog PreOp) of interictal epileptiform discharges (IEDs), both on LD-EEG (recorded during LTEM) and on HD-EEG (recorded as additional investigation in selected patients), followed by clinical interpretation, provided contributive, non-redundant information that changed the management plan in about 40% of our cohort. This is quite similar to the impact of manual ESI that was found to provide significant information in one-third of unselected patients (MRI-negative, MRI-positive, TLE, and ETLE) with refractory focal epilepsy [12]. Moreover, the contribution provided by ESI is non-inferior to what has been recently found in a prospective MSI (Magnetic Source Imaging) study [25]. Currently, MEG remains an extremely expensive and, for this reason, poorly diffused technique while EEG and MRI are compulsory elements in the presurgical evaluation, thus the input data for ESI are available in all centers.

In our study, most of the patients (75%) in which automated ESI analysis modified the initial clinical management, had a change related to the intracranial recording plan: relocation of the depth electrodes and/or implantation of additional electrodes. Moreover, the change in the other quarter of patients was somehow related to invasive recordings: in 2 patients in which SEEG was initially planned, additional non-invasive investigations were indicated to better define the EZ prior to implantation, and in one patient who otherwise would have been stopped in the presurgical evaluation, an invasive recording was recommended, after ESI. These findings are in line with the results of a previous study, in which a percentage as high as 85.7% of patients with contributive manual ESI, had a change in clinical management related to invasive recording procedures [12]. Amongst patients in whom automated ESI modified the clinical decision, intracranial recordings confirmed the localization of the ESI at a sublobar level in 75%. Similar results (69%) were observed in the study of Foged et al. using a manual ESI analysis [12]. When compared with the whole cohort, the SEEG-ESI sublobar concordance dropped to 50% in patients in whom ESI was concordant with presurgical evaluation but did

