COMPLEX SCENARIOS OF DRUG-RESISTANT EPILEPSIES: DIAGNOSTIC CHALLENGES AND NOVEL THERAPEUTIC OPTIONS

EDITED BY: Giuseppe Didato, Taylor J. Abel, Emma Losito and Valentina Chiesa
COORDINATED BY: Ricardo Amorim Leite
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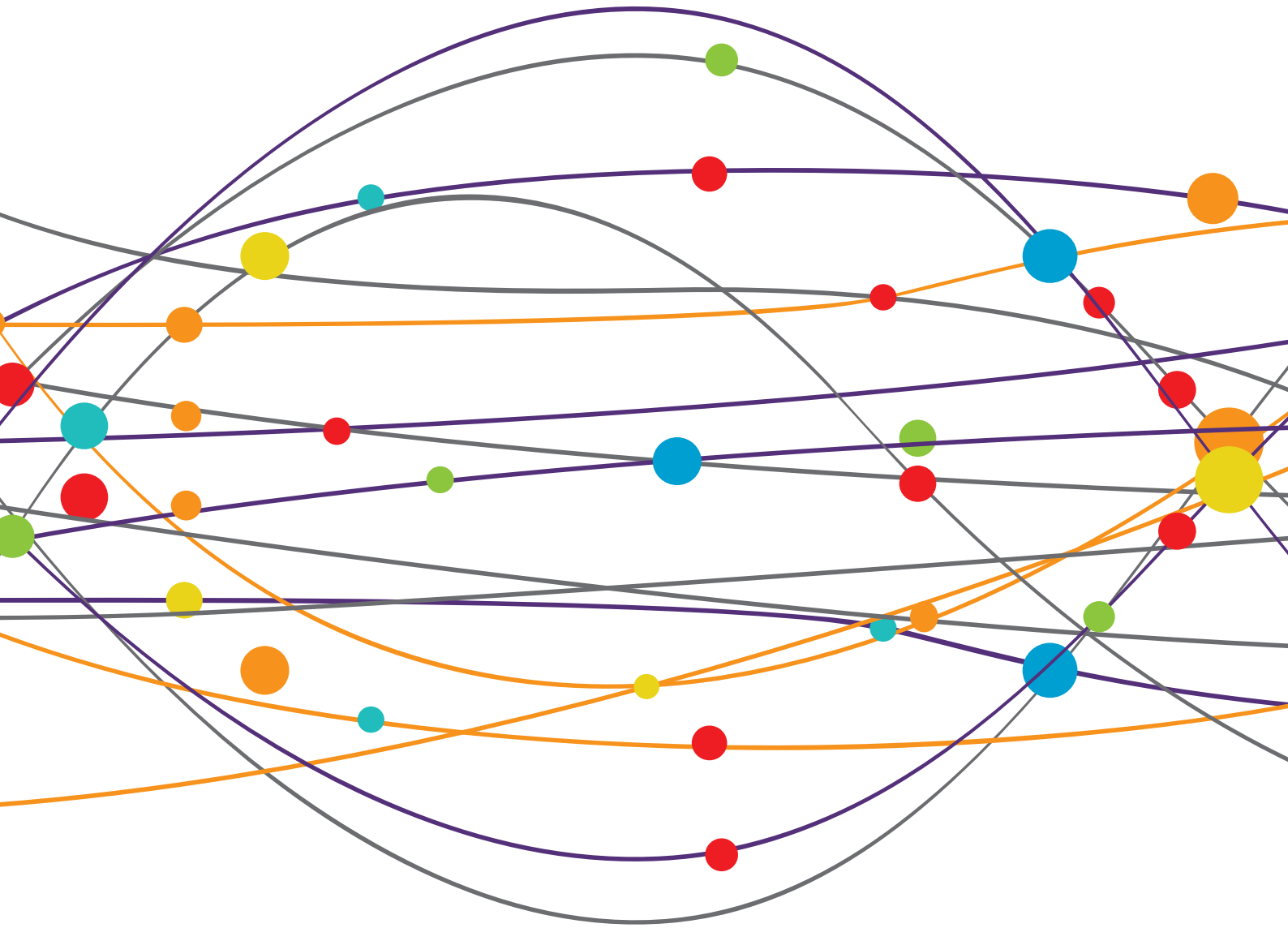

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COMPLEX SCENARIOS OF DRUG-RESISTANT EPILEPSIES: DIAGNOSTIC CHALLENGES AND NOVEL THERAPEUTIC OPTIONS

Topic Editors:
Giuseppe Didato, Epilepsy Unit, Carlo Besta Neurological Institute (IRCCS), Italy
Taylor J. Abel, University of Pittsburgh, United States
Emma Losito, Centre de référence des épilepsies rares, Département de neurologie pédiatrique, Hôpital Necker-Enfants Malades, APHP, France
Valentina Chiesa, Epilepsy Center, Santi Paolo e Carlo Hospital, Italy

Coordinator Editor:
Ricardo Amorim Leite, University of Iowa, Iowa City, United States

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EDITORIAL
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Editorial: Complex Scenarios of Drug-Resistant Epilepsies: Diagnostic Challenges and Novel Therapeutic Options

Giuseppe Didato[1]*, *Valentina Chiesa*[2], *Emma Losito*[3], *Ricardo Amorim Leite*[4] and *Taylor J. Abel*[5,6]

[1] Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, [2] Epilepsy Center, San Paolo Hospital, ASST Santi Paolo e Carlo, Milan, Italy, [3] Department of Clinical Neurophysiology, Assistance Publique - Hôpitaux de Paris, Necker-Enfants Malades Hospital, Paris, France, [4] Video-EEG Unit, Psychiatry Institute of São Paulo University—USP, São Paulo, Brazil, [5] Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, United States, [6] Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, United States

Keywords: drug-resistant epilepsy, epilepsy surgery, non-resective epilepsy surgery, multifocal epilepsy, neurostimulation

Editorial on the Research Topic

Complex Scenarios of Drug-Resistant Epilepsies: Diagnostic Challenges and Novel Therapeutic Options

Epilepsy affects about 70 million people worldwide and in 60% of these patients the origin of epileptic seizures is due to a localized (focal) alteration of the brain. In about 30% of patients with focal epilepsy, drug treatment is ineffective, a condition defined by the International League Against Epilepsy (ILAE) as drug-resistant epilepsy (DRE) (1).

A significant proportion of patients with medically refractory focal epilepsy can benefit from a surgical treatment, which offers the chance of seizure remission in many cases or decrease in seizure frequency and severity (2, 3). The percentage of patients with epilepsy completely cured after surgery is about 70% for temporal lobe epilepsies (2–4), and can reach up to 90% in the case of some brain malformations and tumors (5, 6).

Unfortunately, in certain situations traditional epilepsy surgery approaches are not possible, which include bilateral or multifocal seizures, involvement of eloquent cortical areas, or with associated surgical comorbidities (7, 8). However, recent alternatives to traditional non-pharmacological treatments, other than resective surgery, are now a therapeutic option for these patients.

Recently, novel pre-surgical diagnostic methods and new surgical approaches have been developed. Further, a precise definition of the epileptogenic network can provide an opportunity for surgery in complex refractory epilepsies. For patients who are not good candidates for resective treatments, the evolution in neuromodulation devices and other non-resective surgical procedures also offer good chances of seizure control and improved quality of life (3, 9).

During pre-surgical evaluation for conditions such as multifocal or bitemporal epilepsy, periventricular nodular heterotopia (PNH), tuberous sclerosis complex (TSC), Rasmussen encephalitis, seizures arising from eloquent areas, the localization of the ictal onset zone encompasses diagnostic challenges that can be overcome by means of advanced neurophysiological and radiological methods. This can allow for the epileptogenic zone (EZ) identification of difficult-to-localize focal epilepsies (10, 11).

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Fernando Cendes,
State University of Campinas, Brazil

***Correspondence:**
Giuseppe Didato
giuseppe.didato@istituto-besta.it

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Furthermore, such complex forms of intractable focal epilepsies are challenges for resective epilepsy surgery. Therefore, recent enhancements in surgical techniques, such as laser interstitial thermal therapy (LiTT), magnetic resonance-guided focused ultrasound (MRgFUS), radiofrequency thermocoagulation (RF-THC), radiosurgery (cyber-knife, gamma-knife) can enable surgical treatment for these patients, targeting the EZ even when this is difficult to approach using classical surgical procedures. Moreover, these new techniques can minimize surgical risks, making surgery possible for patients who would otherwise not be candidates due to their comorbidities (3, 12–14).

For patients without possibility of surgical access to the primary EZ, neuromodulation therapies have been an option for several years. However, new developments in technologies and the increasing knowledge of the circuits involved in neuromodulation have expanded the accomplishment of these treatments. The main advanced neurostimulation technologies are Responsive Neurostimulation (RNS®), Deep Brain Stimulation (DBS) and Vagus Nerve Stimulation (VNS) (15–18).

In this Research Topic of Frontiers in Neurology, we have brought together experts in these new areas of epilepsy research, diagnosis, and treatment. This Research Topic provides a balanced collection of eight original research studies, four case reports, one review, and two perspective articles.

The first article, from Wu et al. (Chicago, USA), provides a systematic overview on the seizure outcome of stereotactic laser amygdalohippocampectomy in 30 consecutive patients with mesial temporal lobe epilepsy (mTLE). They demonstrate that scalp EEG findings (interictal regional slow activity on the side of surgery and/or non-lateralizing or contra-lateralizing seizure onset) strongly predicted seizure recurrence after surgery.

Consales et al. (Genoa, Italy), focus on other important indications for laser ablation. They report their experience with six pediatric cases of hypothalamic hamartomas, one case of TSC, and one case of dysembryoplastic neuroepithelial tumor, treated with magnetic resonance-guided laser interstitial thermal therapy (MR-gLiTT). Taken together, their data show that MR-gLiTT is a highly safe and effective procedure for these epilepsy conditions in children.

Welch et al. (Pittsburgh, USA), provide information on the effectiveness of RNS in a 16-year-old male with drug-resistant primary generalized epilepsy with convulsive and absence seizures. This case report demonstrates that bilateral RNS of the centromedian nuclei brought to a complete resolution of the baseline daily absence seizure activity, and to a significant decrease in convulsive seizures.

Ma et al. (China) contribute to the Research Topic describing the use of a new method, named spatio-temporal unifying tomography (STOUT), applied to magnetoencephalography (MEG) to locate a deep source in a patient with insular epilepsy. With this case study they demonstrate that MEG STOUT method can allow the epileptologist to perform a stereo-electroencephalographic (SEEG)-guided RF-THC operation in the event of deep sources, achieving a satisfactory therapeutic effect.

Dimova and Minkin (Sofia, Bulgaria) enrich this Research Topic reporting on a patient affected by a drug-resistant epilepsy involving limbic structures on the left side and associated to anti-GAD65 autoantibodies positivity. The authors describe how the patient benefited from a combination of immunotherapies and surgical treatment (selective amygdalectomy). This case report sheds light on the possibility to consider epilepsy surgery even in patients with complex etiologies.

Iimura et al. (Japan) add another contribution to this Research Topic illustrating how subtotal hemispherotomy dramatically improved epileptic spasms (ES) of a 3-month-old patient with Aicardi syndrome (AS). The authors provide intraoperative neurophysiological evidence as a possible explanation of the successful procedure. They hypothesized that electrocorticography HFOs and phase-amplitude coupling of HFOs and slow wave bands before and after subtotal hemispherotomy could be the biomarkers of efficacy of this surgical procedure in AS with ES.

In addition to the contribution given by the aforementioned authors with regard to possible surgical treatments in complex epilepsy cases, other authors have provided important inputs on new diagnostic procedures aimed at improving EZ localization in focal epilepsies.

The series of contributions to this Research Topic on implemented diagnostic methods in epilepsy opens with an original study by Bacon et al. (China). These authors compare two different tools for quantitative analysis of fluorodeoxyglucose positron emission tomography (FDG-PET) images: statistical parametric mapping (SPM) and its computational anatomy toolbox (SPM-CAT). They demonstrate that SPM-CAT is more efficient than SPM in localizing EZ for DRE. Therefore, this paper underlines the importance of quantitative analysis of FDG-PET images as an objective complementary tool to the visual assessment for EZ localization.

Müller et al. (Bern, Switzerland) highlight how quantitative EEG analysis can enhance the accuracy of identification of the brain tissue generating epileptiform events. They showed that non-linear intracranial EEG analysis may provide information relevant for surgery planning in temporal lobe epilepsy.

Ganti et al. (India) add to this section of the Research Topic their experience on seizure detection algorithms, especially aimed at improving the treatment of non-localizable epilepsies by targeting the thalamus for neuromodulation. They investigated the thalamograms obtained during SEEG evaluation for epilepsy surgery, using a tool based on temporal Generative Adversarial Networks (TGAN). The authors conclude that this approach can be applied to classify electrographic seizure onset patterns or develop patient-specific seizure detectors from implanted neuromodulation devices.

The section of the Research Topic dedicated to new diagnostic procedures for epilepsies continues with the original study of Irannejad et al. (USA) about mapping of the seizure onset zone (SOZ) with direct cortical stimulation (DCS) in TLE. They show that targeted mapping of SOZ in low amplitude fast activity patterns can better distinguish seizure generators (true responders) from hyperexcitable nodes that may be involved in early propagation.

Finally, this section of the Research Topic ends with the contribution of Suresh et al. (Canada). In their original research they demonstrate a negative association between intraoperative somatosensory evoked potentials amplitude and seizure reduction after VNS implantation. Therefore, they discuss a method for the identification of patients with DRE who are most likely to benefit from VNS.

While most contributions to this Research Topic have focused on surgical treatment or enhanced diagnostic procedures of complex focal epilepsies, three contributions tackle the issue of pharmacological therapy for drug-resistant epilepsies that are not eligible to surgery. Iannone et al. (Italy) describe efficacy and tolerability of add-on treatment with cannabidiol in drug-resistant patients with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS). In their systematic review article, Chin et al. (UK) discuss the need for further high-quality international consensus-based treatment guidelines for LGS, DS, and particularly for CDKL5 Deficiency Disorder. In their original research, Li et al. (China) analyze the treatment outcomes of newly diagnosed epilepsy and the risk factors for refractory epilepsy in a population of 466 adult patients. Finally, the last contribution is a perspective article by Ji et al. (China), who performed a meta-analysis on sodium valproate alone or in combination with topiramate (TPM) for treating DRE. They conclude that sodium valproate combined with TPM is more effective than sodium valproate alone.

CONCLUSION

In conclusion, this Research Topic embraces various aspects of DRE treatment and provides an up-to-date series of experts' opinions on advanced and new treatment options especially for more complex forms of DRE. Moreover, this article collection offers the possibility to increase the knowledge about unmet needs that might enhance DRE therapy. Finally, it stimulates the identification of new research areas to develop in the field of DRE.

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GD, VC, EL, RA, and TA edited the Research Topic. All authors contributed and validated the editorial.

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CASE REPORT
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Case Report: Responsive Neurostimulation of the Centromedian Thalamic Nucleus for the Detection and Treatment of Seizures in Pediatric Primary Generalized Epilepsy

William P. Welch[1], *Jasmine L. Hect*[2] *and Taylor J. Abel*[2,3]*

[1] Division of Pediatric Neurology, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [2] Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [3] Department of Bioengineering, University of Pittsburgh Swanson School of Engineering, Pittsburgh, PA, United States

Up to 20% of pediatric patients with primary generalized epilepsy (PGE) will not respond effectively to medication for seizure control. Responsive neurostimulation (RNS) is a promising therapy for pediatric patients with drug-resistant epilepsy and has been shown to be an effective therapy for reducing seizure frequency and severity in adult patients. RNS of the centromedian nucleus of the thalamus may help to prevent loss of awareness during seizure activity in PGE patients with absence seizures. Here we present a 16-year-old male, with drug-resistant PGE with absence seizures, characterized by 3 Hz spike-and-slow-wave discharges on EEG, who achieved a 75% reduction in seizure frequency following bilateral RNS of the centromedian nuclei. At 6-months post-implant, this patient reported complete resolution of the baseline daily absence seizure activity, and decrease from 3–4 generalized convulsive seizures per month to 1 per month. RNS recordings showed well-formed 3 Hz spike-wave discharges in bilateral CM nuclei, further supporting the notion that clinically relevant ictal discharges in PGE can be detected in CM. This report demonstrates that CM RNS can detect PGE-related seizures in the CM nucleus and deliver therapeutic stimulation.

Keywords: case report, responsive neurostimulation, drug-resistant epilepsy, centromedian nucleus, pediatric generalized epilepsy, absence seizures

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Edited by:
Mohd Farooq Shaikh, Monash University, Malaysia

Reviewed by:
Vikram Rao, University of California, San Francisco, United States
Ching Soong Khoo, National University of Malaysia, Malaysia

***Correspondence:**
Taylor J. Abel
abeltj@upmc.edu

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INTRODUCTION

Primary generalized epilepsy (PGE) accounts for ∼15–20% of all children diagnosed with epilepsy (1, 2). Of patients with PGE, 10–20% will meet criteria for drug-resistant epilepsy (3). Unfortunately, there are no FDA-approved neuromodulation treatment options for PGE. Absence seizures are commonly seen in patients with PGE in the form of behavioral arrest with impaired awareness, with concomitant variable motor or behavioral manifestations. Uncontrolled seizures are a significant source of morbidity in PGE, impacting development, academic performance, activities of daily living, and quality of life measures (4–7). Investigation and validation of neuromodulation treatment options for pediatric PGE are necessary to improve patient outcomes and quality of life.

Stimulation of the thalamic centromedian nucleus (CM) is associated with improved frequency and severity of generalized seizures in adult patients, including both deep brain (DBS) stimulation and responsive neurostimulation (RNS) system approaches (8, 9). There is supportive evidence for the use of deep brain stimulation (DBS) in pediatric epilepsy, although data is limited (10, 11). A limitation of DBS devices is that while they are able to deliver programmed stimulation in an open-loop system, they lack the functionality to record or respond to changes in brain activity and, therefore, cannot be programmed to deliver personalized therapy in response to patient-specific seizure patterns (12). The closed-loop RNS system has the functionality of recording and storing patient-specific neuronal activity and can be programmed to deliver stimulation in response to detected changes during seizure activity. RNS has been shown to be safe and effective in the treatment of drug-resistant epilepsy (13, 14). Here, we report the diagnostic utility and outcome of bilateral CMN thalamic RNS implantation in a single pediatric patient for the treatment of PGE.

PATIENT INFORMATION

A 16-year-old male diagnosed with childhood absence epilepsy (CAE) at 4 years of age presented for evaluation for uncontrolled seizures. At the time of diagnosis, he was an otherwise healthy and developmentally appropriate child with no family history of significant neurological disease or parental consanguinity. Genetic testing was not performed at our institution during his evaluation. Initial seizure semiology consisted of behavioral arrest, eye rolling, and variable impaired awareness, with rare progression to bilateral tonic-clonic seizure. Initial EEG captured typical absence seizures with correlating 3 Hz spike-and-slow-wave discharges, as well as interictal high-amplitude spike- and polyspike-and-slow-wave discharges. Repeat EEG over several years remained consistent with this diagnosis. Seizures proved resistant to treatment with ethosuximide, lamotrigine, topiramate, clobazam, valproate, and the modified Atkin's diet. At 12 years of age, repeat brain MRI detected a lesion in the right amygdala suggestive of dysembryoplastic neuroepithelial tumor (DNET). Repeat routine EEG while on medications again demonstrated generalized spike- and polyspike-and-slow-wave discharges and typical absence seizures, with new findings of independent bilateral centroparietal and centrotemporal epileptiform discharges. Additionally, a focal impaired awareness seizure with temporal semiology was captured on prolonged EEG which was electroclinically distinct from his typical absence seizures, with onset characterized by rhythmic theta activity over the left temporal head region and clinical accompaniment speech difficulty, confusion, and oral automatisms lasting over 9 min.

Due to new neuroradiologic and EEG findings, phase 2 pre-surgical evaluation was pursued. Fourteen sEEG electrodes were implanted targeting the right temporal lobe (including the right amygdala lesion) and cingulate, and left hippocampus. Prior to and during weaning of anti-seizure medications, numerous typical absence seizures were captured. Electrographic onset was not localizable, with diffuse onset of 2.5–3.0 Hz spike-wave morphology throughout the intracranial array, including the bilateral hippocampal electrodes. Interestingly, independent rare bursts of 2.5–3.0 Hz spike-wave discharges were detected in peri-lesional contacts in the right amygdala, but never evolving to electrographic seizures.

Robot-assisted stereotactic biopsy of the amygdala lesion was performed at the time of sEEG electrode removal, which was negative due to small sample size. However, given the progression of the lesion and presence of peri-lesional epileptiform activity, stereotactic laser ablation (SLA) of the lesion was performed with simultaneous redo stereotactic biopsy. The redo biopsy was consistent with a low grade glioneuronal neoplasm, however given the small volume of the biopsy, a more specified diagnosis (e.g., DNET was not achieved). A complete ablation of the lesion was achieved. After surgical recovery, the patient continued to have daily typical absence seizures, with occasional progression to bilateral tonic-clonic seizure, despite continuation of prior anti-seizure medications. Given continuance of seizures despite best medical management, vagus nerve stimulation (VNS) was discussed with the family, who were not interested in VNS. CM RNS was thus offered to the family and after discussion of the risks and potential benefits the patient and family elected to proceed.

THERAPEUTIC INTERVENTION

The patient was taken to the operating room for implantation of bilateral CM RNS electrodes. CM targeting was performed using indirect and direct targeting as previously described (10, 15–17). Briefly, MP2RAGE inversion images were merged to a preoperative thin-cut (1 mm) CT angiogram using the ROSA platform. Standard entry points near the coronal suture that would allow an avascular trajectory to the target were selected. Four-contact depth electrodes, with 3.5-mm spacing, were implanted with these trajectories using the ROSA robot (registered via bone fiducials), following previously published methods (18). Intraoperative O-Arm CT scan was used for both registration to bone fiducials and confirmation of final electrode lead position in the CM. RNS-electrodes were automatically pre-localized in native & template space using Lead-DBS software (19) (https://www.lead-dbs.org) and visualized in reference to thalamic nuclei defined by The Thalamus Atlas (20), see **Figure 1**. The patient recovered and was discharged home on postoperative day 1.

After implantation, the device was programmed to record scheduled electrocorticography (ECoG), and a broad detector was programmed (75% power change). Multiple ECoG recordings were saved for patient/caregiver event identification (via magnet swipe) over a period of 4 weeks postop. Review of saved ECoG in the Patient Data Management System (PDMS) revealed well-formed 3 Hz spike-wave discharges in the bilateral thalamic contacts, with highest amplitudes in the distal contacts bilaterally (**Figure 2**). Four weeks after implantation, the detection pattern was adjusted to reliably detect ictal discharges (channel 1: bandpass 2.0–41.7 Hz, amplitude threshold 4%, minimum duration 0.38 s; channel 3: bandpass

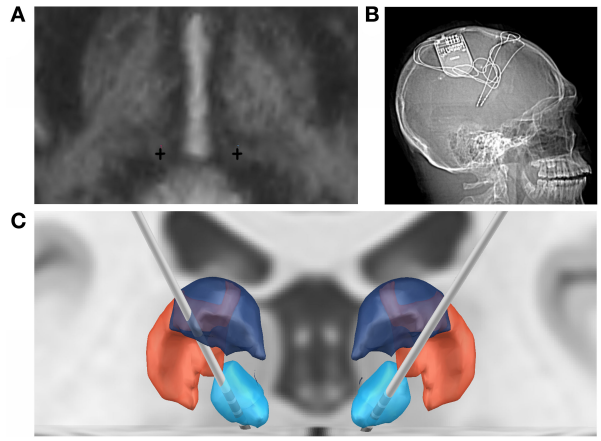

FIGURE 1 | Bilateral RNS CMN implantation. **(A)** Direct targeting of the bilateral CMN (crosses) in AC-PC orientation. **(B)** Post-implant x-ray of RNS system. **(C)** Coronal 3D reconstruction of bilateral RNS implantation targeting the CMN (blue), in relation to the posterior part of the ventral posterolateral nucleus (VPLp; red) and posterior dorsal part of the ventral lateral nucleus (VLpd; purple).

2.0–25 Hz, amplitude threshold 5%, minimum duration 0.38 s). Bipolar stimulation of most distal contacts (contact 1 and 2 bilaterally) was enabled at 0.2 $\mu C/Cm^2$ (0.2 mA, 125 Hz, 160 μS for 5,000 ms), in response to detected 3 Hz spike-wave discharges in these channels. Low charge density was used initially due to patient reporting non-painful left arm paresthesia during stimulation. Additionally, ECOG recordings captured prolonged absence seizure and generalized tonic-clonic seizure activity, see **Figure 3**.

FOLLOW-UP AND OUTCOMES

One month after turning on stimulation, the patient reported improved seizure frequency, although continued to experience multiple weekly absence seizures. At that time, our patient elected to increase stimulation and was willing to tolerate mild left arm paresthesia along with this this increase to 0.4 $\mu C/Cm^2$ (0.4 mA, 125 Hz, 160 μS for 5,000 ms). These paresthesias resolved within a few days of stimulation. Changes to other stimulation parameters were not considered due to the fact that this patient's symptoms were mild and temporary, but may be considered in other cases (21).

At most recent follow-up 6-months post-implant, the patient and family reported no noticeable absence seizures and reported 1 generalized convulsive seizure per month, improved from previous baseline of 3 to 4 per month. Our patient is tolerating increased stimulation parameters with a charge density of 1.5 $\mu C/Cm^2$ (1.5 mA, 125 Hz, 160 μS for 5,000 ms) without side effects, including resolution of left arm paresthesia. Long Episodes were detected at a rate of 4.4/month, with an average of 441 therapies delivered per day. Repeat scalp EEG has not yet been performed.

DISCUSSION

Here we describe the first pediatric PGE patient with absence seizures successfully recorded from bilateral CM RNS, and report on successful RNS targeting absence seizures in drug-resistant CAE. This patient experienced decreased seizure frequency at 1-month follow-up, and patient and family reports resolution of detectable absence seizures as well as 75% reduction in generalized convulsive seizures at 6-month follow up. Our findings suggest that CM RNS can prevent loss of consciousness through disruption of low-frequency thalamocortical ictal recruitment.

RNS is a promising technology which offers personalized therapy based on a patient's own seizure electrophysiology by recording and responding to neural activity through delivery of programmable stimulation directly to seizure foci. Several multi-center outcomes studies have demonstrated the efficacy of the RNS system for the treatment of drug-resistant mesial temporal or neocortical seizures, in which 70% of patients saw a 78% reduction in seizure frequency at 6 years (13, 22–24). While the data captured by the RNS system remains computationally intensive to interpret, there are considerable, promising advances being made in the field to improve RNS as a patient-specific therapy (12, 25). In line with this, bilateral centromedian/ventrolateral thalamic RNS in an adult patient was successful in the treatment of generalized epilepsy (eyelid myoclonia with absence) (26). We provide further evidence to support RNS therapy as a safe and effective treatment option for drug-resistant PGE for pediatric patients and the CM as a targetable foci.

The CM receives converging input from the cortex, basal ganglia, and brainstem and participates in cognition (attention and arousal) and sensorimotor coordination (27). Thalamocortical feedback loops regulate cortical input during wakefulness to maintain attention and awareness and its suppression is implicated in the pathogenesis of CAE (27–31). The loss of awareness associated with absence seizures is theorized to occur during electrical perturbations in this feedback loop, such as seen in the aberrant low frequency thalamocortical signaling that is characteristic of absence seizures (29, 30, 32, 33). Neurostimulation of the CM disrupts the low-frequency ictal thalamocortical recruitment and may therefore help to prevent loss of awareness during seizure activity (31, 34). Leveraging the diffuse connectivity profile of this region, the CM has been successfully targeted by DBS for the treatment of drug-resistant PGE (8, 9, 15, 35, 36). RNS stimulation of the CM has been applied in adult patients for the treatment of drug-resistant regional neocortical epilepsy (37), generalized epilepsy (26), Lennox-Gastaut Syndrome (10, 38), and drug-resistant focal onset-seizures (39). Seizure frequency of patients with implanted RNS systems often continues to improve over months to years, which implicates the role of neural plasticity induced by programmable closed-loop stimulation (16, 23). Further research is needed to better understand the mechanisms underlying the clinical benefits of RNS CM stimulation for the treatment of CAE. We show here that the RNS targeting of the CM in this pediatric patient was able to reliably identify ictal discharges and

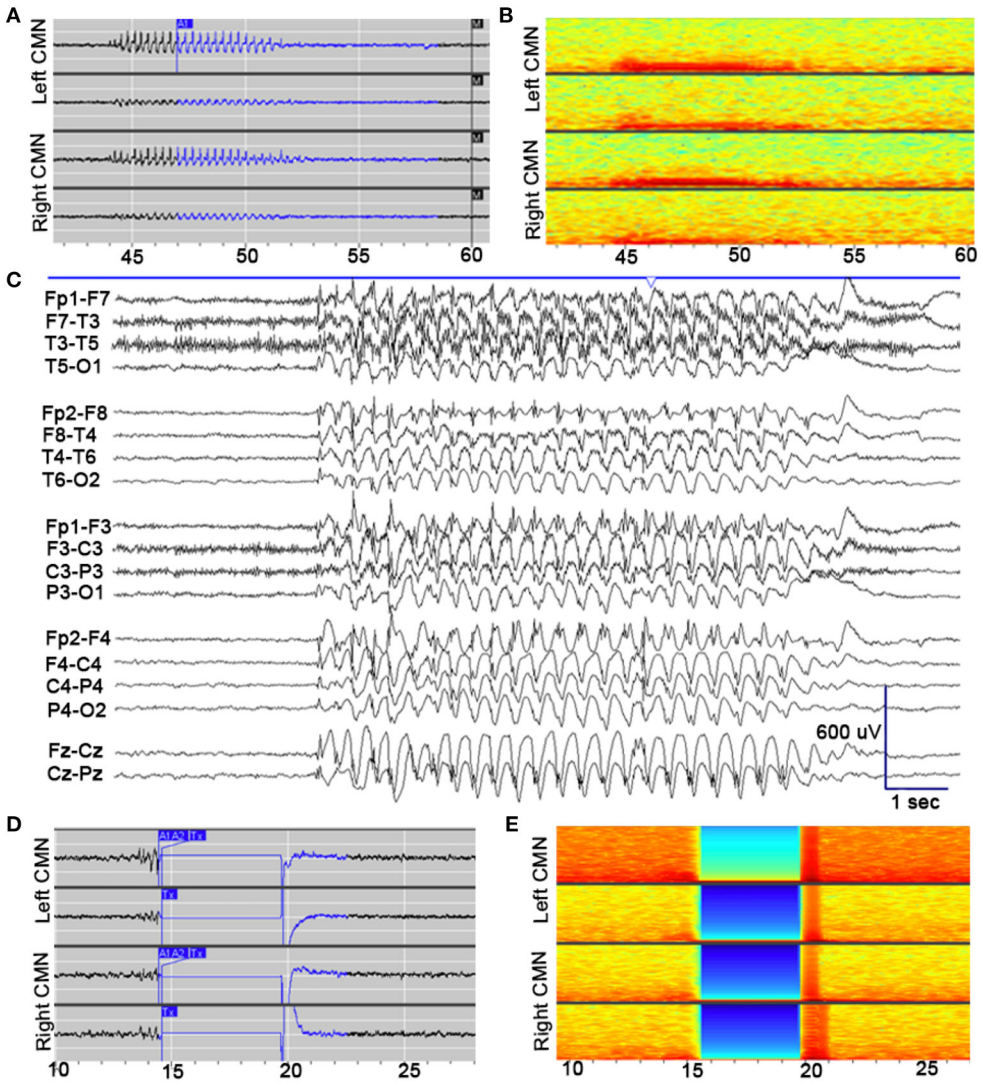

FIGURE 2 | Electrophysiological seizure characteristics. **(A)** Example of an electroclinical seizure stored the NeuroPace Patient Data Management System, detected by device (*A1*) and noted by patient's family with magnet swipe (*M*). Well-formed 3 Hz spike-and-wave discharges are detected maximally in channels 1 (LCM1–LCM2; top row) and 3 (RCM1–RCM2; third row). **(B)** Spectrogram of identical epoch. **(C)** Pre-implantation scalp EEG, capturing electroclinical typical absence seizure (TAS) with behavioral arrest. EEG demonstrates generalized 3 Hz spike- and polyspike-and-wave discharges (longitudinal bipolar montage; sensitivity: 30 μV/mm; timebase 30 mm/s). **(D)** Example of an electroclinical seizure stored the NeuroPace Patient Data Management System, detected by device (*A1, A2*) again detected maximally in channels 1 and 3, with responsive therapy delivered (*Tx*), subsequent amplifier artifact lasting 5 s, and return to electrographic baseline. Therapy delivered to channels 1 and 3: bipolar, current 0.4 mA, frequency 125 Hz, pulse width 160 μs, burst duration 5,000 ms, charge density 0.4 $\mu C/cm^2$. **(E)** Spectrogram of identical epoch.

improve seizure frequency through neurostimulation. Other groups have performed RNS of other targets (i.e., anterior thalamic nucleus) for the treatment of generalized epilepsy and the relative efficacy of subcortical RNS targets remains a topic for further investigation (40).

Electrophysiologic studies reveal that clinically relevant ictal discharges can be detected in the CM nucleus (16, 26). Kokkinos et al. (26), performed direct recording of the CM nucleus via RNS showing 3–5 Hz spike and wave activity consistent with their patient's preoperative EEG pattern. Warren et al. (16), performed simultaneous EEG and CM recordings during DBS implantation to examine the relationship between generalized paroxysmal fast activity (GPFA) and slow spike wave (SSW) on EEG and from direct CM recordings. In this study, 86% of GPFA events were seen in both on both scalp EEG and CM, whereas 25% of SSW was observed from both recordings. Interestingly, these recordings suggested that epileptiform activity occurred in cortex prior to CM. Further work will elucidate the interactions of cortex and CM in generalized epilepsy, but these findings suggest that clinically relevant ictal discharges are present in the CM nucleus.

The CM was targeted in this report using indirect and direct technique as previously described (10, 15–17). The CM remains difficult to demarcate on standard neuroimaging (36), however

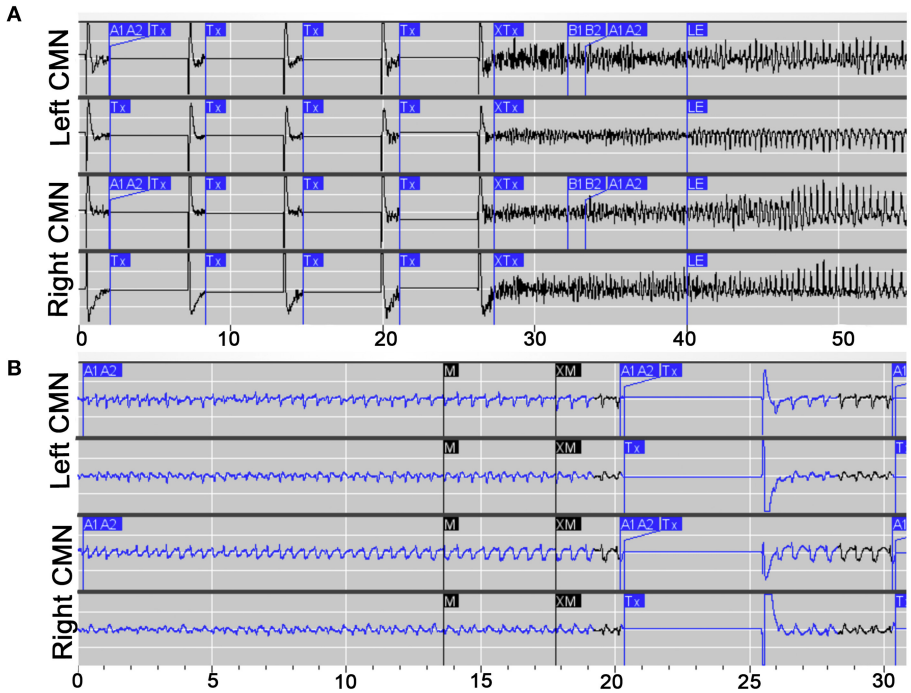

FIGURE 3 | Electrophysiological characteristics of prolonged absence and GTC seizures. **(A)** Example of an electroclinical generalized tonic clonic (GTC) seizure stored the NeuroPace Patient Data Management System, detected by device (A1, A2) and noted by patient's family with magnet swipe (M), with responsive therapy delivered (Tx). **(B)** Example of a prolonged electroclinical absence seizure stored the NeuroPace Patient Data Management System, detected by device (A1, A2) and noted by patient's family with magnet swipe (M), with responsive therapy delivered (Tx).

studies have shown that inverse MP2RAGE and quantitative susceptibility mapping (QSM) can be used to identify the nucleus with good reliability (16, 41). Confirmation of electrode placement using intraoperative microelectrode recording (MER) evaluation of the CMN neurophysiological signature has shown mixed results, given the presence of low frequency firing rate while sedated, considerable interpatient variability, and subtle differences in neural signatures between adjacent thalamic nuclei (16). Further research is needed to improve techniques for identifying thalamic subnuclei.

While this case highlights the promising utility of RNS for the treatment of complex, pediatric, drug-resistant PGE with absence seizures, the conclusions drawn are limited by the single patient sample size, short follow-up duration, and the potential under-reporting of absence seizure frequency. Repeat scalp EEG has not been performed in our patient since placement of RNS device, resulting in reliance on patient and family report for clinical absence seizure frequency. Our patient did have other seizure types emerge throughout his course, which precludes classifying his case as pure PGE, and presented unique challenges to his treatment plan. However, he originally presented with and continued to suffer from clearly well-defined typical absence seizures, which are the primary target of his RNS therapy. Successful treatment in our patient's case may highlight the possible role for thalamic RNS therapy in patients with primary generalized epilepsy as well as other cases of complex epilepsy in which cortico-thalamic networks are thought to play a large role.

The development of novel therapies for the treatment of pediatric drug-resistant PGE remain an important area of investigation. Children with PGE experience considerable burden on their quality of life and often experience cognitive, behavioral, and developmental deficits as a result of uncontrolled epilepsy during this critical period of brain development (4–7). Neocortical RNS implantation has been used successfully for the treatment of pediatric drug-resistant seizures in a few cases (42–45). Together, these provide preliminary evidence that RNS is a viable therapeutic option for patients with drug-resistant epilepsy who are not candidates for resective epilepsy surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.656585/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Surgical Outcomes and EEG Prognostic Factors After Stereotactic Laser Amygdalohippocampectomy for Mesial Temporal Lobe Epilepsy

Shasha Wu[1†], Naoum P. Issa[1†], Maureen Lacy[2], David Satzer[3], Sandra L. Rose[1], Carina W. Yang[4], John M. Collins[4], Xi Liu[5], Taixin Sun[6], Vernon L. Towle[1], Douglas R. Nordli Jr.[7], Peter C. Warnke[3] and James X. Tao[1]*

[1] Department of Neurology, The University of Chicago, Chicago, IL, United States, [2] Department of Psychiatry, The University of Chicago, Chicago, IL, United States, [3] Department of Neurosurgery, The University of Chicago, Chicago, IL, United States, [4] Department of Radiology, The University of Chicago, Chicago, IL, United States, [5] Department of Neurology, Wuhan University, Wuhan, China, [6] Department of Neurology, Beijing Electric Power Hospital, Beijing, China, [7] Department of Pediatric Neurology, The University of Chicago, Chicago, IL, United States

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Edited by:
Emma Losito, APHP, France

Reviewed by:
Kais Gadhoumi, Duke University, United States
Chengyuan Wu, Thomas Jefferson University, United States

****Correspondence:***
Shasha Wu
swu4@neurology.bsd.uchicago.edu

[†]These authors have contributed equally to this work and share first authorship

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Objective: To assess the seizure outcomes of stereotactic laser amygdalohippocampectomy (SLAH) in consecutive patients with mesial temporal lobe epilepsy (mTLE) in a single center and identify scalp EEG and imaging factors in the presurgical evaluation that correlate with post-surgical seizure recurrence.

Methods: We retrospectively reviewed the medical and EEG records of 30 patients with drug-resistant mTLE who underwent SLAH and had at least 1 year of follow-up. Surgical outcomes were classified using the Engel scale. Univariate hazard ratios were used to evaluate the risk factors associated with seizure recurrence after SLAH.

Results: The overall Engel class I outcome after SLAH was 13/30 (43%), with a mean postoperative follow-up of 48.9 ± 17.6 months. Scalp EEG findings of interictal regional slow activity (IRSA) on the side of surgery ($HR = 4.05$, $p = 0.005$) and non-lateralizing or contra-lateralizing seizure onset ($HR = 4.31$, $p = 0.006$) were negatively correlated with postsurgical seizure freedom. Scalp EEG with either one of the above features strongly predicted seizure recurrence after surgery (HR = 7.13, $p < 0.001$) with 100% sensitivity and 71% specificity.

Significance: Understanding the factors associated with good or poor surgical outcomes can help choose the best candidates for SLAH. Of the variables assessed, scalp EEG findings were the most clearly associated with seizure outcomes after SLAH.

Keywords: epilepsy surgery, medication resistant epilepsy, anterior temporal lobectomy, laser ablation, selective amygdalohippocampectomy, minimally invasive epilepsy surgery

INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common type of medication-resistant epilepsy. Despite the development of new generations of anti-seizure medications (ASMs), 30–40% of patients become resistant to ASM treatment (1). Anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SAH) have been the gold standard surgical interventions for these

patients, achieving 60–80% seizure freedom, though in highly selected patient cohorts (2–5). However, patients are often hesitant or unwilling to consider open surgery due to the fear of associated morbidity of a craniotomy, the concern for potential neurological deficits, and the risk of significant cognitive decline (6).

In recent years, there has been a shift from open resection to minimally invasive epilepsy surgery to minimize the complications associated with craniotomy and resection. Emerging data have shown that stereotactic laser amygdalohippocampectomy (SLAH) performed using MR-guided laser interstitial thermal therapy (MRgLITT) is a safe and effective alternative to open surgery for patients with mesial temporal lobe epilepsy (mTLE) (7, 8). In a recent study of 234 patients from 11 epilepsy centers, 58% of patients who underwent SLAH achieved Engel I outcome after 1 and 2 years of postoperative follow-up (9). Compared to open resection, SLAH is more tolerable and offers superior neurocognitive outcomes by sparing the lateral temporal neocortex (10). SLAH has been adopted as the first-line surgical option in many epilepsy centers in the United States for patients with mTLE with or without mesial temporal sclerosis (MTS).

Although early data showed that the seizure freedom rate of SLAH is close to or slightly inferior to that of traditional open surgery (11, 12), its long-term seizure outcome has not been determined. Prognostic factors for identifying ideal candidates for SLAH in a not highly selected group have not been established. In this retrospective study, we aim to assess the seizure outcomes of SLAH in patients with at least 1 year of postoperative follow-up and to identify prognostic factors from the presurgical scalp EEG and imaging that influence the surgical outcomes.

MATERIALS AND METHODS

Patients and History

Thirty consecutive patients with drug-resistant TLE who underwent SLAH by MRgLITT at the University of Chicago Medical Center from January 2014 to December 2019 with at least 1 year follow-up were included in the study. Patients with bilateral interictal activity or bilateral seizures with one side clearly predominating were also included making this cohort more heterogeneous than previously reported (11, 12). In patients who underwent a second SLAH due to persistent seizures, outcomes were reported with respect to reoperation. Exclusion criteria were prior open temporal lobe surgery, ablation of structures outside the mesial temporal lobe at the same time as SLAH, and postoperative psychogenic non-epileptic seizures that precluded Engel classification. Patients' charts, imaging and EEG data were retrospectively reviewed.

Presurgical Evaluation

All patients underwent a comprehensive neurological history interview and examination, inpatient video-EEG monitoring, brain MRI with volumetric 1.0 mm-section T1 coronal and fluid-attenuated inversion recovery (FLAIR) images to assess hippocampal volume, 18-fluorodeoxyglucose positron emission tomography (FDG-PET) (except patients 1, 2, and 28), neuropsychological evaluation and functional MRI (fMRI). Scalp video EEG was recorded using Xltek, Natus Medical Incorporated (Pleasanton, California, USA) at a sampling rate of 512 Hz. Electrodes were placed based on the international 10–20 arrangement with supplementary sub-temporal electrodes F9, T9, F10, T10 from the 10–10 system, and mastoid electrodes M1, M2. Scalp EEG filter settings are 1–70 Hz with notch filter on. No automated artifact rejection was used.

Ictal and interictal electrographic patterns were tabulated. Temporal intermittent rhythmic delta activity (TIRDA) is defined as short bursts of repetitive, rhythmic, 1–4 Hz activity of 50–100 mV in amplitude, predominantly running over the anterior temporal regions (13). Interictal regional slow activity (IRSA) is defined as delta activity over the temporal region, either continuous and polymorphic or intermittent and rhythmic on the same side of surgery which is present for more than 50% of the recording (14). An ictal onset EEG pattern in which the side of onset cannot be determined in one or more seizures was categorized as a "non-lateralizing" seizure onset. Patient 7 had seizures recorded independently from both right and left temporal regions on scalp EEG and was categorized as "contra-lateralizing" seizure onset because a minority of seizures lateralized to the contralateral (non-operative) side.

Brain imaging patterns were classified for each subject. Mesial temporal sclerosis (MTS) was defined as the presence of MRI T_2/FLAIR signal hyperintensity with reduced hippocampal volume or loss of hippocampal internal architecture (15). 18F-FDG PET area of hypometabolism was classified as ipsilateral if it was on the same side of seizure onset and subsequent SLAH, bilateral if hypometabolism was detected in both temporal regions, and multifocal if hypometabolism involved the ipsilateral or bilateral frontal, parietal, or occipital lobe in addition to the temporal lobe.

Intracranial EEG recording with depth (stereo-electroencephalography, SEEG) and/or subdural electrodes was performed in 24 of 30 patients. Intracranial recording was indicated when patients had a normal brain MRI, when there was concern for lateral temporal neocortical onset, extratemporal onset, or if bilateral temporal onset could not be ruled out during non-invasive evaluation. Simultaneous scalp and invasive EEG were recorded using the above-mentioned recording system at a sampling rate of 1,024 Hz. Intracranial EEG filter settings are 1–100 Hz with notch filter off. Eleven of 24 patients had bitemporal intracranial recording due to concerns for bi-mesial temporal onset. The methodology of intracranial recording was detailed in our previous publication (16).

Stereotactic Laser Amygdalohippocampectomy (SLAH)

Patients were eligible for SLAH when their intracranial EEG onset localized to mesial temporal structures or predominantly from one mesial temporal lobe in patients with bilateral mesial temporal onset seizures (patient 7). SLAH was performed in all subjects using the Visualase system (Visualase Medtronic, MN USA) by the same neurosurgeon (PCW). The location and

volume of the ablation were determined either based on the results of intracranial EEG monitoring (the seizure onset zone and immediate spreading zone were ablated) or, in the absence of intracranial electrophysiological data, with the intention of ablating the AHC. Typically, three to five lesions were generated along the longitudinal axis of AHC. The detailed surgical technique used for MRI-guided SLAH has been previously described (16). Seven of 30 patients had a second SLAH due to recurrent seizures (**Table 1**). The second SLAH was designed to target the residual AHC; the remnant mesial amygdala was the target of re-ablation in four of seven patients.