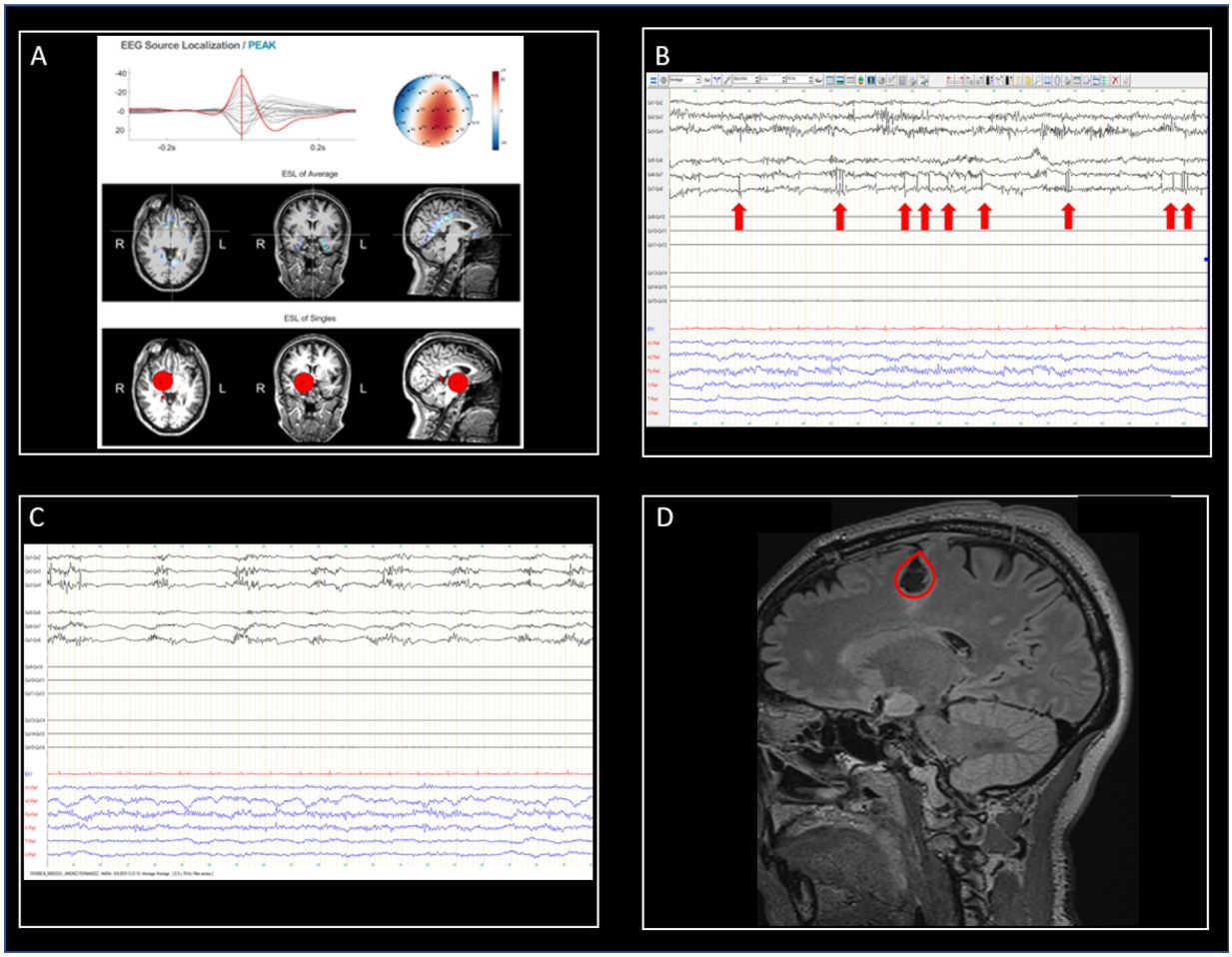

Fig. 3. Case-study 2. A: Results of automated ESI of the first (in red) cluster, at the peak of the averaged waveform (maximum localized at the crosshair), and of the individual spikes in the cluster. Note that both the maximum of the averaged waveform, and the majority of the individual spikes (red circle) indicate a source in subcortical structures (namely, the right thalamus) with bilateral mesial cortical involvement. The automatically detected spikes and corresponding ESI cluster were interpreted by the MDT as the expression of sleep-related physiological activity (K-complexes) and therefore ESI results were classed as discordant; **B**: Intraoperative electrocorticography (ECoG) was realized during the surgical procedure to guide the resection. Near-continuous polyspikes (red arrows) were observed in the posterior part of the right superior frontal gyrus (Grid 7–8) propagating to the ipsilateral middle frontal gyrus (Grid 3–4) and sparing the precentral gyrus (Grid 1–2). The EEG pattern was highly suggestive of focal cortical dysplasia. Note that the epileptic activity is completely overlooked on the concomitant scalp EEG (on the bottom); **C**: Partial (posterior) resection of the right superior frontal gyrus and middle frontal gyrus disconnection were realized, leading to an attenuation of the epileptic activity on the intraoperative ECoG recording. Note the suppression of periodic polyspikes, replaced by a slow-wave activity, indicating the resection of dysplastic cortical tissue; **D**: Postoperative brain MRI showing the surgical cavity. Margins of resection are bordered in red. Despite the proximity to the motor cortex, no major complications were noted postoperatively. Histopathology revealed an FCD type IIa. The patient is ILAE class 2 (only auras, no more seizures since surgery) with a postoperative follow-up of 3.5 years.

not lead to a change in management and ESI was even less performant in patients with discordant results. These findings highlight the importance of ESI clinical interpretation in the context of the multimodal evaluation and suggest that clinically contributive ESI results may be associated with a higher concordance with SEEG-SOZ location.