Assessment of Seizure Outcomes

The current Engel class seizure status and the time from SLAH to the first seizure recurrence were utilized as the endpoints in the analysis. Engel classification is defined as the following: class I, free of seizures (patient may have aura); class II, rare disabling seizures; class III, worthwhile improvement; class IV, no worthwhile improvement (17). For patients who had a second SLAH, the postoperative outcome was based on the second SLAH if there were more than 1 year of follow-up after the second SLAH. Acute postoperative seizures that occurred in the first week after surgery were not counted as recurrent (18). Patients with seizures occurring after unsupervised ASM withdrawal (e.g., missed doses) with subsequent seizure-freedom for more than 2 years after resuming the medications were classified as having an Engel class I outcome with seizure freedom (17). Preoperative ASMs were maintained at least for 6 months after SLAH and in some cases were reduced thereafter if patients remained seizure-free or adjusted if the seizures were not controlled. The surgical complication rate from this cohort has been previously reported (16), and surgical complications are not considered endpoints as we assume that they occur sporadically.

Data Analysis

The goal of the study was to establish prognostic factors in pre-surgical evaluation for the effect of SLAH on seizures. Parameters from the pre-surgical evaluation were tested as independent variables in a univariate Cox proportional hazard model with the outcome being the duration of postsurgical seizure freedom. The parameters tested were: (1) Unilateral MTS on MRI. (2) 18F-FDG PET showed unilateral temporal hypometabolism. (3) Presence of interictal regional slow activity (IRSA) ipsilateral to the side of surgery. (4) Presence of non-temporal interictal findings in the form of contralateral TIRDA, contralateral spikes or sharp waves, or extratemporal interictal epileptiform activity. (5) Presence of non- or contra-lateralizing seizure onset. Stata software was used for data analysis. A power analysis was performed to estimate effect size (Hazard Ratio) from the sample numbers available using a long-rank test (Freedman method; power = 0.8, alpha = 0.05) and an unbalanced design (the number of subjects with a particular characteristic was different from the number of subjects without that characteristic). A Bonferroni correction for multiple comparisons was made; an initial p-value of 0.05 was considered significant, which is reduced to 0.01 because five different parameters were tested.

RESULTS

Demographic Data and Surgical Outcomes

Clinical data from 30 patients (17 female) with medically intractable TLE were reviewed and summarized in **Table 1**. The mean duration of epilepsy was 21.5 ± 16.9 years (mean ± standard deviation; range 1–57 years). The mean age at surgery was 43.6 ± 14.9 years (range 20–69 years). The mean postoperative follow-up was 48.9 ± 17.6 months (range 12–79 months).

At the most recent follow-up, 13/30 (43%) remained seizure-free after the most recent SLAH. The seizure freedom rate was 18/30 (60%) at 1 year and 3/10 (30%) at 5 years. The time from surgery to the first seizure varied between 1 and 36 months. In ten of 17 patients with seizure recurrence, seizures recurred within 6 months after surgery and all had Engel class III or IV outcomes. Seven patients with recurrent seizures underwent a second SLAH to ablate residual mesial temporal tissue (**Table 1**). Four of those seven were seizure-free for more than 1 year after the second SLAH. The remaining three continued experiencing seizures. Postoperative supervised reduction of at least one ASM was conducted in 11 of the 30 patients (**Table 1**).

Factors Associated With Surgery Failure

Five parameters were assessed using a univariate Cox proportional hazards model to identify which, if any, associated with failure of surgery to produce seizure freedom. Hazard ratios >1.0 imply patients were likely to have recurrent seizures after surgery, and hazard ratios <1.0 imply patients were unlikely to have recurrent seizures after surgery. A power analysis suggests that an effect size of 2.7–3 (Hazard Ratio) would likely be detectable with 27–30 total subjects and the observed distribution of characteristics (unbalanced sampling). While several other parameters are likely associated with outcome, analysis was limited to five parameters because of the small overall sample size (30 subjects with 17 that had postoperative seizure recurrence). The calculated hazard ratios are listed in **Table 2**.

The absence of unilateral MTS on MRI or of 18F-FDG PET hypometabolism restricted to the unilateral temporal appeared to be associated with a higher risk of seizure recurrence, but these relationships did not reach statistical significance with the small number of subjects available (**Table 2**). Three patients had MRI findings other than MTS. Patient 19 had diffuse band heterotopia in bifrontal, parietal and temporal regions. Patient 28 had ventricular enlargement due to normal pressure hydrocephalus. Patient 1 had right internal capsule gliosis.

Interictal scalp EEG patterns found outside of the surgical temporal lobe, consisting of bilateral or extratemporal sharp waves, or contralateral TIRDA, also appeared to be associated with a higher risk of seizure recurrence. However, this relationship did not reach statistical significance (**Table 2**). Sixteen of 30 patients had such interictal findings, and 12 of these 16 patients (75%) had postoperative seizures, on average 7.1 months after surgery. By comparison, only five of 14 patients (36%) with unilateral temporal lobe discharges had postoperative

TABLE 1 | Demographic information arranged by surgical outcomes.

ID	Sex	Age	Epi duration	MTS	PET	Non TL EEG	IRSA	Non-lat or contra sz	Side	Postop (months)	Engel outcome	Time to sz	ASM reduction	2nd surg
11	F	41	4	No	Yes	Yes	No	No	R	63	I	NA	No	No
22	M	56	55	No	No	No	No	No	R	44	I	NA	No	No
23	F	51	5	No	Yes	No	No	No	R	42	I	NA	Yes	No
26	F	22	5	No	Yes	No	No	No	R	37	I	NA	Yes	No
4	F	42	26	Yes	Yes	Yes	No	No	L	52	I	NA*	No	Yes
6	M	25	15	Yes	Yes	No	No	No	R	64	I	NA	Yes	No
9	M	42	41	Yes	Yes	No	No	No	L	28	I	NA#	No	Yes
10	F	46	30	Yes	No	No	No	No	R	66	I	NA	No	No
14	F	46	23	Yes	Yes	Yes	No	No	L	38	I	NA@	Yes	Yes
18	F	32	27	Yes	Yes	No	No	No	R	49	I	NA	Yes	No
20	F	61	34	Yes	Yes	Yes	No	No	L	39	I	NA^	No	Yes
29	M	67	50	Yes	Yes	No	No	No	L	18	I	NA	No	No
31	M	69	3	Yes	Yes	No	No	No	L	12	I	NA	No	No
2	F	53	3	No	NA	No	Yes	No	R	78	II	17	Yes	No
15	F	58	11	Yes	No	Yes	Yes	No	R	59	II	10	No	No
17	M	32	23	Yes	Yes	Yes	Yes	No	L	50	II	24	Yes	No
3	M	65	57	Yes	No	Yes	No	Yes	L	74	II	18	Yes	No
19	M	32	22	No	No	No	No	No	R	48	II	18	Yes	No
25	F	46	45	Yes	Yes	Yes	No	No	R	39	II	12	Yes	No
21	F	50	43	No	No	Yes	Yes	No	L	45	III	2	Yes	No
12	M	29	25	Yes	Yes	Yes	Yes	No	L	51	III	2	No	Yes
13	M	32	11	No	Yes	No	No	Yes	L	60	III	1	No	No
24	F	60	13	No	No	Yes	No	Yes	R	42	III	3	No	No
5	F	36	7	No	Yes	Yes	No	No	L	66	III	1	No	No
8	F	50	6	No	Yes	No	No	No	R	69	III	1	No	No
30	F	21	6	Yes	Yes	Yes	No	No	R	14	III	8	No	No
16	F	41	33	No	No	Yes	Yes	Yes	R	41	IV	1	No	Yes
7	M	20	5	No	No	Yes	Yes	Yes	R	62	IV	3	No	Yes
28	M	63	1	Yes	NA	No	Yes	No	R	37	IV	1	No	No
1	M	20	17	No	NA	Yes	No	Yes	L	79	IV	1	No	No

For patients who had a second surgery, time to seizure and postoperative follow-up duration are measured from the time of the second surgery.

Epi duration, duration of the epilepsy; MTS, ipsilateral mesial temporal lobe sclerosis; PET, ipsilateral temporal hypometabolism on positron emission tomography; non-TL EEG, non-temporal lobe interictal EEG findings; IRSA, interictal regional slow activity; Non-lat or contra sz, non-lateralizing or contra-lateralizing seizure onset; side, side of surgery; Post-op, post-op follow-up months; time to sz, time from surgery to first postoperative seizure; ASM; anti-seizure medications; 2nd surg, second surgery.

**Patient 4 had a seizure 11 months after the first ablation and was seizure free at 52 months after the second ablation. #Patient 9 had a seizure 36 months after the first ablation and was seizure free at 28 months after the second ablation. @Patient 14 had a seizure 7 months after the first ablation and was seizure free at 38 months after the second ablation. ^Patient 20 had a seizure 1 month after the first ablation and was seizure free at 39 months after the second ablation.*

seizures, on average 7.6 months after surgery (HR 2.80, CI 0.97–8.03, $p = 0.056$).

One additional interictal scalp EEG parameter was found to be associated with seizure recurrence after surgery. All patients had focal slowing ipsilateral to the surgical side. Twenty-two patients had TIRDA and eight of 30 patients were noted to have prominent, near-continuous focal slowing over the surgical temporal lobe (**Figure 1**), similar to the interictal regional slow activity (IRSA) described by Koutroumanidis et al. (14) All eight patients with IRSA had recurrent seizures (100%, three Engel class II and five class III and IV), with an average of 7.5 months to first seizure after surgery. Koutroumanidis et al. (14) suggested that temporal IRSA was often associated with hypometabolism in the lateral posterior temporal lobe. A PET scan was available for six of the eight subjects with IRSA; in three there was hypometabolism in the lateral posterior temporal neocortex (patients 7, 12, and 15), with hypometabolism extending beyond the temporal cortex into the occipital cortex in two (patients 7 and 15). In the other three there was either no clear hypometabolism (patient 16), exclusively anterior temporal lobe hypometabolism (patient 17), or bilateral anterior temporal lobe hypometabolism (patient 21). For the 22 patients who did not have IRSA, only nine (41%) had seizures after surgery, on average 7.0 months after surgery. The resulting hazard ratio for IRSA was 4.05 (CI 1.51–10.86, $p = 0.005$, which is significant after Bonferroni correction for multiple comparisons; **Table 2**).

Of the parameters assessed, ictal scalp EEG patterns had the closest association with surgery failure. Five patients had scalp ictal EEGs that were non-lateralizing for one or more seizures (**Table 1**; **Figure 2**). One of five had a class II outcome and the

TABLE 2 | Hazard ratios associated with characteristics identified during presurgical planning.

Presurgical characteristic—univariate analysis	HR	p	95% Confidence interval	#with/without characteristic	#postop sz with/without characteristic	Months to 1st sz with/without characteristic
No unilateral MTS	2.22	0.108	0.84–5.87	14/16	10/7	4.8/10.7
No unilateral PET hypometabolism	2.34	0.115	0.81–6.72	9/18	7/7	7.9/7.0
Non-temporal lobe interictal findings	2.80	0.056	0.97–8.03	16/14	12/5	7.1/7.6
Ipsilateral temporal IRSA	4.05	0.005	1.51–10.86	8/22	8/9	7.5/7.0
Non- or contra-lateralizing seizure onset	4.31	0.006	1.51–12.34	6/24	6/11	4.5/8.7
Non- or contra-lateralizing seizure onset or Ipsilateral temporal IRSA	7.13	<0.001	2.41–21.07	12/18	12/5	6.9/8.0

Results of a univariate analysis, with each listed parameter tested as an independent variable. MTS, mesial temporal sclerosis on MRI. IRSA, interictal regional slow activity. HR, hazard ratio for recurrent seizures after surgery, calculated with the Cox proportional hazards model. #with/without characteristic: the number of subjects in the cohort who had the defining characteristic/the number of subjects in the cohort who did not have the defining characteristic; there were 30 subjects in the cohort. #postop sz with/without characteristic: the number of subjects in the group with the characteristic that had a postoperative seizure/the number of subjects in the cohort who did not have the defining characteristic that had a postoperative seizure. Months to 1st sz: the average number of months between surgery and the first seizure in subjects who had a seizure.

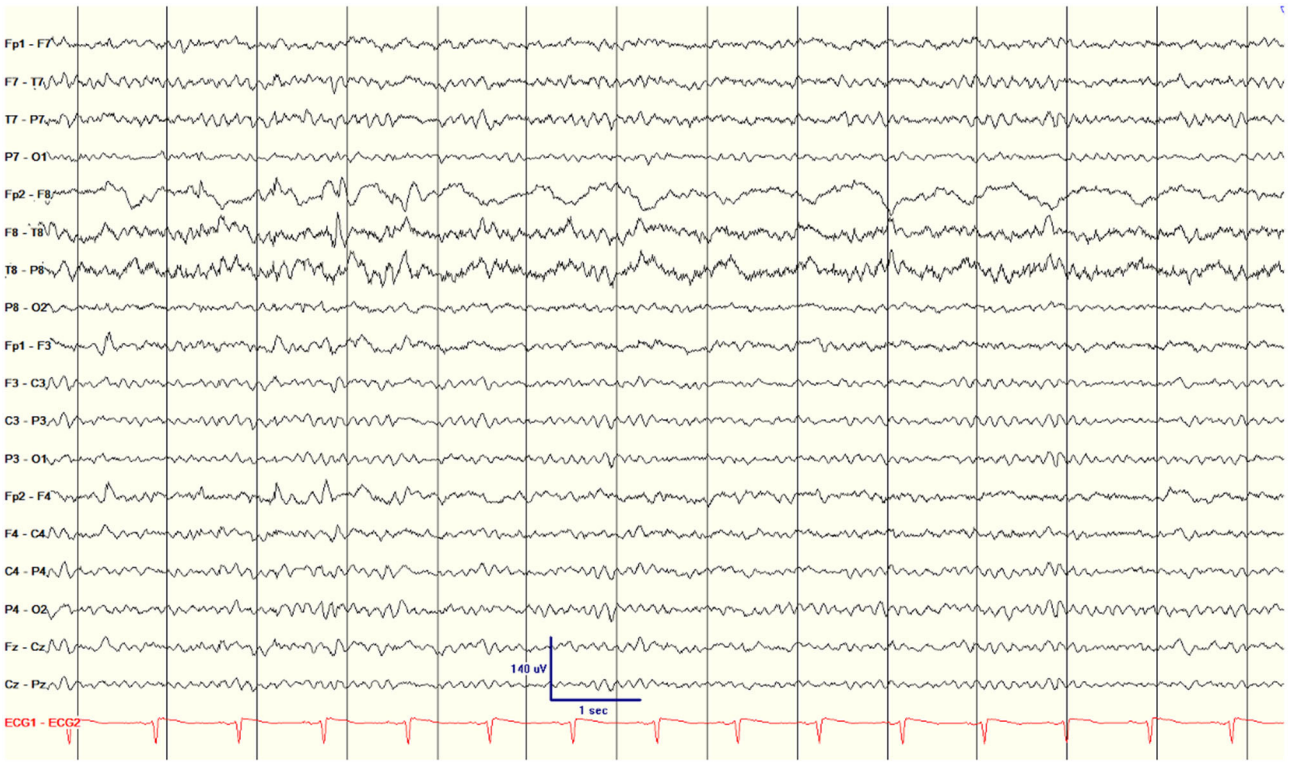

FIGURE 1 | Scalp EEG showing nearly continuous interictal regional slow activity (IRSA) on the surgical side (right hemisphere) in patient 2.

remaining four had class III or IV outcomes. Patient 7 had independent bilateral ictal onset on scalp EEG recording with most of the seizures starting over the right temporal region (R:L = 7:1). His intracranial recording showed independent bitemporal interictal epileptiform discharges (IEDs), but all seizures were recorded from the right hippocampus. The patient underwent right hippocampal SLAH and had a class IV outcome despite two SLAH on the right side. None of the six patients with either non-lateralizing or contra-lateralizing seizure onset were seizure-free (100% recurrence) compared to 11 of 24 (46%) seizure-recurrence in patients who had only unilateral seizure onset. The average time from surgery to first seizure was 4.5

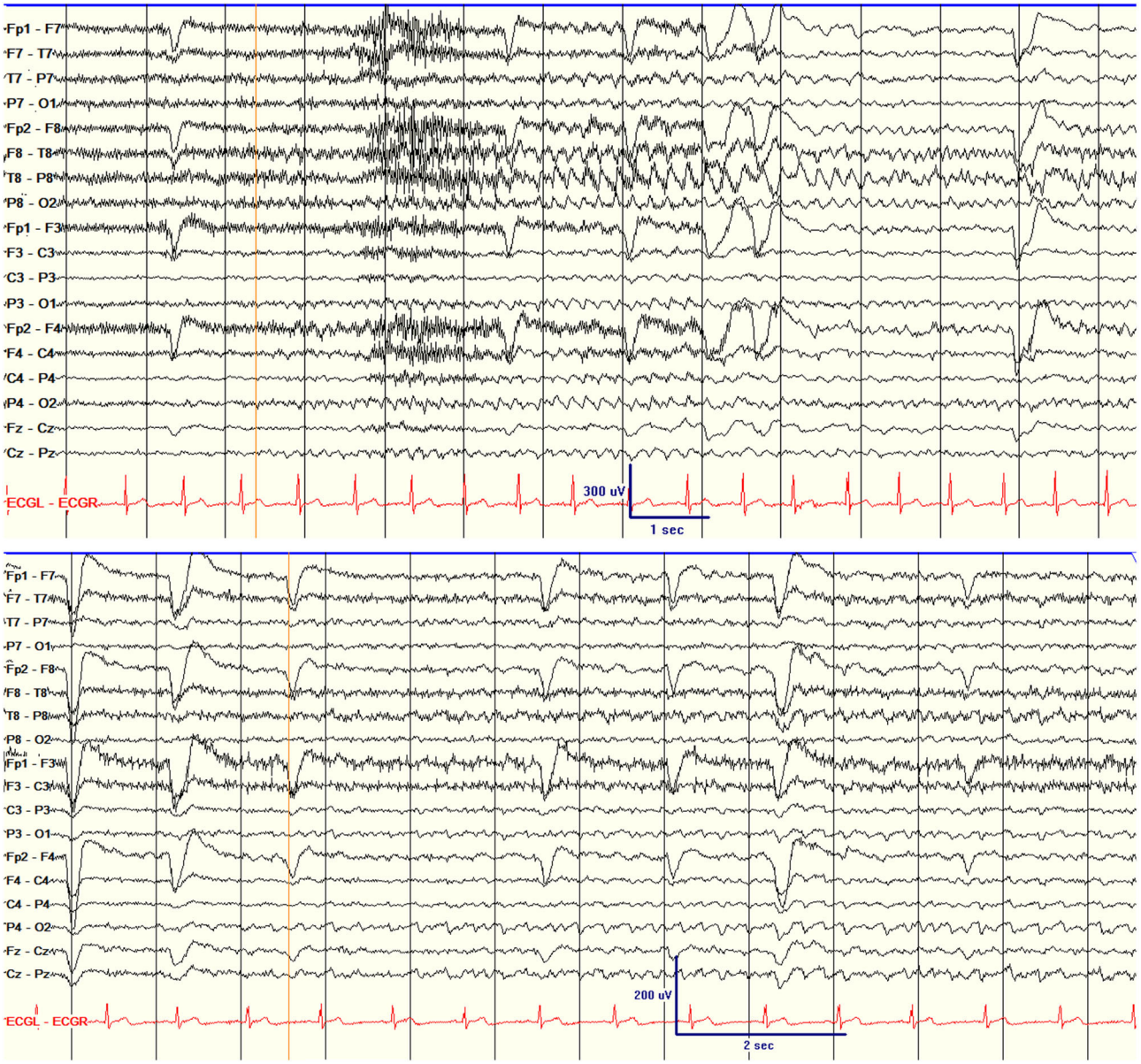

FIGURE 2 | Scalp EEG showing the unilateral seizure onset (right temporal seizure onset) in patient 18 (top) and non-lateralizing seizure onset in patient 1 (bottom). The orange lines indicate EEG seizure onset.

months in patients with non- or contra-lateraling seizure onset compared to 8.7 months in patients with unilateral seizure onset (HR 4.31, CI 1.51–12.34, $p = 0.006$, which is significant after Bonferroni correction for multiple comparisons).

Of the twelve patients who had either non- or contra-lateralizing seizure onset or ipsilateral IRSA, none were seizure-free after surgery (100%) (**Table 2**). The seizures occurred, on average, 6.9 months after surgery. By comparison, only five of 18 patients (28%) with neither of these EEG features had a postoperative seizure, with an average latency of 8 months. The presence of either IRSA or non- or contra-lateralizing ictal onset was associated with a hazard ratio of 7.13 ($p < 0.001$) for recurrent seizures, with 100% sensitivity and 71% specificity. The positive predictive value (PPV) was 0.72, with 13 of 18 patients without either of these patterns becoming seizure-free after surgery. The negative predictive value was 1.0, with all 12 patients with either IRSA or non- or contra-lateralizing ictal onset having a postsurgical seizure. A Kaplan-Meier survival curve shows the longer seizure freedom for the group of patients without either IRSA or non- or contra-lateralizing ictal onset compared to the group of patients with either EEG patterns (**Figure 3**).

DISCUSSION

Prognostic factors have been studied extensively for traditional ATL (19, 20). This study analyzed the association between presurgical characteristics and surgery outcome after SLAH in a cohort of patients that included patients with either unilateral or bilateral EEG findings. This approach was chosen following the findings that in lesional cases even bilateral EEG-changes did not preclude seizure freedom (21). A finding of either non- or contra-lateralizing ictal EEG onset or interictal ipsilateral temporal IRSA associated with the failure to achieve seizure freedom after SLAH with a sensitivity of 100% and a specificity of 71%.

Patients with bitemporal seizures are poor candidates for unilateral resection (22). However, the significance of non-lateralizing ictal EEG regarding surgery outcome is not known. We found that a non-lateralizing EEG or contra-lateralizing seizure onset for even a minority of captured seizures is significantly negatively associated with seizure outcome. The presence of a non-lateralizing ictal EEG could suggest fast bilateral synchronization or a contralateral seizure onset and lead to unfavorable surgical outcomes (23, 24).

Temporal intermittent focal slowing (TIRDA) is a well-known pattern that is considered an interictal marker for TLE (25, 26). By contrast, continuous focal or regional slowing (IRSA) usually suggests an underlying "structural" abnormality and is not considered epileptiform (27). In the current data set, however, IRSA on the surgical side was associated with recurrent seizures after SLAH (HR 4.05). The presence of IRSA could imply an extended epileptogenic zone beyond the mesial temporal region. This is supported by the imaging findings of Koutroumanidis et al. (14) in which IRSA was associated with hypometabolism in the lateral temporal neocortex. However, only half of the subjects that both IRSA and a PET scan showed lateral posterior temporal hypometabolism, suggesting that IRSA, even independent of PET findings, may be a negative predictor of surgical outcome. To our knowledge, this is the first description of IRSA in association with surgery outcomes in TLE.

Bi-temporal IEDs and postoperative contralateral TIRDA have been associated with poor surgical outcome while presurgical unilateral IEDs are good prognostic factors in surgery for TLE (28–30). Our findings suggested that interictal EEG findings outside the affected temporal lobe (bitemporal, extratemporal IEDs and contralateral TIRDA) were not significant independent factors to predict surgical outcome (HR 2.80, $p = 0.06$). However, based on a power analysis, the observed HR of 2.8 would be in the borderline detectable effect size for the small number of subjects (potential type I error), and a larger data set would be needed to determine whether this feature is a significant predictor of surgical failure.