So far, a small number of patients in our cohort have been operated on and have more than one-year postoperative follow-up. The reasons for that are the expected high number of patients rejected for surgery in the study population and the delay in performing invasive recording prior to surgery due to COVID-19 pandemics and relative hospital reorganization. However, using the resection site and the postoperative outcome as the "gold standard", amongst patients in whom ESI changed the clinical management and with the identified EZ included in the resection zone, 80% are seizure-free (ILAE class 1) with a mean follow-up of 18 months. Even though the numbers are too low for an accurate statistical analysis, there was a trend toward a better surgical outcome in those patients with contributive ESI results. This relatively high proportion of patients with good surgical outcome is probably due to the general reluctance to operate on patients with unidentified brain lesions and the stricter selection of MRI-negative cases receiving epilepsy surgery. In the study of Spinelli et al., the authors investigated the accuracy of semiautomatic interictal ESI analysis (SAEA) on LTEM (with 37 scalp electrodes) in 40 patients undergoing curative epilepsy surgery and presenting with at least 2-years of follow-up. 13/40 included patients were MRI-negative (32.5%). The overall diagnostic accuracy of SAEA for localizing the epileptogenic focus was 75%, leading to an odds ratio (OR) of 11.5 to become seizure-free if the source was included in the resection volume ($p < .05$). For MRI-negative only patients ($n = 13$), the authors found an even higher accuracy of the technique compared to the entire group (84.6% vs 75%) and an increased probability to have a good surgical outcome if the ESI source was included in the resection zone (OR = 19) [26].

Previous studies showed that HD-ESI, with a variable number of electrodes, ranging from 64 up to 256, is more accurate than LD-ESI, in relation to the higher spatial sampling of scalp electrodes than the standard 19–25 electrode LD-EEG montage [8,27]. However, the duration of HD-EEG is typically much shorter than the

LD-EEG, derived from LTEM, which leads to a lower number of epileptic abnormalities recorded by HD-EEG. In our study, a proportion of about one-third of the cohort had both LD and HD-EEG recordings. HD-EEG was performed using 76 manually glued scalp electrodes and with adequate duration of recording (minimum 16 hours - maximum 48 hours) to achieve the best compromise between spatial resolution and length of the investigation, including overnight recording, essential to capture a sufficient number of interictal epileptic abnormalities (IEDs). In a recent study, Heers et al. evaluated the added value of semi-automated and automated detection of IEDs for ESI in a prospective head-to-head comparison of LTEM and HD-EEG against the gold standard of visual inspection during presurgical diagnostics. Semiautomated and automated detections of IED types in HD-EEG were significantly concordant with visually identified IED types in LTEM, only when IED types with more than 50 detected single IEDs were selected. The threshold of 50 detected IED in HD-EEG was reached in only half of the 52 patients of their cohort, using a 256-electrode EEG cap and with a mean duration of the recording of 193 min (±274 min) [28]. Indications to perform HD-EEG in 9 patients of our cohort were in line with current clinical practice [29]. In these patients, HD-ESI results did not add any useful information, leading to a change in the management plan, more often than LD-ESI results only. Clusters of spikes appeared to be more restricted on HD-ESI compared to LD-ESI but with a substantial sublobar concordance. In the study of Foged et al. using a manual ESI on both LD-EEG and HD-EEG (based on 90–120 min recordings with 256-electrodes) for all included patients, the authors found that management changes were more often based on HD-ESI than LD-ESI, but the difference was not statistically significant [12]. We cannot exclude that with a larger number of patients in our cohort undergoing both techniques, the results would be different, with more contributive data provided by HD-ESI compared to LD-ESI. Moreover, the distance from the maximum concentration of the ESI cluster and the SOZ (identified by SEEG) is likely to be larger for LD-ESI compared to HD-ESI, but this was out of the scope of our study. Whenever available and to increase the diagnostic gain, one can analyze both datasets, combining the advantages of the high spatial sampling of HD-EEG and the long duration of the LD-EEG. However, there is increasing evidence that adequate diagnostic accuracy in EZ localization may be reached through LD-ESI, solely [16–18].

In our study, we aimed to focus on a selected epilepsy population (MRI-negative) which is generally smaller than the MRI-positive group but includes the most challenging and difficult-to-manage patients. During the study period, the proportion of MRI-negative patients we found was almost one-quarter (22%) of the whole population addressed for pre-surgical evaluation, in line with results largely reported in the literature [4,5]. As a direct consequence of this selection, ETLE was overrepresented in our cohort compared to TLE with a proportion of more than two third of all included patients. In fact, the proportion of MRI-negative patients presenting with electro-clinical features of ETLE is higher compared to TLE, in which a brain structural abnormality is more often detected [30,31]. Moreover, ETLE cases often require the whole armamentarium of presurgical diagnostic tools and they need invasive recordings to identify the EZ [31]. One-third of patients in our cohort were children. This is also not surprising since it is well known that the proportion of MRI-negative cases is higher in the pediatric age compared to adulthood. The ongoing myelination in developing brains makes boundaries between gray and white matter to be ill-defined on MRI scans and therefore can potentially "hidden" subtle cortical malformations such as dysplasia limited to one or few gyri [32].

In our study, we used a fully automated interictal ESI analysis, followed by clinical interpretation. Ictal ESI was not performed, despite its potential advantage and supposed better EZ localization [33]. However, the ictal ESI pipeline does not automatically detect seizures, and manual marking of the seizure onset by the clinician is still required. Moreover, the ictal ESI analysis shows the best performance on seizures with rhythmical patterns. Seizures starting with non-rhythmical patterns, such as high-voltage slow waves followed by voltage attenuation, electro-decremental flattening, or other non-rhythmical irregular activity, are more difficult to explore with ESI and are generally excluded from the analysis [17]. Taking into account the current limitations of ictal ESI, it is important to note the following general considerations regarding the type(s) of patients of our study population: i) visual interpretation of ictal scalp EEG remains challenging in ETLE due to the abundance of artifacts, the short duration of certain seizure types or their rapid propagation, making difficult to exactly define the seizure onset [34]; ii) children, especially the youngest ones, often present with non-rhythmical seizures (such as spasms or tonic/atonic seizures) and ictal abnormalities tend to rapidly diffuse over large brain zones and appear as multifocal or falsely generalized [35]. For these reasons, the interictal EEG and the related ESI analysis might provide sufficient and accurate data for a reliable indication of EZ location in this specific subset of patients. Additionally, several studies have shown that the localization of interictal spikes provides an excellent estimate of the SOZ. For this purpose, Mégevand and colleagues investigated whether interictal ESI provides valuable information on the SOZ in 38 patients with focal epilepsy who later underwent intracranial EEG monitoring. The authors measured the distance between the ESI maximum (i.e., the localization of the solution point with the maximal source amplitude at 50% of the rising phase of the spike) and the nearest intracranial electrodes in the SOZ and irritative zone (IZ, the source of interictal spikes). The resection of the region harboring the ESI maximum was then correlated to surgical outcome. The median distance from the ESI maximum to the nearest electrode involved in the SOZ was 17 mm (IQR 8–27). The IZ and SOZ colocalized in most patients (median distance 0 mm, IQR 0–14), supporting the notion that localizing interictal spikes is a valid surrogate for the SOZ, and there was no difference in accuracy among patients with temporal or extratemporal epilepsy. In 32/38 patients who underwent resective surgery, including the ESI maximum in the resection zone was correlated with favorable postoperative outcome ($p = 0.03$) [36].

Despite the potential application of ESI in clinical practice, it is important to emphasize that the clinicians integrating ESI into the presurgical evaluation need to know the limitations of this method [37]. ESI methods using inverse models are underdetermined and the images are estimates. Hence, ESI results cannot be interpreted as exact spots of the EZ, but rather as sublobar localizations of the assumed origin of the epileptic EEG activity [37].

Limitations of this study are the small sample size and the relatively low number of patients undergoing confirmatory SEEG and/or surgery in the 3 subgroups. This prevented us to assess the diagnostic accuracy of the technique using sensitivity and specificity measures, according to the definitions widely used in studies on presurgical evaluation [24]. Additionally, we did not systematically perform HD-EEG in all patients, limiting the possibility of comparisons between LD-ESI and HD-ESI. As a consequence, results cannot be generalized. However, patients were prospectively enrolled and accurately selected to avoid recruitment bias.

In addition, our study was monocentric. While this undeniably limits the number of eligible patients, on the other hand, it entails a greater homogeneity and reproducibility of the results. All patients underwent the same presurgical work-up and were evaluated by the same MDT, thus avoiding divergent interpretations in relation to technical and/or expertise disparities between different centers. Despite its limitations, our study reflects the real clinical practice

in which physicians deal with challenging patients and have to include new techniques in their diagnostic process, avoiding both underutilization and overinterpretation of the results.