Drug-resistant TLE associated with MTS has the best outcome after traditional ATL or SAH (31–33). Similar findings were also reported after SLAH from our previous study and other epilepsy centers (11, 12, 16, 34). Temporal PET hypometabolism has also been associated with a higher rate of seizure freedom after ATL (35). While the lack of unilateral MTS or ipsilateral PET appeared to be associated with a higher risk of seizure recurrence and a shorter time between surgery and first seizure, the relationships were not statistically significant during the long-term follow-up. Similar findings were reported from other groups recently (8, 36). Again, the observed hazard ratios were smaller than the detectable HR based on a power analysis (potential type I error), so a larger data set would clarify the relationship between the imaging parameters and postsurgical seizure freedom.

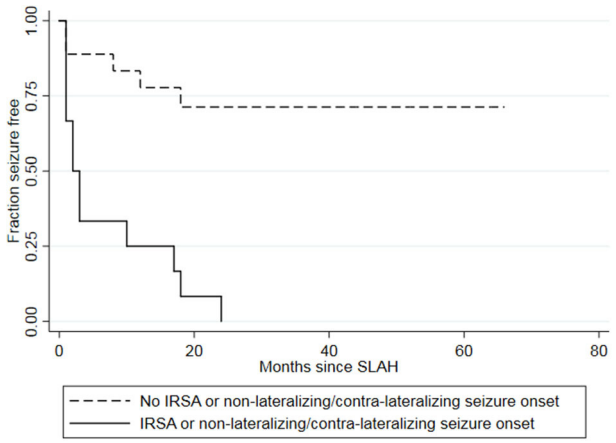

FIGURE 3 | Kaplan-Meier survival curve showing longer seizure freedom for the group of patients without either IRSA or non- or contra-lateralizing seizure onset (dashed lines) than for the group of patients with either IRSA or non- or contra-lateralizing seizure onset (solid line). Two patients had both IRSA and a non- or contra-lateralizing seizure onset on EEG. IRSA, interictal regional slow activity; SLAH, stereotactic laser amygdalohippocampectomy.

While the use of SLAH has been increasing, the long-term outcome after SLAH is not yet well-understood. We found that the seizure-freedom rate after SLAH decreases gradually during the first 5 years of postoperative follow-up in this cohort with bilateral EEG changes and additional IRSA. The long-term seizure outcome of SLAH appears to be marginally lower than that of ATL, in which complete seizure freedom was seen in 55.3% of patients at 2 years and in 47.7% at 5 years after surgery but the ATL cohorts are more selective (5). One possible reason for the difference in seizure freedom between ATL and SLAH could be due to incomplete ablation of extrahippocampal mesial tissues, as suggested by the recent study of Wu et al. (9) With SLAH, structures other than the amygdalohippocampal complex, including piriform, entorhinal, perirhinal, and parahippocampal cortices, are not typically targeted and are inconsistently ablated. These extra-hippocampal mesial structures can be involved in seizure generation and propagation in mTLE and are typically resected during ATL and SAH (37–40). Therefore, ablation of additional mesial temporal structures, perhaps using two laser probes targeting both longitudinal AHC and the mesial part of the amygdala, may be necessary to improve long-term seizure freedom. In a parallel study at our center, an analysis of ablated regions suggests that parahippocampal ablation is associated with seizure freedom in mesial temporal lobe epilepsy.

Another important factor in explaining the inferior seizure outcome after SLAH is the patient's preference. Because of the low risk of complications and much faster recovery time, almost

all patients chose minimally invasive SLAH over traditional ATL or SAH when we offered these two options to treat temporal lobe epilepsy. In some patients, SLAH was offered as a "palliative" procedure due to significant seizure burden and comorbidity despite the presurgical evaluation suggesting the seizure focus was more extensive than a unilateral mesial temporal region. For example, palliative surgery without expectation for seizure freedom was offered to patient 7, who had bitemporal onset seizures on scalp EEG, and patient 19 who had double cortex on MRI brain.

STUDY LIMITATIONS

There are two major limitations to this study. First, its single-center retrospective design limits generalizability since the patient population and indications for surgery may differ at other surgical centers. The more significant limitation is the small sample size. There are many other potential predictors of surgical outcome, for example the duration of epilepsy, seizure type, presence of non-MTS lesions, neuropsychological findings, the extent of hypometabolism, but with only 30 subjects it is not statistically appropriate to test all possibilities. We therefore limited our analysis to five parameters related to imaging and scalp EEG. However, to allow subsequent meta-analyses of other parameters, we have included additional data in a **Supplementary Table**. Similarly, the power analysis suggests that only large effects could be detected with 30 subjects (Hazard Ratios of ∼3). With 17 events, defined as recurrent seizures after completed ablation, a multivariate analysis was not possible. This study is therefore preliminary, identifying two parameters that related to surgical failure with SLAH that should inform future larger prospective studies.

CONCLUSION

In conclusion, of the variables assessed, scalp EEG findings were the most clearly associated with seizure outcomes after SLAH. Interictal regional slow activity and a non- or contra-lateralizing seizure onset are strong negative markers of prognosis after SLAH. The seizure-freedom rate after SLAH gradually decreases over the course of the initial 5-year postoperative follow-up. Understanding the factors associated with good or poor surgical outcomes can help the selection of the best candidates for SLAH and help predict the outcome before surgery. Multi-center and long-term follow-up studies are warranted to clarify the long-term safety and efficacy of SLAH for patients with mTLE.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The University of Chicago Biological Sciences Division/University of Chicago Medical Center AURA Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SW and NI contributed to the study design, data collection, and manuscript preparation. XL and TS contributed to the data collection. PW performed the surgeries. DS, ML, SR, CY, JC, VT, DN, and JT contributed to the study design and data collection. All authors approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.654668/full#supplementary-material

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Results From an Italian Expanded Access Program on Cannabidiol Treatment in Highly Refractory Dravet Syndrome and Lennox–Gastaut Syndrome

Luigi Francesco Iannone[1], Gabriele Arena[1], Domenica Battaglia[2], Francesca Bisulli[3,4], Paolo Bonanni[5], Antonella Boni[3,6], Maria Paola Canevini[7], Gaetano Cantalupo[8], Elisabetta Cesaroni[9], Manuela Contin[3,10], Antonietta Coppola[11], Duccio Maria Cordelli[12], Giovanni Cricchiuti[13], Valentina De Giorgis[14], Maria Fulvia De Leva[15], Marta De Rinaldis[16], Giuseppe d'Orsi[17], Maurizio Elia[18], Carlo Andrea Galimberti[19], Alessandra Morano[20], Tiziana Granata[21], Renzo Guerrini[22], Monica A. M. Lodi[23], Angela La Neve[24], Francesca Marchese[25,26], Silvia Masnada[27], Roberto Michelucci[28], Margherita Nosadini[29], Nicola Pilolli[24], Dario Pruna[30], Francesca Ragona[21], Anna Rosati[22], Margherita Santucci[3,6], Alberto Spalice[31], Nicola Pietrafusa[32], Pasquale Striano[25,26], Elena Tartara[19], Laura Tassi[33], Amanda Papa[34], Claudio Zucca[35], Emilio Russo[1], Oriano Mecarelli[36] and The CBD LICE Italy Study Group*

[1] Science of Health Department, School of Medicine, University Magna Graecia, Catanzaro, Italy, [2] Pediatric Neurology, Department of Woman and Child Health and Public Health, Child Health Area, A. Gemelli University Polyclinic Foundation, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS), Catholic University of the Sacred Heart, Rome, Italy, [3] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy, [4] Epilepsy Center (Reference Center for Rare and Complex Epilepsies - EpiCARE), Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, [5] Epilepsy and Clinical Neurophysiology Unit, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Eugenio Medea, Scientific Institute, Treviso, Italy, [6] Child Neuropsichiatry, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Delle Scienze Neurologiche di Bologna, Bologna, Italy, [7] Department of Health Sciences, Epilepsy Center, San Paolo Hospital, University of Milan, Milan, Italy, [8] Child Neuropsychiatry, Department of Surgical Sciences, Dentistry, Gynecology, and Pediatrics, University of Verona, Verona, Italy, [9] Child Neurology and Psychiatry Unit, G. Salesi Children's Hospital-University of Ancona, Ancona, Italy, [10] Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Delle Scienze Neurologiche di Bologna, Bologna, Italy, [11] Department of Neuroscience, Reproductive, and Odontostomatological Sciences, Epilepsy Centre, University of Naples Federico II, Naples, Italy, [12] IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Neuropsichiatria dell'età Pediatrica, Bologna, Italy, [13] Department of Pediatrics, Epilepsy Center, Institute of Medicine, University Hospital of Udine, Udine, Italy, [14] Department of Child Neurology and Psychiatry, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Mondino Foundation, Pavia, Italy, [15] Pediatric Neurology, Department of Neuroscience, Santobono-Pausilipon Children's Hospital, Naples, Italy, [16] Unit for Severe Disabilities in Developmental Age and Young Adults (Developmental Neurology and Neurorehabilitation), Scientific Institute Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) "E. Medea", Brindisi, Italy, [17] Epilepsy Centre - Clinic of Nervous System Diseases, Riuniti Hospital, Foggia, Italy, [18] Oasi Research Institute Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS), Troina, Italy, [19] Epilepsy Center, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Mondino Foundation, Pavia, Italy, [20] Neurology Unit, Department of Human Neurosciences, "Sapienza" University, Rome, Italy, [21] Department of Pediatric Neuroscience, Fondazione Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Neurologico Carlo Besta, Milan, Italy, [22] Pediatric Neurology, Neurogenetics, and Neurobiology Unit and Laboratories, A. Meyer Children's Hospital, Florence, Italy, [23] Pediatric Neurology Unit, Epilepsy Center, Department of Neuroscience, "Fatebenefratelli e Oftalmico" Hospital, Milan, Italy, [24] Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Bari, Italy, [25] Pediatric Neurology and Muscular Diseases Unit, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) 'G. Gaslini' Institute, Genoa, Italy, [26] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal, and Child Health, University of Genoa, Genoa, Italy, [27] Department of Pediatric Neurology, V. Buzzi Children's Hospital, Milan, Italy, [28] Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto delle Scienze Neurologiche di Bologna, Unit of Neurology, Bellaria Hospital, Bologna, Italy, [29] Paediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University Hospital of Padua, Padua, Italy

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Taylor J. Abel, University of Pittsburgh, United States

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Tyler Gaston, University of Alabama at Birmingham, United States
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***Correspondence:**
Emilio Russo
erusso@unicz.it

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[30] Pediatric Neurology and Epileptology Unit, Brotzu Hospital Trust, Cagliari, Italy, [31] Child Neurology Division, Department of Pediatrics, Sapienza University of Rome, Rome, Italy, [32] Neurology Unit, Department of Neurosciences (N.S., M.T.), Bambino Gesù Children's Hospital, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS), Rome, Italy, [33] Claudio Munari" Epilepsy Surgery Centre, Azienda Socio Sanitaria Territoriale (ASST) Grande Ospedale Metropolitano Niguarda, Milan, Italy, [34] Child Neuropsychiatry Department, Maggiore della Carità University Hospital, Novara, Italy, [35] Clinical Neurophysiology Unit, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Eugenio Medea, Scientific Institute, Lecco, Italy, [36] Department of Human Neurosciences, Sapienza University, Rome, Italy

Background: Purified cannabidiol (CBD) was administered to highly refractory patients with Dravet (DS) or Lennox–Gastaut (LGS) syndromes in an ongoing expanded access program (EAP). Herein, we report interim results on CBD safety and seizure outcomes in patients treated for a 12-month period.

Material and Methods: Thirty centers were enrolled from December 2018 to December 2019 within the open-label prospective EAP up to a maximum of 25 mg/kg per day. Adverse effects and liver function tests were assessed after 2 weeks; 1, 3, and 6 months of treatment; and periodically thereafter. Seizure endpoints were the percentage of patients with ≥50 and 100% reduction in seizures compared to baseline.

Results: A total of 93 patients were enrolled and included in the safety analysis. Eighty-two patients [27 (32.9%) DS, 55 (67.1%) LGS] with at least 3 months of treatment have been included in the effectiveness analysis; median previously failed antiseizure medications was eight. Pediatric and adult patients were uniformly represented in the cohort. At 3-month follow-up, compared to the 28-day baseline period, the percentage of patients with at least a 50% reduction in seizure frequency was 40.2% (plus 1.2% seizure-free). Retention rate was similar according to diagnosis, while we found an increased number of patients remaining under treatment in the adult group. CBD was mostly coadministered with valproic acid (62.2%) and clobazam (41.5%). In the safety dataset, 29 (31.2%) dropped out: reasons were lack of efficacy [16 (17.2%)] and adverse events (AEs) [12 (12.9%)], and one met withdrawal criteria (1.1%). Most reported AEs were somnolence (22.6%) and diarrhea (11.9%), followed by transaminase elevation and loss of appetite.

Conclusions: CBD is associated with improved seizure control also in a considerable proportion of highly refractory patients with DS and LGS independently from clobazam use. Overall, CBD safety and effectiveness are not dose-related in this cohort.

Keywords: cannabidiol, epilepsy, Dravet syndrome, lennox-gastaut syndrome, expanded access program

INTRODUCTION

Cannabidiol (CBD) is a non-psychoactive phytocannabinoid derived from the *Cannabis sativa* plant with antiseizure effects through a still partially unknown mechanism that does not activate or bind directly cannabinoid receptors, unlikely to tetrahydrocannabidiol (1). Several mechanisms have been proposed to mediate antiseizure proprieties so far, including the inhibition of the GPR55 orphan receptor and adenosine reuptake, as well as the activation/desensitization of TRPV1 (2, 3). A pharmaceutical formulation of highly purified CBD has been recently approved by US Food and Drug Administration (FDA) (4) and European Medicine Agency (EMA) (5) for the treatment of seizures associated with two treatment-resistant epilepsies (TREs), Dravet (DS), and Lennox–Gastaut (LGS) syndromes, typically refractory to currently available antiseizure medications (ASMs) and more recently for the treatment of seizures associated with tuberous sclerosis (6). Pharmacokinetic and pharmacodynamic drug–drug interactions can occur between CBD and clobazam (CLB), with an up to 5-fold increase in *N*-desmethylclobazam plasma concentration. Notably, and in line with this observation, EMA authorization imposes the coadministration with CLB as a prescription rule in contrast to FDA. Subsequently, a meta-analysis indicated the lack of difference in seizure outcome in CLB-off patients (7); undoubtedly, any regulatory discrepancy should be addressed following convincing clinically relevant results.

CBD has demonstrated efficacy and an acceptable safety profile both in four phase III clinical trials and in expanded access programs (EAPs), also referred to as Compassionate Use

Programs. Although, biased by the lack of a control group and open-label design, EAPs have the advantage to be more reflective of clinical practice and to facilitate access to innovative treatments before approval. We report the *interim* results on CBD safety and seizure outcomes from an Italian EAP.

MATERIALS AND METHODS

Patient Population and Study Design

Thirty Italian epilepsy centers enrolled LGS and DS patients from December 2018 through an open-label prospective and ongoing EAP with eligibility criteria (**Supplementary Material**) comparable to placebo-controlled trials and other EAPs (8–10), with dosages up to a maximum of 25 mg/kg per day. The protocol was approved by each site (DM 07/09/2017; Italian Official Gazette on November 2, 2017), and written informed consent has been provided by patients or parents/caregivers. The study was conducted following the Good Clinical Practice guidelines and local standard operating procedures. Overall data collection has been approved by the Ethics Committee, Catanzaro, Italy, protocol no. 115/19.

Procedures

Data were collected on all seizure types and according to the previous studies (8, 10, 11), convulsive seizures were defined as tonic, clonic, tonic–clonic, atonic, or secondary generalized. Non-convulsive seizures were defined as myoclonic, absence, or myoclonic–absence seizures, and focal seizures with or without impaired consciousness.

During a 4-week baseline period, diaries of all countable seizures have been provided by patients or parents/caregivers. Afterward, patients received an oral solution of purified CBD (100 mg/ml; Epidyolex GW Research Ltd.), starting dosage between 2 and 5 mg/kg per day up to 18–25 mg/kg per day, depending on the site.

Concomitant ASMs were recorded at baseline and during the treatment period. CBD and ASM dose modifications, as well as adding/removing co-ASMs, were allowed as clinically appropriated.

Visits have been performed after 2 weeks; 1, 3, and 6 months of treatment; and periodically thereafter. However, scheduled visits to assess treatment were programmed at 3, 6, 9, at 12 months.

Assessment of adverse events (AEs) and clinical laboratory parameters was performed approximately after 2 weeks; 1, 3 and 6 months of treatment; and periodically thereafter. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA, version 22.0). All AEs have been reported and detailed as severe or leading to discontinuation as appropriate. Finally, the incidence of AEs has been reported according to concomitant ASMs.

Assessment of Effectiveness

Seizure frequency has been provided per week since the previous visit, and efficacy outcomes were assessed at 3, 6, 9, and 12 months. According to other similar published studies (8, 11, 12), weekly seizure frequency was converted to frequency per 28 days (weekly frequency × 4). Percentage change in seizure frequency for each patient was calculated as ([seizure frequency per 28 days]–[seizure frequency at baseline])/[seizure frequency at baseline] × 100. Median percentage changes in seizure frequency were calculated due to interpatient variability (8, 11, 12).

Seizure endpoints were the percentage of patients with ≥50 and 100% reduction in monthly convulsive and total seizures compared to 4-week baseline (response rate). Additional variables assessed were episodes of status epilepticus, use of rescue medications, and hospital admissions.

Some sites assessed changes in electroencephalography before and during treatment. Furthermore, questionnaires on quality of life (i.e., QOLIE-31), sleep disturbance (i.e., Sleep Disturbance Scale for Children, Epworth Sleepiness Scale), behavior (Neurological Disorders Depression Inventory for Epilepsy, Child Behavior Check List, Beck Depression Inventory for Primary Care), and the Clinical Global Impression Scale have been collected. However, data have not been provided consistently through sites and have not been reported in the current analysis.

Analysis

The sample size was based on patients' enrolment on each study site and not precalculated. Patients treated with at least one dose of CBD and post baseline evaluation have been assessed in the safety analysis. Effectiveness analysis was composed of all patients with at least 3 months of treatment. Kaplan–Meier curves have been built to evaluate CBD retention rates in effectiveness population and in patients with at least 1-month follow-up. The Mann–Whitney U-test for continuous variables and the two-tailed Pearson χ^2 test or the Fisher test for categorical variables have been applied as appropriate. Finally, univariate and multivariate logistic regression analyses were carried out [odds ratios (ORs) and 95% confidence intervals (CIs)] to explore the variables independently associated with responder status at 3 and 12 months; variables included in the equation variables were significant in previous analysis or had a clinical interest. A $p < 0.05$ was considered significant for all variables. All the data were analyzed using SPSS software version 26.0 (SPSS Statistics; IBM Corp., Armonk, NY, USA).

RESULTS

Clinical Features

A total of 93 patients were enrolled in the EAP; the median number of patients per site was 3 (range = 1–11), and all patients have been included in the safety analysis. Eighty-two patients [27 (32.9%) DS, 55 (67.1%) LGS] with at least 3 months of treatment have been included in the effectiveness analysis. In the safety dataset, 29 (31.2%) dropped out; reasons were lack of efficacy [16 (17.2%)] and AEs [12 (12.9%)], and one met withdrawal criteria (1.1%; concomitant use of other cannabis-derived products) (**Figure 1**).

Overall, the mean (SD) treatment duration was 8.7 (4.1) months, and effectiveness data for the 12-month follow-up were available for 51 of 82 patients (62.2%). In both analysis groups, the mean age was 21 years (range = 3–56 years), about 32.0% had DS, and adults were 50.5% and the 52.4% in safety and effectiveness analyses, respectively. Demographic

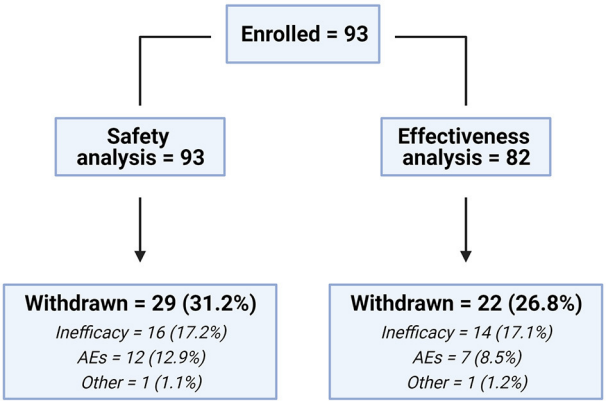

FIGURE 1 | Patients' distribution flowchart. AEs, adverse events. Created with Biorender.com.

TABLE 1 | Patients baseline demographic and clinical features.

	Safety ($n = 93$)	Effectiveness ($n = 82$)
Age (years), mean ± SD	21.4 ± 13.5	21.0 ± 13.1
Sex, male/female, *n* (%)	49 (52.7)/44 (47.3)	46 (56.1)/36 (43.9)
Body weight (kg), mean ± SD	50.8 ± 23.1	50.8 ± 21.9
Pediatrics/adults, *n* (%)	46 (49.5)/47 (50.5)	39 (47.6)/43 (52.4)
Diagnosis		
Dravet, *n* (%)	30 (32.3)	27 (32.9)
Lennox–Gastaut, *n* (%)	63 (67.7)	55 (67.1)
Concomitant ASMs taken at baseline, median (Q1–Q3)	3 (3–4)	3 (3–4)
Convulsive seizures/28 d, median (Q1–Q3)*	—	49 (12–147)
Total seizures/28 d, median (Q1–Q3)*	—	71.5 (23.6–181)

*ASMs, antiseizure medications. *During 4-week baseline period.*

and clinical features at baseline are presented in **Table 1**. Patients' stratifications by diagnosis and age are detailed in **Supplementary Tables 1, 2**.

At baseline, a median of eight ASMs utilized before CBD administration has been reported, with the median number of concomitant ASMs at the time of CBD administration being 3 (range = 1–5).

Concomitant ASMs are detailed in **Supplementary Table 3**. The most common concomitant ASMs were valproic acid (62.2%, including sodium valproate), CLB (41.5%), lamotrigine (25.6%), and stiripentol (19.5%). The mean doses administered before CBD treatment were 19 (9.8) mg/day for CLB and 916 (557.7) mg/day for valproate.

Seizure Outcomes

At baseline, the median (Q1, Q3) monthly frequency of convulsive and total seizures was 49 (12, 147) and 71.5 (23.6, 181) (**Table 1**). At the first 3-month follow-up, 24 patients (40.2%), compared to the 28-day baseline period, reported at least a 50% reduction in total-seizure frequency plus *one* patient seizure-free (1.2%).

At 12-month follow-up (51/82 patients, 62.2%), the percentage of patients with at least a 50% reduction in total-seizure frequency was 49.0% (plus 3.9% seizure-free), whereas 21.6% had a reduction <50%, 15.7% had no change, and 9.8% seizures worsening (**Table 2**). Median reductions of 50.7 and 55.0% in total and convulsive seizures frequencies have been reported (**Figure 2A**). No differences were highlighted in achieving responder status at 12 months in patients cotreated with CLB ($p = 0.64$) (**Supplementary Figure 1**).

The median dose of CBD between 3 and 12 months was 14 mg/kg per day. The CBD doses related to achieving responder status (defined as reduction ≥50% in seizure frequency plus seizure-free) at different follow-up are reported in **Figure 2B**; no difference was observed between responders and non-responders. Twenty patients (20/82; 24.4%) reduced the CBD dose at any time during follow-up. Approximately 25% of the patients taking concomitant CLB and/or valproate modified their dose from baseline during the study (**Table 3**).