5. Conclusions

Automated ESI has a clinical added value as much as manual ESI, which is so far the benchmark, but it does not require additional specific expertise in data post-processing. This advantage could lead to wider use of ESI in the centers providing a presurgical evaluation for refractory epilepsy. The major contribution of ESI concerns the management of invasive recordings, provided that ESI results are integrated into the whole multimodal evaluation and clinically interpreted. Larger multicenter studies with uniformity in the technical equipment and expertise among participating centers are needed to confirm our results.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PvM is co-founder and CTO of Epilog NV. AGB is an Operations Engineer of Epilog NV. The remaining authors have no potential conflicts of interest to be disclosed.

Acknowledgements

The research work was supported by Fond de Recherche Clinique (Cliniques Universitaires Saint-Luc, Brussels, Belgium) and Queen Elisabeth Medical Foundation for Neurosciences is a Belgian non-profit organization that support clinical research in the field of neurosciences (https://www.fmre-gske.be/pages/en/actual.html).

Cliniques Universitaires Saint-Luc and Centre Hospitalier Neurologique William Lennox are part of the Brussels Rare and Complexes Epilepsies (BRACE) Consortium, a full member of EpiCARE.

References

[1] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia 2010;51:1069–77. https://doi.org/10.1111/j.1528-1167.2009.02397.x.

[2] Cramer SW, McGovern RA, Wang SG, Chen CC, Park MC. Resective epilepsy surgery: assessment of randomized controlled trials. Neurosurg Rev 2020. https://doi.org/10.1007/s10143-020-01432-x.

[3] Zijlmans M, Zweiphenning W, van Klink N. Changing concepts in presurgical assessment for epilepsy surgery. Nat Rev Neurol 2019;15:594–606. https://doi.org/10.1038/s41582-019-0224-y.

[4] Bien CG, Szinay M, Wagner J, Clusmann H, Becker AJ, Urbach H. Characteristics and surgical outcomes of patients with refractory magnetic resonance imaging-negative epilepsies. Arch Neurol 2009;66:1491–9.

[5] Duncan JS, Winston GP, Koepp MJ, Ourselin S. Brain imaging in the assessment for epilepsy surgery. Lancet Neurol. 2016 Apr;15(4):420-33. doi: 10.1016/S1474-4422(15)00383-X. Epub 2016 Feb 24. PMID: 26925532; PMCID: PMC6736670.

[6] Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non- lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res 2010;89(2–3):310–8. https://doi.org/10.1016/j.eplepsyres.2010.02.007. Epub 2010 Mar 15 PMID: 20227852.

[7] Juhász C, John F. Utility of MRI, PET, and ictal SPECT in presurgical evaluation of non-lesional pediatric epilepsy. Seizure 2020;77:15–28. https://doi.org/10.1016/j.seizure.2019.05.008. Epub 2019 May 11. PMID: 31122814; PMCID: PMC6842677.

[8] Brodbeck V, Spinelli L, Lascano AM, Wissmeier M, Vargas MI, Vulliemoz S, et al. Electroencephalographic source imaging: A prospective study of 152 operated epileptic patients. Brain 2011;134:2887–97. https://doi.org/10.1093/brain/awr243.

[9] Lascano AM, Perneger T, Vulliemoz S, Spinelli L, Garibotto V, Korff CM, et al. Yield of MRI, high-density electric source imaging (HD-ESI), SPECT and PET in epilepsy surgery candidates. Clin Neurophysiol 2016;127:150–5. https://doi.org/10.1016/j.clinph.2015.03.025.

[10] Sharma P, Scherg M, Pinborg LH, Fabricius M, Rubboli G, Pedersen B, et al. Ictal and interictal electric source imaging in pre-surgical evaluation: a prospective study. Eur J Neurol 2018;25:1154–60. https://doi.org/10.1111/ene.13676.

[11] Sharma P, Seeck M, Beniczky S. Accuracy of interictal and ictal electric and magnetic source imaging: A systematic review and meta-analysis 10. Front Neurol 2019. https://doi.org/10.3389/fneur.2019.01250.