Univariate logistic regression was performed to determine the effects of several variables on achieving responder status at 3 and 12 months of treatment (**Table 4**). Multivariate logistic regressions using the variables included in the univariate analysis were performed. Both models explained 30% (Nagelkerke R^2) of the variance to achieve responder status at 3 and 12 months. Only CLB use was independently associated with higher responder rate (OR = 4.04, CI = 1.1–14.5, $p = 0.03$) at 3 months but not at 12 months (**Table 5**). No variables have been significantly associated at 12 months.

CBD Retention

In patients with at least 1 month of treatment, the overall retention rate was 68.5%, and log-rank tests were run to determine differences in the CBD retention rate for diagnosis (DS and LGS) or age (pediatrics and adults). The survival distribution was statistically significantly different for age, $\chi^2 = 7.38$, $p = 0.007$ (80.4% retention rate for patients ≥18 years), whereas no statistical significance was reached for diagnosis $\chi^2 = 3.04$, $p = 0.06$ (82.1% retention rate for DS) (**Figure 3**). Notably, when considering the diagnosis in the age subgroups, DS pediatric patients have a higher retention rate than LGS patients ($\chi^2 = 9.96$, $p = 0.002$), whereas no difference was observed in adult patients ($\chi^2 = 0.03$, $p = 0.87$) (**Supplementary Figure 2**).

Tolerability

In the safety analysis, 48 patients (51.6%) experienced at least one AE. Overall, the most common AEs reported were somnolence [21 (22.6%)] and diarrhea [11 (11.8%)], followed by elevated liver enzymes (alanine aminotransferase/aspartate aminotransferase >3 upper than the normal limit) (10, 10.7%) and loss of appetite (8, 8.6%) (**Table 6**). Eight AEs (8.6%) have been classified as serious, with the most common being status epilepticus (9.6%) and vomiting (2.1%); 12 AEs [12/91 (13.2%)] led to CBD discontinuation. AEs are detailed in **Supplementary Tables 4, 5**. Patients with elevated liver enzymes or hyperammonemia

TABLE 2 | Treatment response rate for convulsive seizures (A) and total seizures (B).

	Full cohort	Worsened	Unchanged	<50%	≥50%	Seizure-free
(A)						
Outcome 3 months, *n* (%)	82 (100)	11 (13.4)	21 (25.6)	24 (29.3)	24 (29.3)	2 (2.4)
Outcome 6 months, *n* (%)	71 (86.5)	8 (11.3)	13 (18.3)	17 (23.9)	29 (40.8)	4 (5.6)
Outcome 9 months, *n* (%)	61 (74.4)	7 (11.5)	9 (14.7)	14 (22.9)	28 (45.9)	3 (4.9)
Outcome 12 months, *n* (%)	51 (62.2)	6 (11.7)	6 (11.7)	12 (23.5)	23 (45.1)	4 (7.8)
(B)						
Outcome 3 months, *n* (%)	82 (100)	10 (12.2)	18 (22.0)	20 (24.4)	33 (40.2)	1 (1.2)
Outcome 6 months, *n* (%)	72 (87.8)	6 (8.3)	14 (19.4)	17 (23.6)	32 (44.5)	3 (4.2)
Outcome 9 months, *n* (%)	61 (74.4)	3 (4.9)	10 (16.4)	13 (21.3)	33 (54.1)	2 (3.3)
Outcome 12 months, *n* (%)	51 (62.2)	5 (9.8)	8 (15.7)	11 (21.6)	25 (49.0)	2 (3.9)

Total seizures included convulsive seizures (i.e., clonic, tonic, tonic–clonic, atonic, focal secondary generalized) and non-convulsive seizures (i.e., myoclonic, absence, myoclonic absence, focal with and without impaired consciousness). All response rate percentages are reported considering the total number of patients per follow-up. Seizure-free is not included in ≥50% cohort.

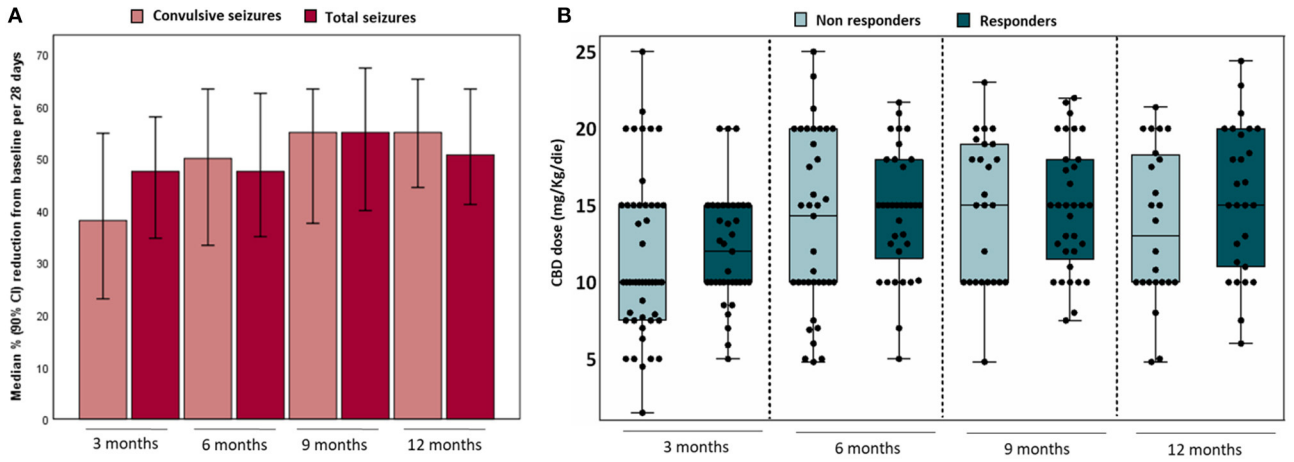

FIGURE 2 | Percentage reduction in median seizures per 28 days from baseline in convulsive and total# seizures for effectiveness analysis **(A)** and CBD doses related to achieving responder status at different outcomes **(B)**. #Total seizures included convulsive seizures (i.e., clonic, tonic, tonic–clonic, atonic, focal secondary generalized) and non-convulsive seizures (i.e., myoclonic, absence, myoclonic-absence, focal with and without impaired consciousness). NR, non-responders; R, responders (≥50% frequency reduction and seizure-free).

TABLE 3 | Dosing information coadministered ASMs.

ASMs dose adjustment at all visits, *n* (%)	Valproate (*n* = 51)	Clobazam (*n* = 34)	Lamotrigine (*n* = 21)
Baseline dose stable	39 (74.5)	26 (76.5)	16 (76.2)
Baseline dose increased	1 (1.9)	0	0
Baseline dose decreased	8 (15.6)	1 (2.9)	3 (14.3)
Baseline dose increased and decreased	3 (5.9)	7 (20.6)	2 (9.5)

ASMs, antiseizure medications.

[occurred in 10 (10.7%) and 7 patients (7.7%), respectively] were always cotreated with valproate. Somnolence occurred in 27.5% of patients taking CLB (11/40) compared to 15.1% (8/53) not cotreated. No thrombocytopenia (i.e., platelets count < 140,000/μL) has been reported.

DISCUSSION

In our cohort of highly treatment-resistant patients with DS and LGS, add-on treatment of CBD for 12 months was associated with a reduction in seizure frequency and was generally well-tolerated.

Overall, the percentage of patients achieving a seizure reduction ≥50% for total seizures comprised between 41.4% (34/82 patients) at 3 months and 52.9% (27/51 patients) at 12 months. Our results are in line with the 38–52% reported in several studies involving different TREs (8, 12) and the 43–50% in an EAP with DS and Lennox syndrome only (10). Furthermore, a consistent percentage of patients achieved a seizure-free status compared to baseline after 3 months of treatment and during the 12-month follow-up period.

No differences have been highlighted in median seizure frequency reductions comparing patients on CLB and those without, as well as in responder status achievement. However,

TABLE 4 | Univariate regressions with selected variables for clinical response.

	Clinical response at 3 months			Clinical response at 12 months		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age	1.02	0.98–1.05	0.21	0.99	0.95–1.04	0.90
Sex, female	2.85	1.15–7.09	**0.02**	1.85	0.59–5.78	0.28
Diagnosis (Lennox–Gastaut)	1.05	0.41–2.66	0.93	1.42	0.45–4.46	0.54
Pediatrics	0.52	0.21–1.28	0.15	0.83	0.26–2.63	0.75
Patients experienced AEs	1.55	0.64–3.77	0.33	0.77	0.25–2.33	0.64
CBD dose (3 or 12 months)	1.04	0.94–1.15	0.41	1.08	0.96–1.21	0.18
Concomitant ASMs	0.89	0.55–1.47	0.66	0.88	0.47–1.64	0.69
Cotreatment with clobazam	1.82	0.74–4.46	0.19	1.30	0.43–3.93	0.64
Cotreatment with stiripentol	0.40	0.12–1.37	0.14	0.68	0.18–2.60	0.57
Cotreatment with valproate	0.63	0.25–1.56	0.32	0.47	0.12–1.37	0.15
Cotreatment with lamotrigine	1.40	0.51–3.80	0.50	1.26	0.36–4.36	0.71
Convulsive seizures frequency at baseline	0.99	0.99–1.00	0.19	1.00	0.99–1.01	0.17
Total seizures frequency at baseline	1.00	0.99–1.00	0.57	1.00	0.99–1.00	0.09

ASMs, antiseizure medications; CBD, cannabidiol; AEs, adverse events. Bold values are statistically significant.

TABLE 5 | Multivariate regressions with selected variables for clinical response.

	Clinical response at 3 months			Clinical response at 12 months		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age	1.01	0.94–1.08	0.86	0.99	0.19–1.07	0.89
Sex, female	2.30	0.76–6.91	0.14	1.66	0.38–7.23	0.50
Diagnosis (Lennox–Gastaut)	0.41	0.08–2.07	0.28	0.28	0.04–2.24	0.23
Pediatrics	0.73	0.14–3.81	0.71	0.41	0.05–3.26	0.40
Patients experienced AEs	0.97	0.30–3.17	0.97	1.12	0.23–5.24	0.88
CBD dose (3 or 12 months)	1.06	0.93–1.21	0.34	1.14	0.98–1.31	0.08
Concomitant ASMs	0.74	0.38–1.40	0.35	1.01	0.43–2.36	0.98
Cotreatment with clobazam	4.04	1.12–14.57	**0.03**	3.39	0.58–19.87	0.17
Cotreatment with stiripentol	0.23	0.04–1.37	0.11	0.69	0.08–5.65	0.73
Cotreatment with valproate	0.62	0.18–2.08	0.44	0.23	0.04–1.24	0.08
Cotreatment with lamotrigine	2.80	0.72–10.7	0.14	3.98	0.65–24.45	0.13
Convulsive seizures frequency at baseline	0.96	0.92–1.01	0.10	1.03	0.98–1.08	0.21
Total seizures frequency at baseline	1.02	0.99–1.06	0.14	1.01	0.98–1.03	0.58

Nagelkerke $R^2 = 0.31$ for 3 months and 0.30 for 12 months. All the variables have been included in the model. ASMs, antiseizure medications; CBD, cannabidiol; AEs, adverse events. Bold values are statistically significant.

CLB use has been associated with higher responder status (only at 3 months), as already reported (12). These findings confirm that CBD has antiseizure activity independent of concomitant CLB, but it is unknown to which extent CBD efficacy is enhanced (13).

The AE rates were lower (51.6%) than those reported in other EAPs and randomized clinical trials (79–94%), although, the most common reported AEs, somnolence, and diarrhea, were in line with the literature. On the other hand, an unexpected higher percentage of patients discontinued CBD because of AEs (12.8%), considering reported rates of 5.1, 8, and 3% in previous EAPs. However, one-third of discontinuations due to AEs belong to a single enrolling site, and this might overestimate the overall rate. Withdrawals for any reason were distributed regularly through the study follow-up period. The most common serious AEs reported, status epilepticus (9%) and vomiting (2%), were consistent with previous studies and randomized controlled trials (RCTs) (2, 14).

Notably, the overall incidence of AEs was higher in the group administered <10 mg/kg per day than the other dose group, in sharp contrast to the suggested dose effect (mainly for somnolence) reported in previous studies. Recently, one study has reported thrombocytopenia in one-third of patients treated concurrently with CBD and valproic acid (15). In our study, no cases of thrombocytopenia occurred, even though 62% of patients were cotreated with CBD and VPA.

Retention rate is generally used as a combined measure of effectiveness, tolerability, and patient/clinician preference. During the follow-up period, 68.5% of the patients with at least

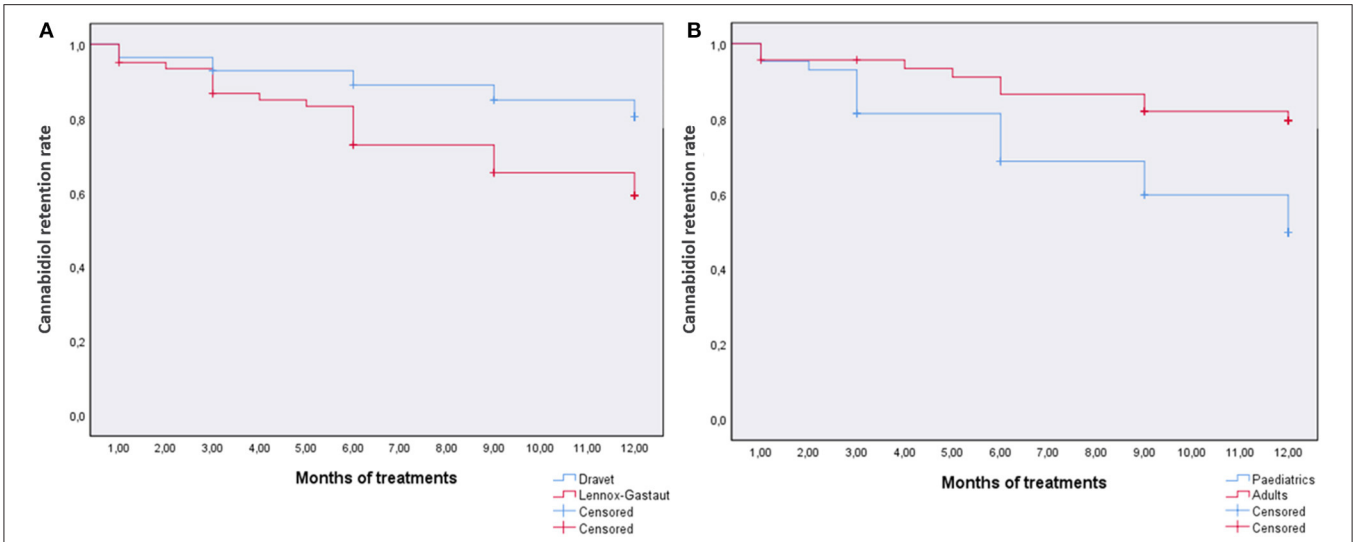

FIGURE 3 | The retention rate of cannabidiol in patients with at least 1-month follow-up stratified by diagnosis (Dravet syndrome and Lennox–Gastaut syndrome) **(A)** or age (pediatrics and adults) **(B)**.

TABLE 6 | Summary of adverse events in safety analysis.

	CBD dose (mg/kg per day)			
	0–10 (*n* = 28)	**11–15 (*n* = 29)**	**16–25 (*n* = 36)**	**All (*n* = 93)**
Overall AE rate, *n* (%)	25 (89.3)	19 (65.5)	4 (11.1)	48 (51.6)
Overall serious AE rate, *n* (%)	3 (10.7)	4 (10.3)	1 (2.7)	8 (8.6)
AEs leading to CBD discontinuation, *n* (%)	4 (14.3)	6 (20.6)	2 (5.5)	12 (12.8)
AEs reported ≥2% in any group				
Somnolence, *n* (%)	12 (42.8)	7 (24.1)	2 (5.5)	21 (22.6)
Diarrhea, *n* (%)	3 (10.7)	3 (10.3)	5 (13.8)	11 (11.8)
Transaminases elevated, *n* (%)	4 (14.3)	3 (10.3)	3 (8.3)	10 (10.7)
Status epilepticus, *n* (%)	1 (3.5)	5 (17.2)	3 (8.3)	9 (9.6)
Loss of appetite, *n* (%)	6 (21.4)	1 (3.4)	1 (2.7)	8 (8.6)
Hyperammonemia, *n* (%)	5 (17.8)	1 (3.4)	1 (2.7)	7 (7.5)
Balance disorder, *n* (%)	3 (10.7)	2 (6.8)	1 (2.7)	6 (6.4)
Irritability, *n* (%)	0	3 (10.3)	1 (2.7)	4 (4.3)
Vomit, *n* (%)	2 (7.1)	0	1 (2.7)	3 (3.2)

1 month of treatment remained on CBD, relatively in line with the other EAPs at 12 months (∼60%) (11) and studies with no TREs (63–81%) (16). Bearing in mind the limitation of the low number of patients treated, we found that the retention rate for adults was significantly higher than that for pediatric patients; this parameter is not accompanied by a significant difference on seizures, but it is worth noting that in our ancillary study on CBD plasma concentrations, we observed that concentration/dose ratio is significantly lower in patients younger than 18 years (17). Also in this latter case, no correlation was found between dose, plasma concentration, and efficacy, and further studies are warranted to understand whether this low trough CBD concentration is meaningfully linked to efficacy and safety.

The median CBD dose (14 mg/kg per day) remains stable at all follow-ups, although, 20 patients reduced the dose as allowed by the protocol. Unfortunately, the reason for reductions was not consistently reported by sites and could not be analyzed.

CBD has well-known bidirectional drug–drug interactions with CLB (increasing nordesmethylclobazam and 7-hydroxy-CBD) and valproate (probably pharmacodynamic rather than pharmacokinetic interactions) (18, 19), and several AEs have been reported due to drug–drug interactions. In our cohort, all the patients reporting transaminase elevation or hyperammonemia were taking concomitant valproate, further confirming the role of this interaction in the development of such AEs, as reported in the aforementioned EAPs and RCTs. As expected, somnolence has been experienced twice in patients on concomitant CLB compared to patients without, but no patients withdrew due to somnolence.

Main limitations of this study are open-label design and uncontrolled EAP. Furthermore, reporting methods could be different among enrolling sites and motivation for CBD, or concomitant ASM dose reductions were not consistently reported. However, EAP can provide useful data being closer to clinical practice compared to randomized clinical trials and therefore more generalizable.

Of note, we found a high rate of patients on treatment at 12 months without a clear improvement in seizure count, raising the question whether other aspects and effects of CBD may have a positive impact on the overall clinical state. An alternative explanation is that Italian doctors, in the context of an EAP and of a public health–based medical system

where no restrictions exist in the duration of a treatment irrespective of its cost and actual efficacy, have a careless attitude toward withdrawing it, even after it has proven ineffective. On the other hand, public interest and expectancy in cannabis-based/derived therapies have been rising in the past 10 years and may have influenced patients and caregivers in a similar manner (20).

In conclusion, we confirm CBD effectiveness and tolerability in highly refractory DS and LGS patients also without the concomitant use of CLB. Of note, dose dependency for both efficacy and tolerability is not evidenced by our data. Finally, whether other potential CBD effects on the central nervous system (e.g., anxiolytic, antipsychotic) (21) may have a role in clinical practice warrants further research, and other parameters than seizure outcome may be worth a clinical evaluation (22, 23).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The protocol was approved by each site (DM 07/09/2017; Italian Official Gazette on November 2nd, 2017) and written informed consent has been provided by patients or parents/caregivers. The study was conducted following the Good Clinical Practice guidelines and local standard operating procedures. Overall data collection has been approved by the Ethics Committee, Catanzaro, Italy, protocol number 115/19.

AUTHOR CONTRIBUTIONS

ER and OM contributed to conception and design of the study. LI and GA organized the database. LI performed the statistical analysis. ER, LI, and PS wrote the manuscript. DB, FB, PB, AB, MPC, GCa, EC, MC, AC, DC, GCr, VD, MFD, MD, Gd'O, ME, CG, AM, TG, RG, ML, AL, FM, SM, RM, MN, NPil, DP, FR, AR, MS, AS, NPie, PS, ET, LT, AP, CZ, and OM provide patients' data. All authors contributed to manuscript revision, read, and approved the submitted version.

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CBD LICE ITALY STUDY GROUP

Clementina Boniver (Paediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University Hospital of Padua, Padua, Italy), Maria Bottitta (Oasi Research Institute IRCCS, Troina, Italy), Carlo Di Bonaventura (Neurology Unit, Department of Human Neurosciences, "Sapienza" University, Rome, Italy), Viola Doccini (Pediatric Neurology, Neurogenetics, and Neurobiology Unit and Laboratories, A. Meyer Children's Hospital, Florence, Italy), Roberta Epifanio (Clinical Neurophysiology Unit, IRCCS Eugenio Medea, Scientific Institute, Lecco, Italy), Giovanni Falcicchio (Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Bari, Italy), Massimo Mastrangelo (Department of Pediatric Neurology, V. Buzzi Children's Hospital, Milan, Italy), Sara Matricardi (Child Neurology and Psychiatry Unit, G. Salesi Children's Hospital-University of Ancona, Ancona, Italy), Ludovica Pasca (Department of Child Neurology and Psychiatry, IRCCS Mondino Foundation, Pavia Italy), Federica Pondrelli (Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy), Patrizia Pulitano (Department of Human Neurosciences, Sapienza University, Rome, Italy), Antonella Riva (Pediatric Neurology and Muscular Diseases Unit, IRCCS 'G. Gaslini' Institute, Genoa, Italy; Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal, and Child Health, University of Genova, Genova, Italy), Paola Russo (Department of Neuroscience, Reproductive, and Odontostomatological Sciences, Epilepsy Centre, University of Naples Federico II, Naples, Italy), Nicola Specchio (Department of Pediatric Neuroscience, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy), Silvia Spolverato (Child Neuropsychiatry, Department of Surgical Sciences, Dentistry, Gynecology, and Pediatrics, University of Verona, Verona, Italy), Aglaia Vignoli (Department of Health Sciences, Epilepsy Center, San Paolo Hospital, University of Milan, Milan, Italy), Maurizio Viri (Child Neuropsychiatry Department, Maggiore della Carità University Hospital, Novara, Italy), Lilia Volpi (IRCCS Istituto delle Scienze Neurologiche di Bologna, Unit of Neurology, Bellaria Hospital, Bologna, Italy).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.673135/full#supplementary-material

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CASE REPORT
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Case Report: Subtotal Hemispherotomy Modulates the Epileptic Spasms in Aicardi Syndrome

Yasushi Iimura[1], Hidenori Sugano[1], Takumi Mitsuhashi[1], Tetsuya Ueda[1], Kostadin Karagiozov[1], Shimpei Abe[2] and Hiroshi Otsubo[1,3]*

[1] Department of Neurosurgery, Epilepsy Center, Juntendo University, Tokyo, Japan, [2] Department of Pediatrics, Epilepsy Center, Juntendo University, Tokyo, Japan, [3] Division of Neurology, The Hospital for Sick Children, Toronto, ON, Canada

The mechanism of epileptic spasms (ES) in Aicardi syndrome (AS) remains obscure. We compared intraoperative high-frequency oscillations (HFOs) and phase-amplitude coupling (PAC) before and after subtotal hemispherotomy in a 3-month-old girl with drug-resistant ES secondary to AS. Fetal ultrasonography showing corpus callosum agenesis, bilateral ventricular dilatation, and a large choroid plexus cyst confirmed AS diagnosis. Her ES started when she was 1 month old and had ten series of clustered ES per day despite phenobarbital and vitamin B6 treatment. After subtotal hemispherotomy, her ES dramatically improved. We analyzed two intraoperative electrocorticography modalities: (1), occurrence rate (OR) of HFOs; (2), PAC of HFOs and slow wave bands in the frontal, central, and parietal areas. We hypothesized that HFOs and PAC could be the biomarkers for efficacy of subtotal hemispherotomy in AS with ES. PAC in all three areas and OR of HFOs in the frontal and parietal areas significantly decreased, while OR of HFOs in the central area remained unchanged after subtotal hemispherotomy. We have demonstrated the usefulness of evaluating intraoperative HFOs and PAC to assess subtotal hemispherotomy effectiveness in AS patients with ES. Disconnecting the thalamocortical and subcortical pathways in the epileptic network plays a role in controlling ES generation.

Keywords: epileptic spasms, high frequency oscillations, phase-amplitude coupling, subtotal hemispherotomy, modulation index

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***Correspondence:**
Hidenori Sugano
debo@juntendo.ac.jp

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INTRODUCTION

Aicardi syndrome (AS) is a neurodevelopmental disorder characterized by seizures and agenesis of the corpus callosum and chorioretinal lacunae (1). Children with AS have psychomotor retardation and poor functional outcomes (2). Epileptic spasms (ES) are the most typical seizure type in AS, becoming drug-resistant with time (3). The therapeutic purpose in children with AS is to control the ES and improve the functional outcome.

Reported medical treatments for ESs in general include adrenocorticotropic hormone (ACTH), vigabatrin, ketogenic diet, and various antiepileptic drugs, but the seizure outcome is unsatisfactory (4). Seizure control was also unsatisfactory following lesionectomy, hemispherectomy, multilobar resection, and vagus nerve stimulation (VNS) as a surgical treatment for the ES (3–6). Chugani et al.

reported that subtotal hemispherectomy effectively controlled ES, however, this procedure has not been reported in patients with AS (4, 7).

Clinically, the mechanism of ES has not been determined yet, so it is categorized into focal, generalized, or unknown onset based on the seizure type (8). Several electrophysiological analyses, including high-frequency oscillations (HFOs) and phase-amplitude coupling (PAC), were used to reveal the mechanism of ES. HFOs have become a promising biomarker for the epileptogenic zones in invasive and non-invasive EEG (9–11). PAC of HFOs and slow wave bands, rather than HFOs alone, was applied to localize the epileptic foci (12). Children with ES were reported to demonstrate high occurrence rate (OR) of HFOs and high values of PAC (13, 14).

We describe a case of an AS patient without hemiparesis who developed drug-resistant ES and in whom we performed subtotal hemispherotomy. Intraoperative electrocorticography (ECoG) was performed, and HFOs and PAC were analyzed before and after surgery as an assessment of subtotal hemispherotomy efficacy. To the best of our knowledge, this is the first report of intraoperative ECoG recording and quantitative analysis in an AS patient with ES. We hypothesized that intraoperative HFOs and PAC could act as biomarkers for ES network disconnection.

CASE DESCRIPTION

History and Examinations

The female fetus was diagnosed with AS by ultrasonography (US) at 30 weeks of gestation. The US showed corpus callosum agenesis, bilateral ventricle dilatation, and a large choroid plexus cyst in the left trigone of the lateral ventricle. The baby was born without any complications at 41 weeks of gestation at 3,128 g. She had no family history of epileptic disorders, her muscle tone was normal, and there was no paresis. Ophthalmologic examination revealed bilateral chorioretinal lacunae.

The ES started when she was 1 month old and escalated to ten series of clustered ES per day despite treatment with phenobarbital and vitamin B6. The semiology of her ES was symmetric. Prolonged scalp video interictal EEG showed that multifocal epileptiform abnormalities were generated only over the right hemisphere (**Figure 1A**). Interictal background EEG in the left hemisphere was grossly normal. Ictal EEG findings demonstrated that high amplitude positive slow waves were originated from the right hemisphere. Electromyogram showed as a rhombus shape, consistent with ES. Magnetic resonance imaging (MRI) demonstrated corpus callosum agenesis, bilateral ventricle dilatation with right-side predominance, and a large choroid plexus cyst in the left trigone of the lateral ventricle (**Figure 2A**). Fluorodeoxyglucose positron emission tomography- computed tomography (PET-CT) showed hypometabolism in the right hemisphere (**Figure 2B**). EEG and PET-CT findings were lateralized, suggesting that epilepsy surgery may improve the seizure outcome. In addition, due to the absence of hemiparesis, we performed the right subtotal hemispherotomy at the age of 3 months based on the results of the multidisciplinary consensus conference. At the time of surgery, her head control was unstable, but she had no hemiparesis.

Surgical Procedure and Postoperative Seizure Outcome

The patient's head was fastened on a horseshoe-shaped headrest at 45 degrees rotation to the opposite side of the craniotomy. We used a neuronavigation system (StealthStation surgical navigation system cranial application, Version 5; Medtronic, Minneapolis, MN, USA) to decide on the disconnection line and simulate it over the scalp before incising the skin. Subsequently, we performed a craniotomy with a curvilinear scalp incision, based on our preliminary design, to expose an adequate surgical field. After the craniotomy, we opened the Sylvian fissure and identified the limen insulae. The inferior horn of the lateral ventricle was opened through the inferior periinsular sulcus. The fornix and tail of the hippocampus were disconnected until the ambient cistern was visualized. These steps completely disconnected between the temporal lobe structures and basal ganglia. Parietal disconnection was performed along with the postcentral sulcus. Operative findings indicated that the Roland vein was absent, and the central sulcus was ambiguous (**Figure 3A**). The sclerotic cortex was identified in the central area. Corpus callosotomy was not done due to corpus callosum agenesis. Subsequently, we performed frontal disconnection along the precentral sulcus. Subtotal hemispherotomy was performed, sparing the motor cortex (**Figure 3C**).

The patient experienced no complications during or after the subtotal hemispherotomy. The postoperative ES frequency has decreased to three series per day. Postoperative interictal scalp EEG showed that the multifocal epileptiform abnormalities were originated from the right central and posterior quadrant region. Ictal EEG findings demonstrated that high amplitude positive slow waves were originated from the right hemisphere same as before subtotal hemispherotomy. Both frequency and amplitude during interictal and ictal epileptic discharges have decreased (**Figure 1B**). We administered ACTH therapy (0.015 mg/kg/day) for 2 weeks at the age of 4.6 months. Despite phenobarbital (90 mg/day), valproic acid (400 mg/day), and perampanel (1 mg/day) with no adverse events, the three daily ES series remained even 19 months after the surgery. She had psychomotor developmental delay despite of the absence of hemiparesis.

HFOs and PAC Analysis in the Intraoperative ECoG

We used NeuroFax (Nihon-Koden, Tokyo, Japan) at a sampling rate of 2,000 Hz to record intraoperative ECoG under total propofol-based intravenous anesthesia. The recording was done before and after performing the subtotal hemispherotomy and lasted 10 min at each time point (**Figures 3D,E**). We placed a 4×6 subdural grid (Unique Medical Co., Ltd., Tokyo, Japan), consisting of 24 platinum electrodes (4-mm diameter and 10-mm distance), from the frontal to the parietal lobes (**Figure 3B**). The electrodes were placed over the frontal, central, and parietal areas, $n = 8$ in each.

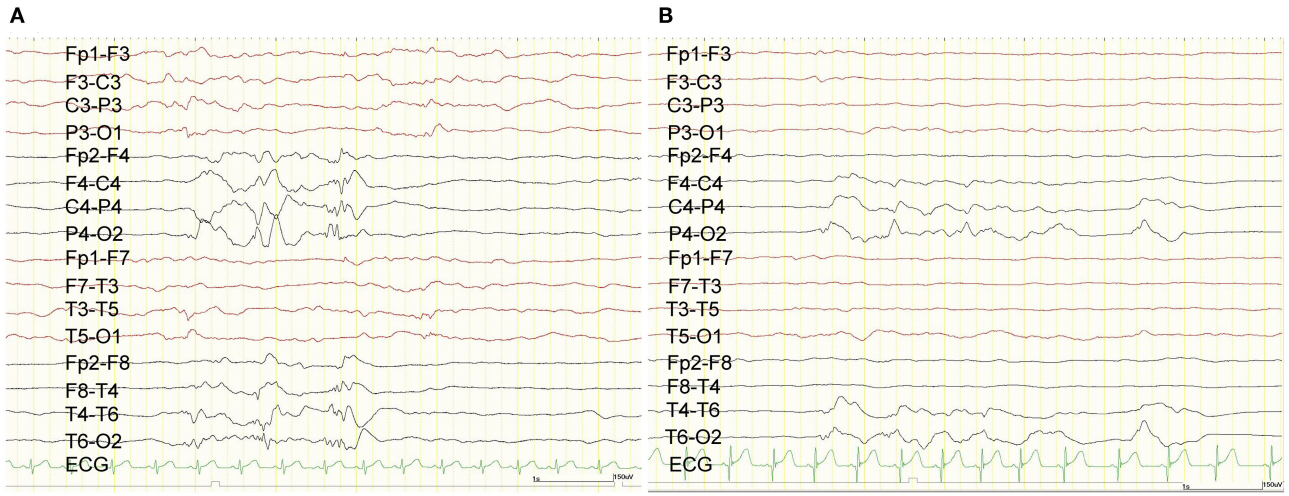

FIGURE 1 | Scalp EEG. Preoperative scalp EEG revealed interictal epileptic discharges originating from the right hemisphere **(A)**. Postoperative scalp EEG demonstrated that the interictal epileptic discharges from the right hemisphere were reduced **(B)**.

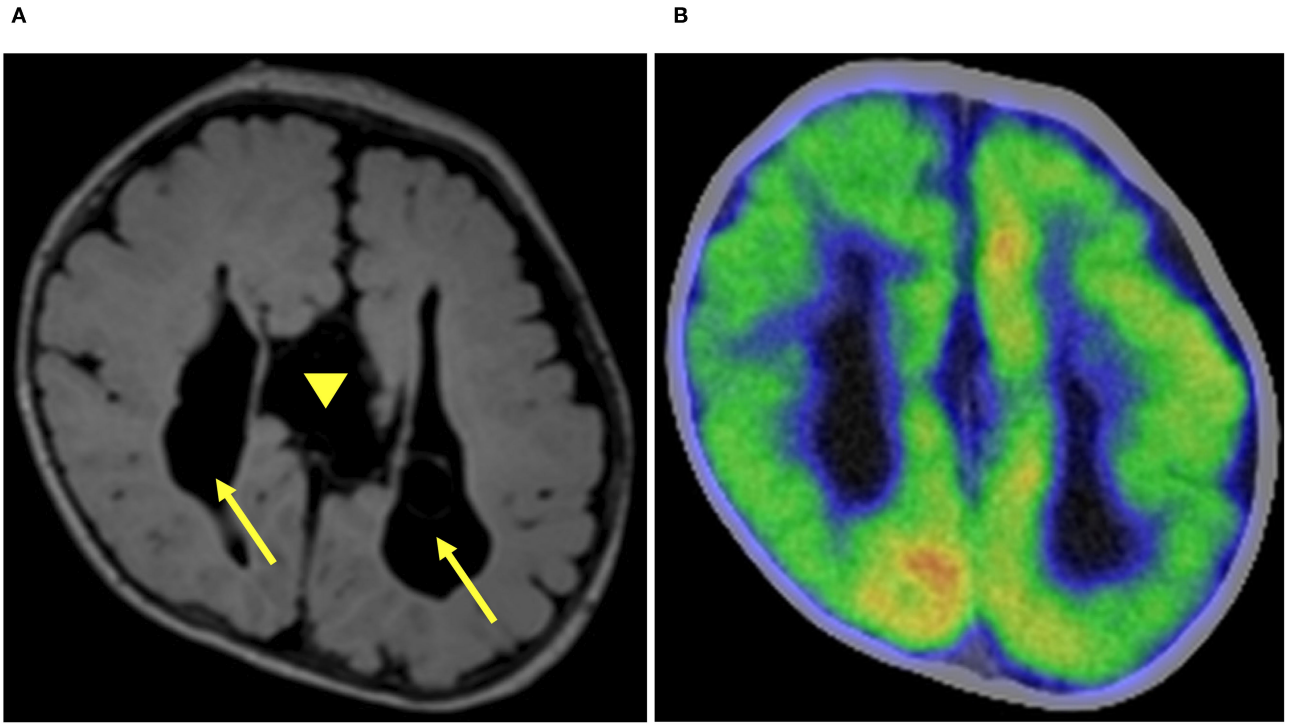

FIGURE 2 | Preoperative imaging. Preoperative axial fluid-attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) demonstrated corpus callosum agenesis (arrow head) and bilateral (right dominant) ventricular dilatation (arrow) **(A)**. Fluorodeoxyglucose-positron emission tomography-computed tomography showed hypometabolism in the right hemisphere **(B)**.

HFOs on the bipolar montage were automatically detected by MATLAB same as previous report (10). A band-pass filter at 80–200 Hz and a high-pass filter at 200 Hz were used to extract ripples (80–200 Hz) and fast ripples (FRs; 200–300 Hz), respectively. Because the interictal HFOs appear as intermittent peaks in the envelope curve, the envelope curve of the filtered ECoG was calculated by Hilbert transform. Events of ripples and FRs are detected by thresholding. Epochs with the envelope curve exceeding the threshold are detected as events of ripples and FRs, respectively. We visually

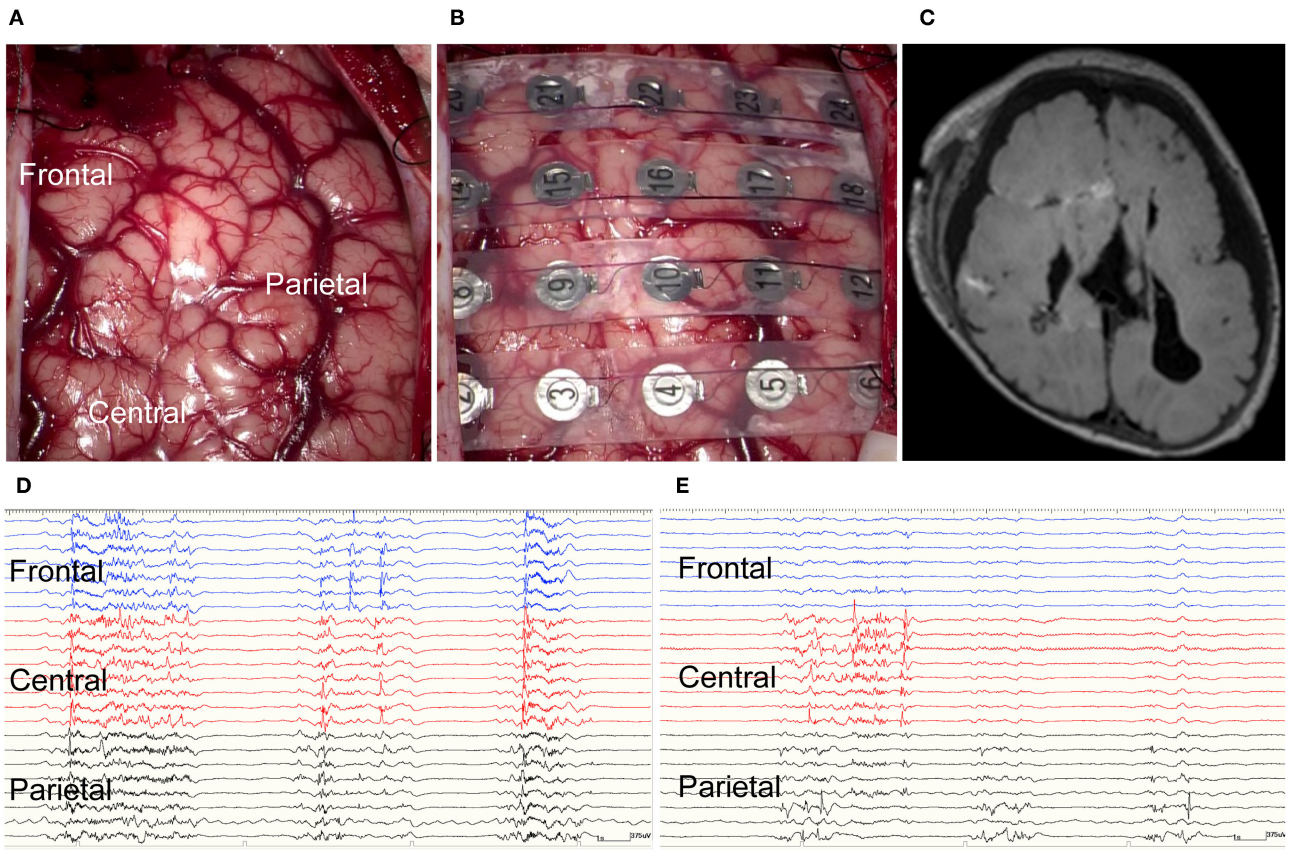

FIGURE 3 | Intraoperative electrocorticography and postoperative imaging. **(A)** Intraoperative findings included absent Roland vein and ambiguous central sulcus. The sclerotic cortex was identified in the central area. **(B)** Intraoperative electrocorticography. **(C)** Postoperative axial fluid-attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) demonstrated the disconnection line. **(D)** Intraoperative electrocorticography before subtotal hemispherotomy. **(E)** Intraoperative electrocorticography after subtotal hemispherotomy.

inspected each ECoG epoch with a high-pass filter at 0.5 Hz and at 200 Hz to ensure that they were not contaminated by significant artifacts, such as environmental artifacts and muscle artifacts.

We defined the occurrence rate (OR) as the index of the HFOs. We calculated the OR of ripples and FRs after dividing each of the 10-min intraoperative ECoG recordings into ten 1-min epochs, and acquired ten OR of HFOs values for each of the three brain areas, before and after subtotal hemispherotomy.

The modulation index (MI) reflects the PAC degree of strength (13). It was calculated on the monopolar montage for each area using the EEGLAB, Phase-Amplitude Coupling Toolbox (PACT), v.0.17 (13). We analyzed the MI between HFOs (ripples and FRs) and the slow wave bands (0.5–4 Hz). We acquired ten MI values (HFOs and slow wave bands) in each area by analyzing the ten intraoperative ECoG epochs. We then compared the OR of HFOs and MI values in each area before and after subtotal hemispherotomy. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). We compared the two groups by the Mann-Whitney *U*-test. Pair-wise comparisons were made by the Steel-Dwass test after testing for data normality with the *F*-test. Statistical significance was set at $p < 0.05$.

RESULTS OF THE HFOS AND PAC ANALYSIS IN THE INTRAOPERATIVE ECOG

HFO

OR of HFOs in Each Area Before Subtotal Hemispherotomy

OR of the ripples in the frontal, central, and parietal areas before subtotal hemispherotomy were 47.5 ± 7.7, 56.0 ± 13.3, and 33.3 ± 13.2, respectively (mean ± standard deviation) (**Figure 4A**). The OR of ripples in the central area was higher than that in the frontal and parietal areas, and that in the frontal area was higher than in the parietal area ($p < 0.01$ for all).

The OR of FRs in the frontal, central, and parietal areas before subtotal hemispherotomy were 9.7 ± 8.8, 6.6 ± 3.9, and 2.7 ± 2.8, respectively (**Figure 4B**). The OR of FRs in the frontal and central areas were higher than in the parietal area ($p < 0.01$ for both).

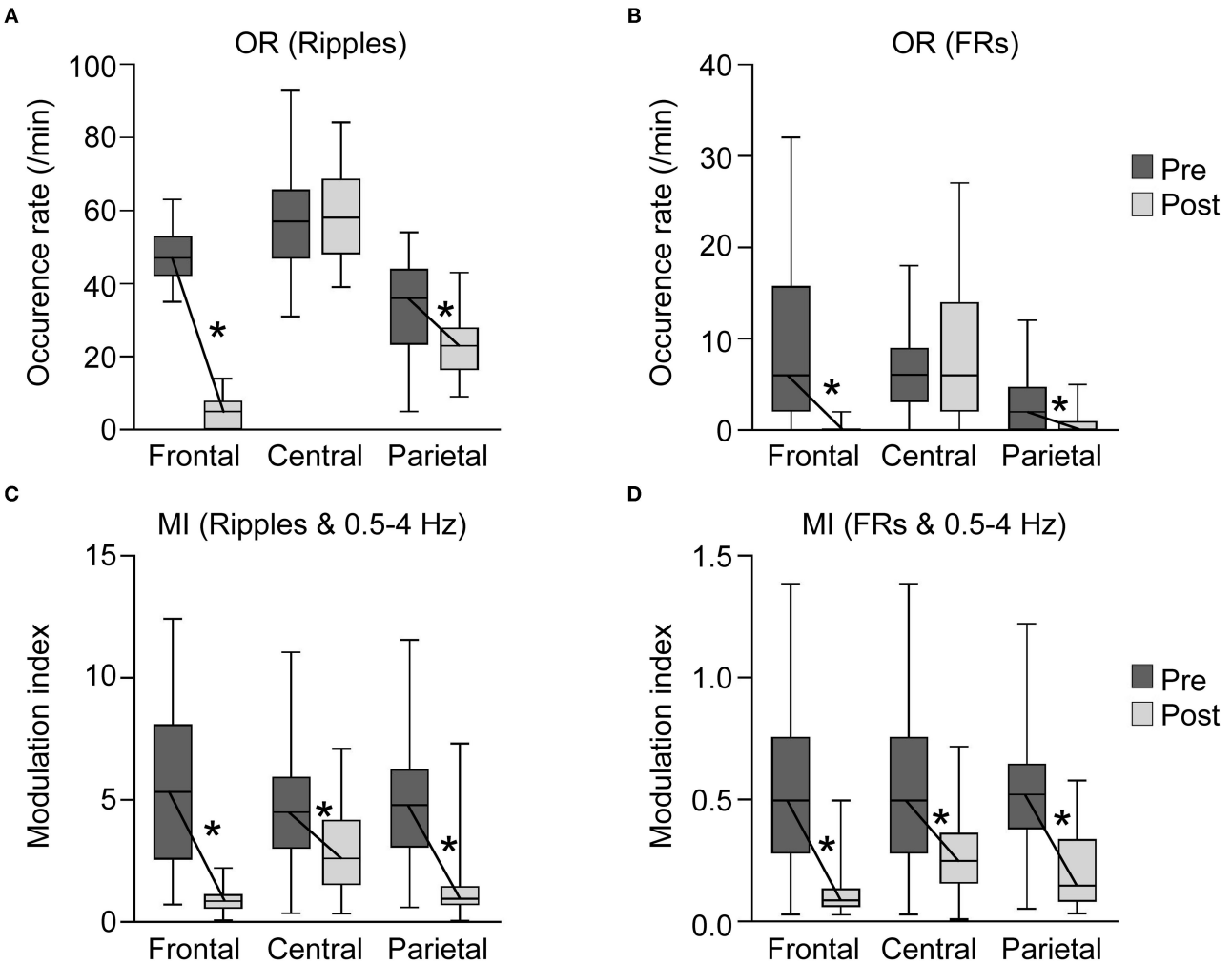

FIGURE 4 | Occurrence rates (ORs) of high-frequency oscillations (HFO) and modulation index (MI) in each area before and after subtotal hemispherotomy. **(A,B)** OR of HFOs in the frontal and parietal areas decreased significantly after subtotal hemispherotomy ($p < 0.01$ for all), while they remained unchanged in the central area. **(C,D)** MI (HFO and slow wave bands) in all three areas decreased significantly after subtotal hemispherotomy ($p < 0.01$ for all). Pre, before subtotal hemispherotomy; Post, after subtotal hemispherotomy; *indicates $p < 0.01$.

OR of HFOs in Each Area After Subtotal Hemispherotomy

The OR of ripples in the frontal, central, and parietal areas after subtotal hemispherotomy were 4.8 ± 3.9, 58.9 ± 11.4, and 23.2 ± 7.9, respectively, and those of FRs were 0.3 ± 0.6, 7.5 ± 6.7, and 0.8 ± 1.4, respectively. The OR of ripples and FRs in the central area remained higher than in the frontal and parietal areas ($p < 0.01$ for all).