[12] Foged MT, Martens T, Pinborg LH, Hamrouni N, Litman M, Rubboli G, et al. Diagnostic added value of electrical source imaging in presurgical evaluation of patients with epilepsy: A prospective study. Clin Neurophysiol 2020;131:324–9. https://doi.org/10.1016/j.clinph.2019.07.031.

[13] Brodbeck V, Spinelli L, Lascano AM. Electrical source imaging for presurgical focus localization in epilepsy patients with normal MRI. Epilepsia 2010;51:583–91.

[14] Abdallah C, Maillard LG, Rikir E, Jonas J, Thiriaux A, Gavaret M, et al. Localizing value of electrical source imaging: Frontal lobe, malformations of cortical development and negative MRI related epilepsies are the best candidates. Neuroimage Clin 2017;16:319–29. https://doi.org/10.1016/j.nicl.2017.08.009. PMID: 28856095; PMCID: PMC5565782.

[15] Mouthaan BE, Rados M, Barsi P, Boon P, Carmichael DW, Carrette E, et al. Current use of imaging and electromagnetic source localization procedures in epilepsy surgery centers across Europe. Epilepsia 2016;57:770–6. https://doi.org/10.1111/epi.13347.

[16] van Mierlo P, Strobbe G, Keereman V, Birot G, Gadeyne S, Gschwind M, et al. Automated long-term EEG analysis to localize the epileptogenic zone. Epilepsia Open 2017;2:322–33. https://doi.org/10.1002/epi4.12066.

[17] Vespa S, Baroumand AG, Ferrao Santos S, Vrielynck P, de Tourtchaninoff M, Feys O, et al. Ictal EEG source imaging and connectivity to localize the seizure onset zone in extratemporal lobe epilepsy. Seizure 2020;78:18–30. https://doi.org/10.1016/j.seizure.2020.03.001.

[18] Baroumand AG, van Mierlo P, Strobbe G, Pinborg LH, Fabricius M, Rubboli G, et al. Automated EEG source imaging: A retrospective, blinded clinical validation study. Clin Neurophysiol 2018;129:2403–10. https://doi.org/10.1016/j.clinph.2018.09.015.

[19] Baroumand AG, Arbune AA, Strobbe G, Keereman V, Pinborg LH, Fabricius M, et al. Automated ictal EEG source imaging: A retrospective, blinded clinical validation study. Clin Neurophysiol 2022;141:119–25. https://doi.org/10.1016/j.clinph.2021.03.040. Epub 2021 Apr 27 PMID: 33972159.

[20] El Tahry R, Santos SF, Vrielynck P, de Tourtchaninoff M, Duprez T, Vaz GR, et al. Additional clinical value of voxel-based morphometric MRI post-processing for MRI-negative epilepsies: a prospective study. Epileptic Disord 2020;22(2):156–64. https://doi.org/10.1684/epd.2020.1152. PMID: 32310136.

[21] Bernasconi A, Cendes F, Theodore WH, Gill RS, Koepp MJ, Hogan RE, et al. Recommendations for the use of structural magnetic resonance imaging in the care of patients with epilepsy: A consensus report from the International League Against Epilepsy Neuroimaging Task Force. Epilepsia 2019;60(6):1054–68. https://doi.org/10.1111/epi.15612. Epub 2019 May 28 PMID: 31135062.

[22] Huppertz HJ, Grimm C, Fauser S, Kassubek J, Mader I, Hochmuth A, et al. Enhanced visualization of blurred gray-white matter junctions in focal cortical dysplasia by voxel-based 3D MRI analysis. Epilepsy Res. 2005 Oct-Nov;67(1-2):35-50. doi: 10.1016/j.eplepsyres.2005.07.009. Epub 2005 Sep 19. PMID: 16171974.

[23] Seeck M, Koessler L, Bast T, Leijten F, Michel C, Baumgartner C, et al. The standardized EEG electrode array of the IFCN. Clin Neurophysiol 2017;128:2070–7.

[24] Beniczky S, Aurlien H, Brøgger JC, Hirsch LJ, Schomer DL, Trinka E, et al. Standardized computer-based organized reporting of EEG: SCORE – second version. Clin Neurophysiol 2017;128:2334–46. https://doi.org/10.1016/j.clinph.2017.07.418.