Comparison OR of HFOs in Each Area Before and After Subtotal Hemispherotomy

The OR of ripples and FRs in the frontal and parietal areas decreased significantly after subtotal hemispherotomy ($p < 0.01$ for all), while they remained unchanged in the central area.

PAC

MI in Each Area Before Subtotal Hemispherotomy

The MI in the frontal, central, and parietal areas before subtotal hemispherotomy were 5.6 ± 3.3, 4.7 ± 2.2, and 4.7 ± 2.1, respectively for ripples and slow wave bands, and 0.54 ± 0.32, 0.51 ± 0.23, and 0.52 ± 0.23, respectively, for FRs and slow wave bands (**Figure 4C**).

MI in Each Area After Subtotal Hemispherotomy

The MI in the frontal, central, and parietal areas after subtotal hemispherotomy were 0.9 ± 0.5, 2.9 ± 1.6, and 1.4 ± 1.5, respectively, for ripples and slow wave bands, and 0.11 ± 0.09, 0.28 ± 0.15, and 0.20 ± 0.15, respectively, for FRs and slow wave bands (**Figure 4D**). The MI of ripples or FRs and slow wave bands in the central area remained significantly higher than in the frontal and parietal areas ($p < 0.01$ for all).

Comparison of MI in Each Area Before and After Subtotal Hemispherotomy

MI of ripples or FRs and slow wave bands in all three areas significantly decreased after subtotal hemispherotomy ($p < 0.01$ for all).

DISCUSSION

The Effectiveness of Subtotal Hemispherotomy for AS With ES

Previous surgical studies reported that hemispherectomy, multilobar resection, and VNS to treat ES in AS patients led to variable seizure outcomes (3, 6, 7). A hemispherectomy was performed in three AS patients with ES, and multilobar resection surgery was performed in two. Only one patient, who underwent hemispherectomy, became seizure-free. VNS was performed as a palliative surgery for AS patients with ES (3, 7, 15). Five of eleven children implanted with a VNS device in three previous studies showed some degree of seizure improvement (3, 7, 15). The contribution of surgical treatment for AS patients with ES has still been established.

In this study, we applied subtotal hemispherotomy to an AS patient with intractable ES. Subtotal hemispherectomy is effective in patients with ES with absent or mild hemiparesis (4, 5). In one study, ten of seventeen non-AS patients who underwent subtotal hemispherectomy became seizure-free (4). As our AS patient with intractable ES did not have hemiparesis, we applied subtotal hemispherotomy. The procedure successfully reduced the severity of ES. In addition, improvement in EEG findings suggest that subtotal hemispherotomy is effective for AS patients with ES.

Even in AS, where bilateral hemispheric abnormalities are often observed, epilepsy surgery may be considered when EEG and PET-CT findings are lateralized. Similarly, when EEG or PET-CT findings are lateralized after corpus callosotomy for ES, two-stage surgery, including subtotal hemispherotomy, may be applied. Earlier epilepsy surgery for ES is recommended to promote plasticity and psychomotor development (4). Although psychomotor development was not accelerated in this case, early surgical intervention for AS may be considered if it can be done safely.

Epilepsy surgery was expected to improve the seizure outcome because the lateralization of the epileptic focus was assumed by the EEG and PET-CT findings. We administered the ACTH therapy after performing the subtotal hemispherotomy. In general, only some patients with ES and without AS respond to ACTH therapy (16). In the presence of AS however, this therapy has been applied to a very limited number of cases, and remains controversial.

HFOs and PAC Assessment During the Disconnection Surgery

HFOs

HFOs can be a physiological or pathological phenomenon (17). The resection of areas with high OR of HFOs led to good seizure control outcomes in children with ES (13). We documented intraoperative OR of HFOs in this AS patient, showing them to decrease significantly in the frontal and parietal areas after subtotal hemispherotomy. Thalamic inactivation was reported to reduce the occurrence of fast oscillations (18). Subtotal hemispherotomy includes disconnecting the thalamocortical pathway to the frontal and parietal areas. The decrease in HFOs in these areas after subtotal hemispherotomy indicated that they were pathological HFOs.

However, we cannot tell if the residual HFOs in the central area are physiological or pathological. The residual HFOs in the central area could be pathological as they were associated with the persisting ES. On the other hand, the ES had decreased to one-third of the preoperative frequency, and the patient showed no hemiparesis, suggesting that the residual HFOs in the central area could be physiological and originated in the motor cortex. We will need to investigate more patients undergoing subtotal hemispherotomy as a treatment for ES to verify whether the residual HFOs are physiological or pathological.

PAC

The resection of areas with high MI values led to a good seizure control in children with ES (13). MI could be a valuable biomarker for epileptogenic zones in ES. The post-disconnection MI of PAC decreased in our patient in all three areas, including the central area with its remaining HFOs.

The slow oscillations in the cortex originate from the corticothalamic system (18). High MI values might indicate that the slow oscillations originating from the thalamus play an important role in the generation of ES. Because subtotal hemispherotomy deafferentates thalamocortical pathway which are connecting thalamus and frontal, and thalamus and parietal areas, MI in frontal and parietal areas decreased. Moreover, disconnection of the subcortical pathway in the central area from frontal and parietal areas may have reduced the MI in the central area. Subcortical pathway may also play a role in the generation of slow oscillations. Hence, the MI decreased significantly in all three areas following subtotal hemispherotomy, consequently resulted in the improvement of ES.

These EEG analysis methods have limitations. A methodological problem in identifying interictal HFOs after filtering the signals is that "false" HFOs can be detected (19). It is necessary to carefully compare the data after filtering with the raw data. We have to pay attention to distinguish between false HFOs and true epileptic oscillations. PAC may falsely be identified using MI when both measured signals have a common driving source (20, 21). A modified MI is supposed to be robust to spurious PAC detections and may be worth investigating (22). We need to carefully analyze EEG and interpret the results, keeping in mind the limitations of these methods and the possible occurrences of "false" HFOs and PAC.

We used intraoperative HFOs and PAC to demonstrate the effectiveness of subtotal hemispherotomy as a treatment for ESs in a subset of patients with AS. The thalamocortical and subcortical pathways play a role in the ES network.

Written informed consent was obtained from the infant's parents. The ethics committee of Juntendo University (Tokyo, Japan) approved this study (No. 16-163).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The ethics committee of Juntendo University (Tokyo, Japan) approved this study (No. 16-163). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Epileptogenic Zone Localization in Refractory Epilepsy by FDG-PET: The Comparison of SPM and SPM-CAT With Different Parameter Settings

Eric Jacob Bacon[1,2], *Chaoyang Jin*[1], *Dianning He*[1], *Shuaishuai Hu*[3], *Lanbo Wang*[4], *Han Li*[3]* and *Shouliang Qi*[1,2]*

[1] College of Medicine and Biological Information Engineering, Northeastern University, Shenyang, China, [2] Key Laboratory of Intelligent Computing in Medical Image, Ministry of Education, Northeastern University, Shenyang, China, [3] Department of Neurosurgery, Shengjing Hospital of China Medical University, Shenyang, China, [4] Department of Radiology, Shengjing Hospital of China Medical University, Shenyang, China

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Giuseppe Didato,
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***Correspondence:**
Shouliang Qi
qisl@bmie.neu.edu.cn
Han Li
leoincmu@gmail.com

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Refractory epilepsy is a complex case of epileptic disease. The quantitative analysis of fluorodeoxyglucose positron emission tomography (FDG-PET) images complements visual assessment and helps localize the epileptogenic zone (EZ) for better curative treatment. Statistical parametric mapping (SPM) and its computational anatomy toolbox (SPM-CAT) are two commonly applied tools in neuroimaging analysis. This study compares SPM and SPM-CAT with different parameters to find the optimal approach for localizing EZ in refractory epilepsy. The current study enrolled 45 subjects, including 25 refractory epilepsy patients and 20 healthy controls. All of the 25 patients underwent surgical operations. Pathological results and the postoperative outcome evaluation by the Engel scale were likewise presented. SPM and SPM-CAT were used to assess FDG-PET images with three different uncorrected p-values and the corresponding cluster sizes (k), as in voxels in the cluster, namely $p < 0.0002$, $k > 25$; $p < 0.001$, $k > 100$; $p < 0.005$, and $k > 200$. When combining three settings, SPM and SPM-CAT yielded overall positive finding scores of 96.0% (24/25) and 100.0% (25/25) respectively. However, for the individual setting, SPM-CAT achieved the diverse positive finding scores of 96.0% (24/25), 96.0% (24/25), and 88.0% (22/24), which are higher than those of SPM [88.0% (22/25), 76.0% (19/25), and 72.0% (18/25)]. SPM and SPM-CAT localized EZ correctly with 28.0% (7/25) and 64.0% (16/25), respectively. SPM-CAT with parameter settings $p < 0.0002$ and $k > 25$ yielded a correct localization at 56.0% (14/25), which is slightly higher than that for the other two settings (48.0 and 20.0%). Moderate concordance was found between the confirmed and pre-surgical EZs, identified by SPM-CAT (kappa value = 0.5). Hence, SPM-CAT is more efficient than SPM in localizing EZ for refractory epilepsy by quantitative analysis of FDG-PET images. SPM-CAT with the setting of $p < 0.0002$ and $k > 25$ might perform as an objective complementary tool to the visual assessment for EZ localization.

Keywords: refractory epilepsy (RE), cortical dysplasia, epileptogenic zone (EZ), FDG-PET, SPM

INTRODUCTION

Epilepsy is among the most common neurological disorders affecting people of all ages. It is characterized by unpredictable seizures and can give rise to other health problems. Recent statistics indicate that epilepsy affects more than 50 million people worldwide (1). Refractory epilepsy is a drug-resistant epilepsy; patients are considered to suffer from refractory epilepsy if disabling seizures continue despite treatment trials with two anti-seizure drugs, either alone or in combination (2). Diagnosing refractory epilepsy remains a tedious task. While several researchers investigated refractory epilepsy to diagnose and reveal possible causes (3, 4), the main cause remains unknown, and doctors are yet to determine why some patients are receptive to medicine and others not.

Advances in neuroimaging continue to improve the surgical treatment of refractory epilepsy (5). Powerful neuroimaging techniques have been developed to make the diagnosis straightforward. Among these techniques, the fluorodeoxyglucose positron emission tomography (FDG-PET) has shown particular efficiency during the pre-surgical evaluation. It exhibits high sensitivity in detecting the epileptogenic zone (EZ) of cortical dysplasia (CD), which is known to occur in refractory epilepsy patients. Hence, FDG-PET contributes to localizing seizure onset zone (SOZ) in epilepsy surgery (6, 7). It has furthermore demonstrated high sensitivity to detect hyper-metabolic areas in patients with refractory epilepsy (8).

Although FDG-PET is to date a promising imaging modality technique in detecting the EZ, its visual assessment may lack accuracy, as its sensitivity is estimated to span 35–86% (9–11). However, visual interpretation can be improved by applying further analysis (12).

Advanced tools or software can be used for the improvement of visual interpretation of FDG-PET. A typical example is voxel-based morphometry (VBM), whose pipeline follows a standard procedure that includes brain tissue segmentation, spatial normalization, registration, and smoothing. During VBM procedures, the changes in gray matter (GM) and white matter (WM) in individual patients are evaluated. One of the most common tools used when performing VBM is statistical parametric mapping (SPM). This tool has revealed its effectiveness in the EZ localization (13). Computational Anatomy Toolbox 12 (CAT12) is a toolbox of SPM12 and it can be used to perform VBM through SPM[1]. SPM-CAT performs better than SPM by efficiently identifying brain morphological abnormalities in patients with temporal lobe epilepsy (TLE) (14). SMP-CAT is assumed to be more accurate in localizing the EZ than SPM; however, no such report is available.

Pre-surgical evaluation using FDG-PET images is necessary for refractory epilepsy, improving accurate EZ localization and providing better surgery outcomes. However, the tool's performance and how to set the appropriate parameters for SPM and SPM-CAT are unknown. This study aims to compare SPM and SPM-CAT with different parameter settings and find the appropriate localizing EZ in refractory epilepsy by FDG-PET images. The performance of each approach and setting has been first compared to each other, and subsequently the identified pre-surgical EZ was compared to the confirmed EZ according to the postsurgical follow-up. To the best of our knowledge, no studies have been performed for such an evaluation using both VBM approaches with different settings.

[1]http://brainmap.org/training/BrettTransform.html.

MATERIALS AND METHODS

Materials

Participants

Our dataset contains data collected form 81 FDG-PET subjects (47 patients with refractory epilepsy and 34 healthy controls). All subjects and datasets were subjected to some selection criteria, such as age and the obtained image quality, respectively. **Figure 1** provides further detail about the selection criteria. In total, 45 subjects were selected for our current study, including 25 patients and 20 healthy controls. The mean age of the patients was 31.1 years [standard deviation (SD), 10.8 years], of which 72.0% (18/25) were male and 28.0% (7/25) female. For healthy controls, the mean age was 25.8 years, SD, 7.7 years, of which 42.9% (8/20) were male and 57.1% (12/20) female. Patients underwent pre-surgical evaluation from January 2018 to July 2019 at Shengjing Hospital of China Medical University (Shenyang, China). The evaluation involved a detailed clinical history and neurological examination, complete neuropsychological evaluation, psychiatric assessment, inter-ictal and ictal onset patterns in long-term scalp video-electroencephalogram (video-EEG), magnetic resonance imaging (MRI), and PET results. Images for both groups of patients and healthy controls were acquired following the clinical routine of epilepsy. The ethics committee of China Medical University's Shengjing Hospital (Shenyang, China) granted their approval to the report. The study protocol was explained to all participants, after which they signed an informed consent form.

In some cases, the epileptic zone can be localized by pre-operative stereoelectroencephalography (SEEG). If this epileptic zone does not include the eloquent area (e.g., motor or language), then this zone will be surgically removed. If the epileptic zone identified by SEEG includes the eloquent area, intraoperative electrocorticography (ECoG) was used to avoid the eloquent area and specify the resection zone. In case SEEG is not required, the epileptic and resection zones were determined by intraoperative ECoG. The electrode with eight contactors is commonly employed in SEEG, while 32 (four rows and eight columns) or 16 contactors (two rows and eight columns) are usually included in ECoG according to the size of the epileptic zone.

For the surgical operation of temporal lobe epilepsy, there is a standard procedure to follow by the surgeons. According to international practice, some standard anatomical marks in both neocortex and medial structure can be referred for the surgical resection. For the surgery of extra-temporal lobe (medial or deep epileptic foci) epilepsy, cerebral gyrus, sulcus and superficial blood vessels should be visualized through multi-modality images, and the epileptic zone should be clearly marked

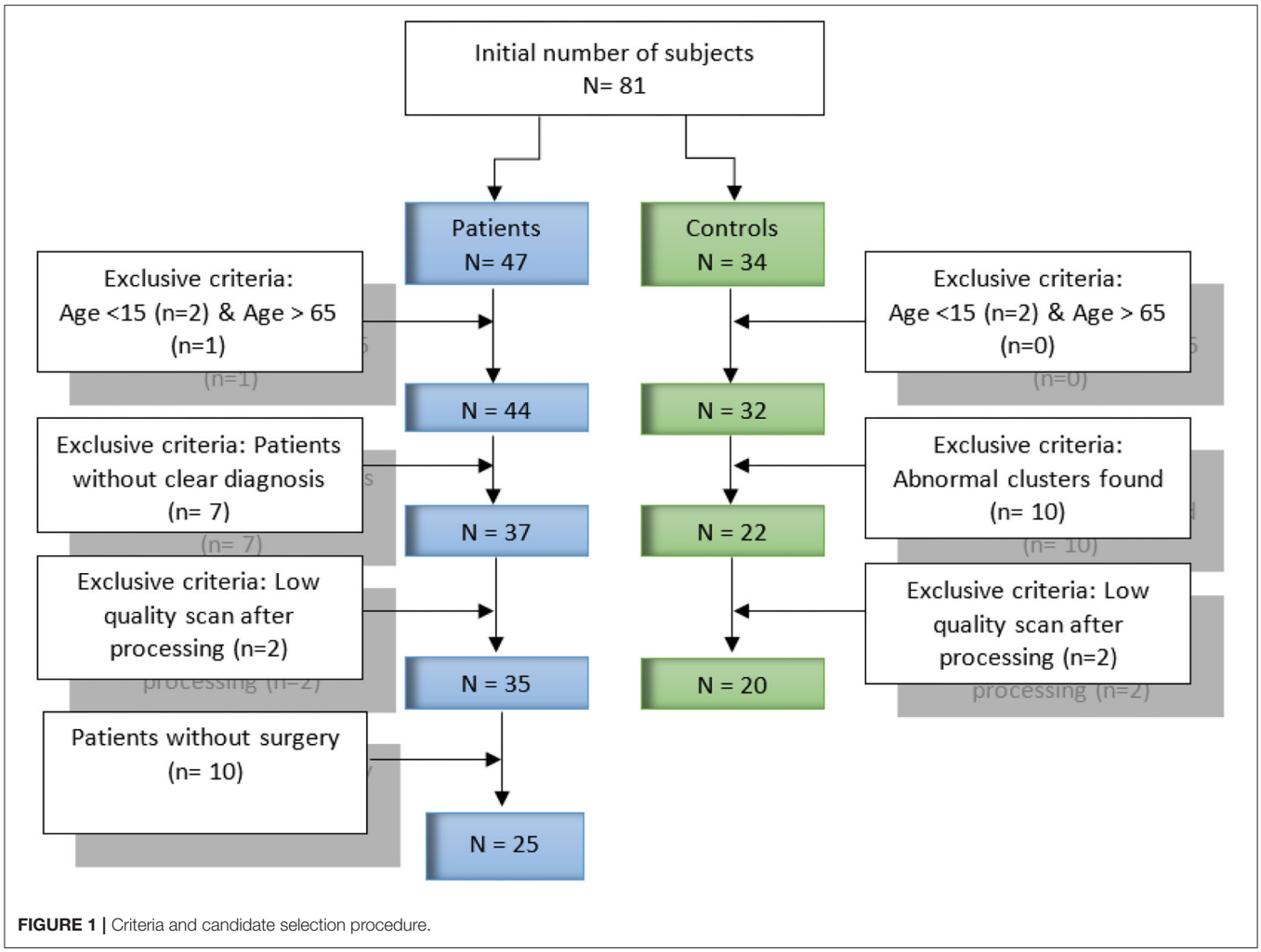

FIGURE 1 | Criteria and candidate selection procedure.

TABLE 1 | Clinical characteristics of epilepsy patients and healthy controls.

Characteristics		Epilepsy patients	Healthy controls
Number of patients		25	20
Gender	Male	18	8
	Female	7	12
Age (years)		15–63	15–48
(mean ± S.D.)		(31.12 ± 10.8)	(25.8 ± 7.7)

in the pre-operative plan. Meanwhile, intraoperative navigation and localization are required.

Table 1 provides the demographic information of patients and healthy controls. For the 25 patients who underwent surgery, the outcomes were evaluated in terms of the Engel value, and EZ was confirmed by the postsurgical follow-up. The Engel value was defined after 6 months following the surgery. **Table 2** gives the detailed semiology of 25 epilepsy patients in this study. This semiology has referred to the 2017 International League Against Epilepsy (ILAE) classification of epilepsies (15).

For healthy controls, 32 subjects were retained after the age criteria. We selected each of these 32 subjects and compared it with the others by SPM and SPM-CAT analysis to find abnormal clusters. In case of an abnormal cluster, this subject was excluded. Finally, 24 and 22 patients were retained for SPM and SPM-CAT analysis, respectively. The overlapping 22 subjects were determined as healthy controls for further exclusive criteria. Two subjects with low-quality data were excluded, and 20 subjects were finally retained. This procedure is the same as the one employed by Mayoral et al. (16).

PET Data Acquisition

All PET measurements were acquired and processed with a specific epilepsy protocol as used in clinical routine, irrespective of being conducted on the patients or control group. Images of patients were acquired using a PET/MRI scanner (SIGNA PET/MR; GE Healthcare, Waukesha, WI, USA). The subjects were asked to rest quietly in a dimly lit room for about 45–60 min after the intravenous administration of 18F-FDG with 3.7 MBq/kg. The default 3D ordered subsets expectation maximization (OSEM) algorithm (32 subsets and

TABLE 2 | Semiology of epilepsy patients in this study.

No.	Semiology
1	Hand automatism with impaired awareness, sometimes secondary head/eye versive
2	Autonomic auras, dialeptic seizure
3	Versive with impaired awareness, tachycardia
4	Head/eye versive with impaired awareness, tonic
5	Hand automatism with impaired awareness, versive
6	Oroalimentary and hand automatism with impaired awareness, tonic
7	Hypermotor with impaired awareness
8	Hand automatism with impaired awareness
9	Eyelid fluttering with impaired awareness, nonversive head turning, oroalimentary automatism
10	Hand versive with impaired awareness, tonic
11	Oroalimentary and hand automatism with impaired awareness, versive
12	Tonic with impaired awareness, hand automatism
13	Asymmetric tonic with impaired awareness
14	Psychic aura, oroalimentary automatism without impaired awareness
15	Hand automatism with impaired awareness
16	Oroalimentary and hand automatism with impaired awareness
17	Clonic with impaired awareness, secondary bilateral tonic-clonic
18	Dialeptic seizure
19	Tachycardia, myodystonia with impaired awareness, tonic
20	automatism with impaired awareness
21	Oroalimentary and hand automatism with impaired awareness
22	Tonic
23	Oroalimentary and hand automatism with impaired awareness
24	Gelastic, hypermotor
25	Oroalimentary and hand automatism with impaired awareness

three iterations) was used to reconstruct PET images. The restored data has a 192 × 192 × 16 matrix and a 1.56 × 1.56 × 2.40 mm^3 voxel scale. The acquisition time of each scan was 15 min.

Images of healthy controls were acquired with the General Electric Discovery 690 PET (GE Medical Systems) in Shengjing Hospital of China Medical University because the PET/MRI scanner was newly installed and no image data of healthy controls is available. After the intravenous administration of ∼5 MBq/kg of 18F-FDG, the patients were asked to rest quietly in a dimly lit room for about 40 min. The projection data of 25 tomographic attenuation-corrected brain parts of 3.27-mm thickness were obtained through a standard routine of 11 min. The scan mode was the helical mode with a rescale slope of 1.0 and a reconstruction diameter of 700 mm. PET data were reconstructed using the OSEM algorithm (16 subsets and six iterations). The restored data have a 512 × 512 × 16 matrix and a 3.65 × 3.65 × 3.27 mm^3 voxel scale.

Methods

Procedure of SPM and SPM-CAT

The procedure used in this study involves applying the VBM pipeline mentioned in (13). In total, data from 25 patients with refractory epilepsy were used in our evaluation. **Figure 2** outlines three main steps: (1) data preparation, (2) data processing, and (3) statistical evaluation. For the data preparation, SPM and SPM-CAT have the same procedure. The images in Dicom were first converted into the format of Nifti, and the alignment check-up and registration to canonical templates were followed.

For the data processing of SPM, the brain tissue was first segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Subsequently, the proportional scaling intensity normalization was performed. After selecting the canonical template, the diffeomorphic anatomic registration through an exponentiated lie (DARTEL) algebra algorithm was used to normalize the segmented scans into a standard Montreal Neurological Institute (MNI) space (17). This spatial normalization was only conducted for the segmented GM to find the EZ. Furthermore, the spatially normalized GM was smoothed by a Gaussian kernel of full width at half maximum (FWHM) 8 × 8 × 8 mm^3. Statistical evaluation was performed as the final step of processing using the SPM model. A two-sample *t*-test comparison with age as a covariate was performed between each patient and the healthy control database using an implicit mask based on a gray-level threshold of 0.3. A digital human brain atlas tool called xjview was used to determine the location of hypo-metabolic areas (18, 19). These hypo-metabolic areas or clusters with the most significant volume are assumed to be the EZ.