[25] Duez L, Tankisi H, Hansen PO, Sidenius P, Sabers A, Pinborg LH, et al. Electromagnetic source imaging in presurgical workup of patients with epilepsy: A prospective study. Neurology 2019;92:e576–86. https://doi.org/10.1212/WNL.0000000000006877.

[26] Spinelli L, Baroumand AG, Vulliemoz S, Momjian S, Strobbe G, van Mierlo P, et al. Semiautomatic interictal electric source localization based on long-term electroencephalographic monitoring: A prospective study. Epilepsia 2022. https://doi.org/10.1111/epi.17460. Epub ahead of print. PMID: 36346269.

[27] Lantz G, Grave de Peralta R, Spinelli L, Seeck M, Michel CM. Epileptic source localization with high density EEG: how many electrodes are needed? Clin Neurophysiol 2003;114:63–9.

[28] Heers M, Böttcher S, Kalina A, Katletz S, Altenmüller D-M, Baroumand AG, et al. Detection of interictal epileptiform discharges in an extended scalp EEG array and high-density EEG—A prospective multicenter study. Epilepsia 2022;63:1619–29. https://doi.org/10.1111/epi.17246.

[29] Stoyell SM, Wilmskoetter J, Dobrota MA, Chinappen DM, Bonilha L, Mintz M, et al. High-Density EEG in Current Clinical Practice and Opportunities for the Future. J Clin Neurophysiol 2021;38(2):112–23. https://doi.org/10.1097/WNP.0000000000000807. PMID: 33661787; PMCID: PMC8083969.

[30] Carne RP, O'Brien TJ, Kilpatrick CJ, MacGregor LR, Hicks RJ, Murphy MA, et al. MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. Brain 2004;127(Pt 10):2276–85. https://doi.org/10.1093/brain/awh257. Epub 2004 Jul 28 PMID: 15282217.

[31] Hong KS, Lee SK, Kim JY, Lee DS, Chung CK. Pre-surgical evaluation and surgical outcome of 41 patients with non-lesional neocortical epilepsy. Seizure 2002;11(3):184–92. https://doi.org/10.1053/seiz.2001.0616. PMID: 12018962.

[32] Dorfmüller G, Ferrand-Sorbets S, Fohlen M, Bulteau C, Archambaud F, Delalande O, et al. Outcome of surgery in children with focal cortical dysplasia younger than 5 years explored by stereo-electroencephalography.

Childs Nerv Syst 2014;30(11):1875–83. https://doi.org/10.1007/s00381-014-2464-x. Epub 2014 Oct 9 PMID: 25296549.
[33] Megevand P, Seeck M. Electroencephalography, magnetoencephalography and source localization: their value in epilepsy. Curr Opin Neurol 2018;31:176–83. https://doi.org/10.1097/WCO.0000000000000545.
[34] Foldvary N, Klem G, Hammel J, Bingaman W, Najm I, Lüders H. The localizing value of ictal EEG in focal epilepsy. Neurology 2001;57(11):2022–8.
[35] Taussig D, Dorfmüller G, Fohlen M, Jalin C, Bulteau C, Ferrand-Sorbets S, et al. Invasive explorations in children younger than 3 years. Seizure 2012;21 (8):631–8. https://doi.org/10.1016/j.seizure.2012.07.004. Epub 2012 Jul 25 PMID: 22835665.
[36] Mégevand P, Spinelli L, Genetti M, Brodbeck V, Momjian S, Schaller K, et al. Electric source imaging of interictal activity accurately localises the seizure onset zone. J Neurol Neurosurg Psychiatry 2014;85(1):38–43. https://doi.org/10.1136/jnnp-2013-305515. Epub 2013 Jul 30 PMID: 23899624.
[37] Kaiboriboon K, Lüders HO, Hamaneh M, Turnbull J, Lhatoo SD. EEG source imaging in epilepsy–practicalities and pitfalls. Nat Rev Neurol 2012;8:498–507. https://doi.org/10.1038/nrneurol.2012.150.