SPM-CAT went through the regular VBM pipeline using both SPM and CAT12 GUI to analyze the images. In the data processing of SPM-CAT, the first part is the tissue segmentation performed with CAT GUI. During the tissue segmentation, CAT12 uses the standard tissue probability maps (TPMs) as provided in SPM. The latter dynamically uses the appropriate template for spatial registration, either DARTEL (20) or Geodesic Shooting (21) with a predefined template. As with SPM, only the gray matter was analyzed. The second part of the data processing involved the segment quality check and total intracranial volume estimation. The third part was the spatial smoothing implemented in the same manner as in SPM. Finally, the statistical evaluation was performed using CAT12 GUI and its statistical model. However, the same two-sample *t*-test and settings as in SPM were adopted.

Performance Comparison and Statistical Analysis

For each patient, SPM and SPM-CAT were performed with three different parameter settings: $p < 0.0002$, $k > 25$; $p < 0.001$, $k > 100$; and $p < 0.005$, $k > 200$. The uncorrected *p*-value is the statistical threshold specifying the level of variation of FDG activity considered to be significant, while performing the segmentation of statistical parametric maps. k is the predetermined size of the cluster (i.e., the number of voxels in the cluster).

In this study, cluster is defined as a group of voxels. In the case of abnormal clusters, this patient was defined as the "positive study". The positive finding score was calculated as the percentage or rate of the number of positive studies over the total number of patients (i.e., 25). In SPM, if any of the three-parameter settings reports the positive finding for one patient, we assume this patient as the "overall positive study". Therefore,

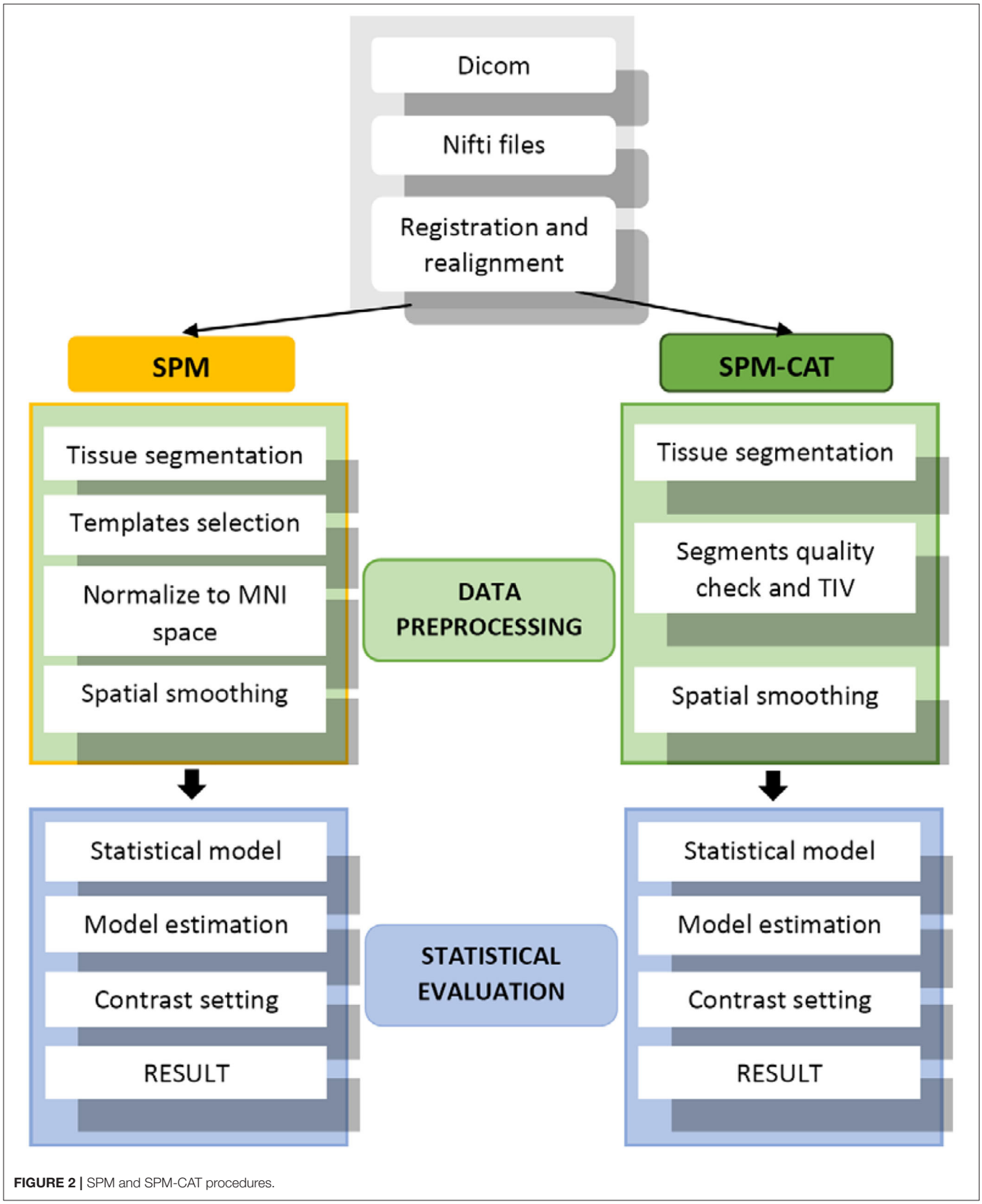

FIGURE 2 | SPM and SPM-CAT procedures.

the overall positive finding score of SPM can be calculated. This is similar to SPM-CAT.

By using SPM and SPM-CAT with different parameter settings, one or more hypo-metabolic clusters will be identified for each patient. If more than one clusters are identified, as commonly done in previous studies (10, 22), the cluster with the largest volume is defined as the pre-surgical EZ identified by SPM and SPM-CAT.

EZ was identified by SPM and SPM-CAT with the confirmed EZ according to the postsurgical follow-up. The identified EZ location is given as the left or/and right hemisphere and the temporal, frontal, parietal, and occipital lobe. If the identified and the confirmed EZs match, a correct localization is considered to be achieved for this patient. A correct localization percentage can be determined for the 25 patients with surgery.

In SPM, for each patient, if any of the three-parameter settings identifies the EZ matching with the confirmed EZ, we assume that this patient is the "overall correct localization study". In this manner, we obtain the overall correct localization percentage for SPM. The overall correct localization percentage of SPM-CAT is determined in the same manner.

The positive finding score is compared within three-parameter settings and the overall situation by McNemar's test for SPM and SPM-CAT. The overall positive finding scores of SPM and SPM-CAT were also compared. If $p < 0.05$, a significant difference is available. The same comparison is made for the correct localization percentage.

To compare the identified EZ among different settings, different locations (or lobes) are assigned values from zero to two (0–negative, 1–left hemisphere, 2–right hemisphere). For each setting, one vector of 25 elements will be obtained, and the value of each element will be 0, 1, or 2. For the overall situation, the value of the element will be 1 if the patient is determined as "overall correct localization study"; otherwise, it will be 0. McNemar's test is applied to determine the significance of the differences between different vectors (parameter settings).

A statistical analysis was conducted between the identified EZ with SPM and SPM-CAT with different parameter settings and the confirmed EZ by Cohen's kappa's test. Its 95% confidence interval (CI 95%) was likewise given. The kappa value (k) can be interpreted as follows: $k \leq 0$ indicating no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement. All of the statistical analyses were performed using SPSS software, ver. 16.0 (IBM-SPSS, Armonk, NY, USA).

RESULTS

Epileptogenic Zone Identified by SPM and SPM-CAT

In the examples shown in **Figure 3**, SPM and SPM-CAT localized different hypo-metabolic areas through the analysis in three patients (1, 3, and 12) with different parameter settings. **Table 3** lists significant metabolic changes in different areas of the brain of three patients (L = left, F = frontal, T = temporal, and li = limbic lobes) for the same three patients as presented in **Figure 3**. For each patient, the clusters with the largest voxel size have been selected associated with their spatial information (coordinates, peak intensities, voxels size, and brain region) and presented as significant findings. The aim of **Figure 3** and **Table 3** is to present typical results as examples.

Positive Finding Scores of SPM and SPM-CAT

The finding score for positives is different for SPM and SPM-CAT with different parameter settings (**Figure 4**). For the three settings ($p < 0.0002$, $k > 25$; $p < 0.001$, $k > 100$; $p < 0.005$, $k > 200$), the positive finding score was 88.0% (22/25), 76.0% (20/25), and 72.0% (18/25), respectively. There were no significant differences among the three settings ($p > 0.05$, McNemar's test). The overall positive finding score of SPM was 96.0% (24/25) and significantly higher than that of the setting of $p < 0.0002$ and k > 25 ($p < 0.05$, McNemar's test).

The positive finding score of SPM-CAT with the three respective settings was 96.0% (24/25), 96.0% (24/25), and 88.0% (22/25). SPM-CAT has a significantly higher positive finding score for each setting than that of SPM ($p < 0.05$, McNemar's test).

SPM-CAT has a better overall positive finding score than SPM [100.0% (25/25) and 96.0% (24/25) respectively], i.e., the abnormal findings (hypo-metabolic areas) were observed in FDG-PET images of 25 epilepsy patients.

Correct Localization Percentage of EZ

Table 4 presents the clusters with a significant difference in FDG-PET images identified by SPM and SPM-CAT with different parameter settings, as well as the confirmed EZ according to the postsurgical follow-up, and the outcomes of patients with surgery. For SPM, three different parameter settings generated the same EZ (or negative results) for 17 patients. For the remaining eight patients, one or two settings yielded the negative finding. For SPM-CAT; the same EZ was found only for four patients when using three different settings. The variations among different settings are larger in SPM-CAT than in SPM. Among 25 patients with surgery, 20 have the confirmed EZ at the temporal lobe, three patients at the frontal lobe, one patient at the parietal lobe, and one at both temporal and occipital lobes. The outcomes of patients with surgery were good (Engel I to Engel III). Specifically, Engel I accounted for 68% (17/25), Engel II for 8% (2/25), and Engel III for 24% (6/25).

To compare the identified EZ by SPM and SPM-CAT with different settings, we obtain the corrected localization percentage, as given in **Figure 5**. For SPM, the correct localization percentage is 20.0% (5/25) for all the three settings ($p < 0.0002$, $k > 25$; $p < 0.001$, $k > 100$; $p < 0.005$, $k > 200$). The overall correct localization of SPM is 28.0% (7/25) and is significantly higher than that of the three settings ($p < 0.05$, McNemar's test).

The correct localization percentage of SPM-CAT with the three settings is 56.0% (14/25), 48.0% (12/25), and 20.0% (5/25), respectively. For each setting, SPM-CAT has a significantly higher correct localization percentage than SPM. SPM-CAT has obtained an overall correct localization percentage of 64.0% (16/25), which is significantly higher than that of SPM ($p < 0.05$, McNemar's test).

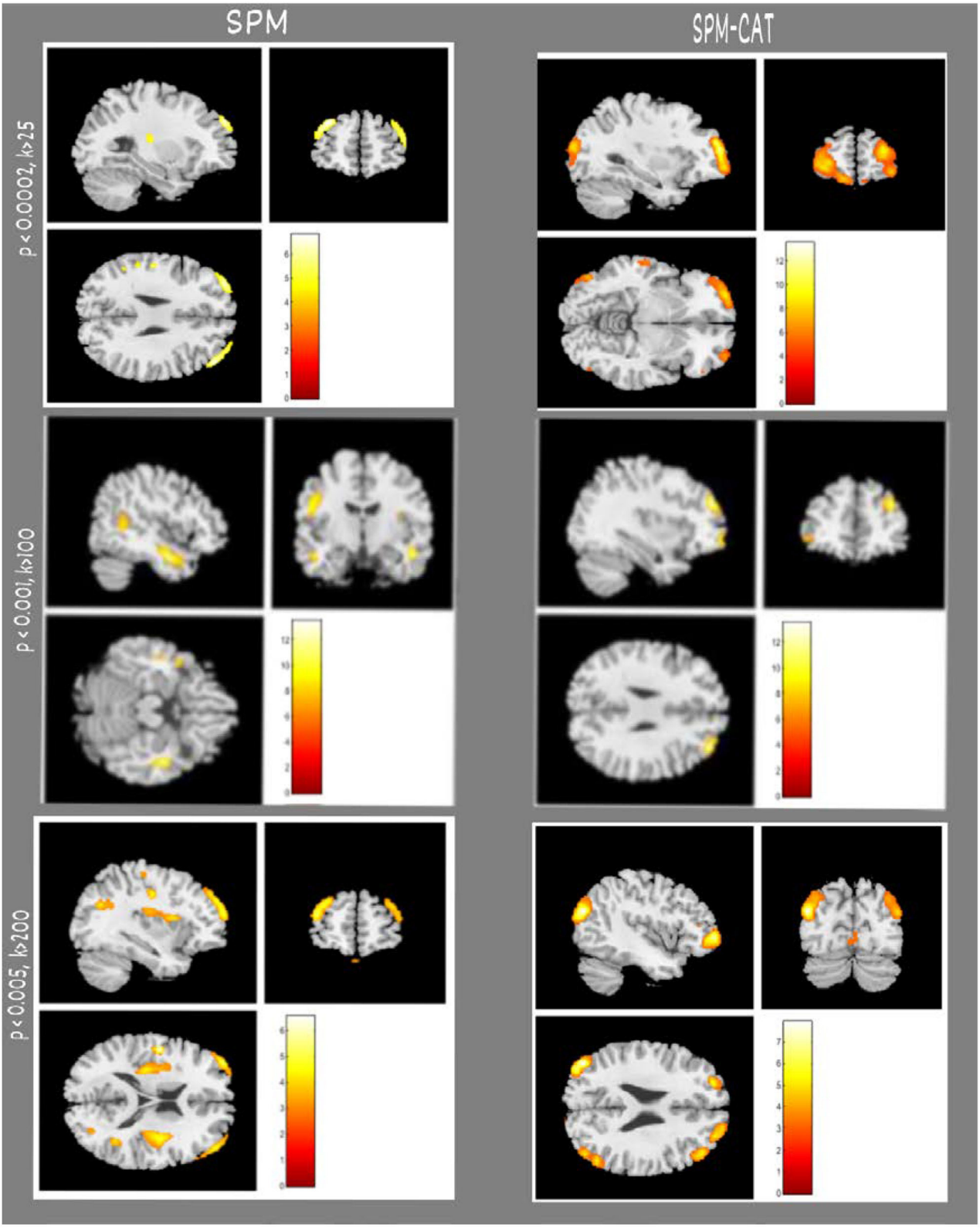

FIGURE 3 | Examples of epileptogenic zones identified by SPM and SPM-CAT in three patients. Each row indicates the results of a patient (e.g., No. 01, 03, 12). From the first to the third row, the parameter settings of SPM and SPM-CAT are $p < 0.0002$, $k > 25$; $p < 0.001$, $k > 100$; $p < 0.005$, and $k > 200$. The left two columns are for SPM with sagittal and coronal views, and the right two columns are for SPM-CAT with sagittal and coronal views.

TABLE 3 | Comparison of epileptogenic zones identified by SPM and SPM-CAT (cluster with largest volume) in three patients as examples.

No.	SPM				SPM-CAT				Parameter setting
	Brain areas	Voxels per cluster	Coordinates	Peak intensity	Brain areas	Voxels per cluster	Coordinates	Peak intensity	
01	L/F	215	−28.9, 54.0, 28.9	5.2	L/F	402	−33.0, 60.0, −6.0	8.5	$p < 0.0002, k > 25$
03	R/T	759	−18.5, −8.8, 47.0	7.3	R/F	204	34.9, 45.0, 28.9	4.3	$p < 0.001, k > 100$
12	L/F	1,587	−39.0, 57.0, 18.0	5.6	L/T	2,171	−43.5, −78.0, 22.5	7.7	$p < 0.005, k > 200$

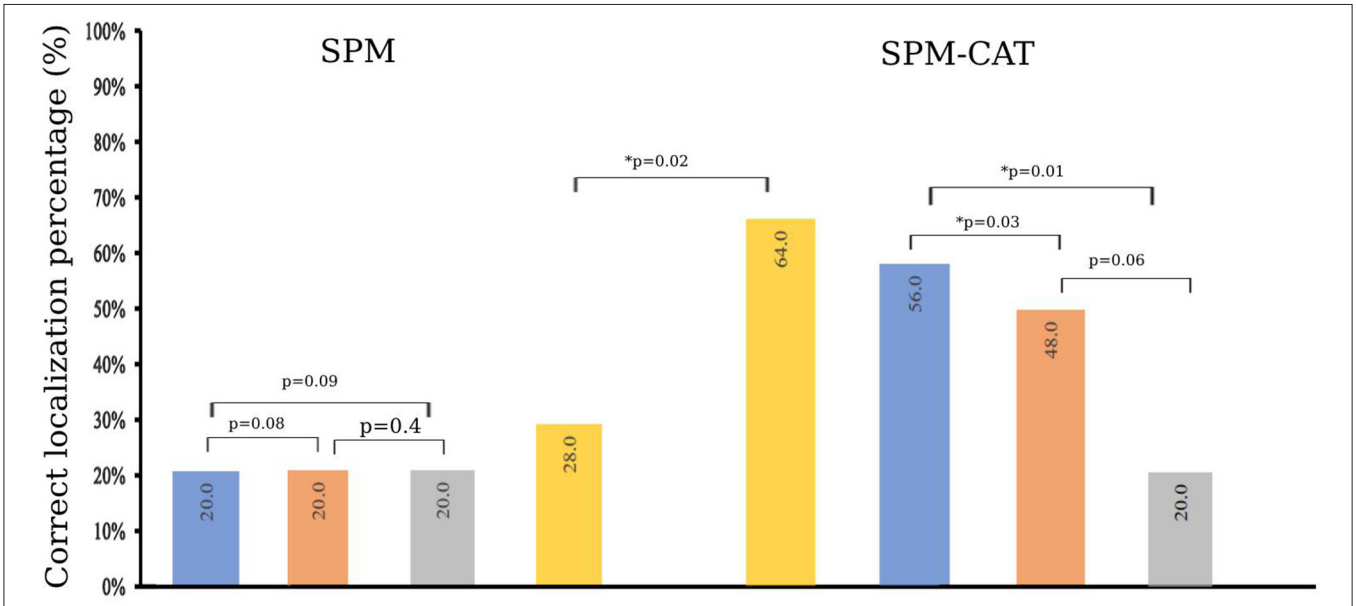

FIGURE 4 | Positive finding score of SPM and SPM-CAT with different parameter settings (*p*-value is from McNemar's test).

Concordance Between the Identified EZ by SPM and SPM-CAT and the Confirmed EZ

Table 5 shows the agreement between the identified EZ with SPM and SPM-CAT with different parameter settings and the confirmed EZ according to the postsurgical follow-up. For SPM, k is 0.04 for the first setting ($p < 0.0002, k > 25$) and lower than that of the other two settings (0.1 and 0.5). In contrast, k is 0.5 for the first setting and higher than that of the other two settings (both 0.3) for SPM-CAT. The overall concordance of SPM-CAT is moderate ($k = 0.5$, CI 95% = 0.3, 0.7) while SPM is fair ($k = 0.22$, CI 95% = 0.06, 0.4).

The Number and Volume of Clusters Identified by SPM and SPM-CAT

It is noted that one or more hypo-metabolic clusters can be found by SPM and SPM-CAT with different parameter settings. Therefore, the average number of hypo-metabolic clusters is presented in **Figure 6A** for each parameter setting ($p < 0.0002, k > 25$; $p < 0.001, k > 100$; $p < 0.005, k > 200$). The value for each setting identified for SPM-CAT (4.2, 3.7, and 3.05) is higher than that of SPM (1.3, 1.05, 1.2). The first setting ($p < 0.0002, k > 25$) identified more clusters than the other two settings. However, the average number of clusters is similar for three different settings in SPM.

Figure 6B shows the average volume (number of voxels) of the identified hypo-metabolic clusters of 25 epilepsy patients. For SPM, the average number of voxels per cluster is 8,674, 10,905, and 13,587 for the respective settings. This value is significantly higher than that of SPM-CAT: 2,372, 4,766, and 5,229. For both approaches, the highest value was obtained with the third setting ($p < 0.005, k > 200$).

DISCUSSION

Utility of FDG-PET in the Identification of the Epileptogenic Zone

We assessed an FDG-PET data series from 25 subjects of a pre-surgical study lasting for more than a year that have been diagnosed with refractory epilepsy. Recent studies revealed that refractory epilepsy remains one of the most complicated cases of epilepsy in terms of its diagnosis (5). Several researchers have confirmed the utility of FDG-PET for the pre-surgical evaluation of refractory epilepsy patients, such as for CD. Salamon et al. conducted FDG-PET/MRI co-registration in their efforts to explore novel neuroimaging methods to detect cortical lesions (23). Their study's outcome has added value for the 33% of patients with no concordant EEG and neuroimaging findings. According to their study, the advantages of using the FDG-PET/MRI co-registration technique allowed for more

TABLE 4 | Comparison between clusters with a significant difference in FDG-PET images and confirmed EZ according to postsurgical follow-up.

No.	SPM			SPM-CAT			EZ	Engel
	$p < 0.0002, k > 25$	$p < 0.001, k > 100$	$p < 0.005, k > 200$	$p < 0.0002, k > 25$	$p < 0.001, k > 100$	$p < 0.005, k > 200$		
01	LF	L/F	L/F	L/F	L/T	LF	L/F	1
02	L/F	L/F	L/F	R/T	R/T	L/F	R/mT	2
03	R/T	Neg	Neg	R/F	R/F	R/T	R/mT	3
04	L/F	L/F	L/F	L/T	L/T	L/F	L/mT	1
05	L/li	L/li	L/s-l	R/O	R/O	L/li	R/mT	1
06	L/T	L/T	Neg	R/O	R/O	L/T	R/m&laT	1
07	R/O	Neg	Neg	R/T	R/T	R/O	R/mT	3
08	L/T	Neg	Neg	R/F	R/F	L/T	R/mT	1
09	L/F	L/T	L/F	L/T	L/T	L/F	L/mT	1
10	L/F	L/F	L/F	L/F	L/F	L/F	L/F	1
11	R/O	R/O	R/O	R/F	R/F	R/O	R/mT	1
12	L/F	L/F	Neg	L/T	L/T	L/F	L/mT	1
13	L/F	L/F	L/F	L/O	L/O	L/F	L/mT	2
14	Neg	Neg	Neg	L/T	L/T	Neg	L/mT	1
15	L/li	L/li	L/li	Neg	Neg	L/li	R/P	3
16	L/F	L/F	L/F	L/T	L/T	L/F	L/mT	1
17	L/T	L/T	L/T	L/T	L/T	L/T	L/m&laT	3
18	Neg	Neg	R/O	R/F	R/F	Neg	R/mT	1
19	L/F	Neg	Neg	L/P	L/P	L/F	L/mT	1
20	L/li	L/li	L/li	L/T	L/T	L/Fli	L/T &L/mT	1
21	L/F	L/F	R/T	R/O	R/O	L/F	R/TO	1
22	R/F	R/F	R/F	R/F	R/F	R/F	R/mT	1
23	Neg	R/F	R/F	L/T	L/T	Neg	L/mT	1
24	R/F	R/F	R/F	R/T	R/T	R/F	R/F	3
25	L/li	R/T	R/T	L/T	L/O	L/li	L/mT	3

L, left; R, right; T, temporal; F, frontal; Neg, no finding; P, parietal; O, Occipital; L &R, left and right; l, lateral; m, medial; li, limbic; s-l, sub-lobar.

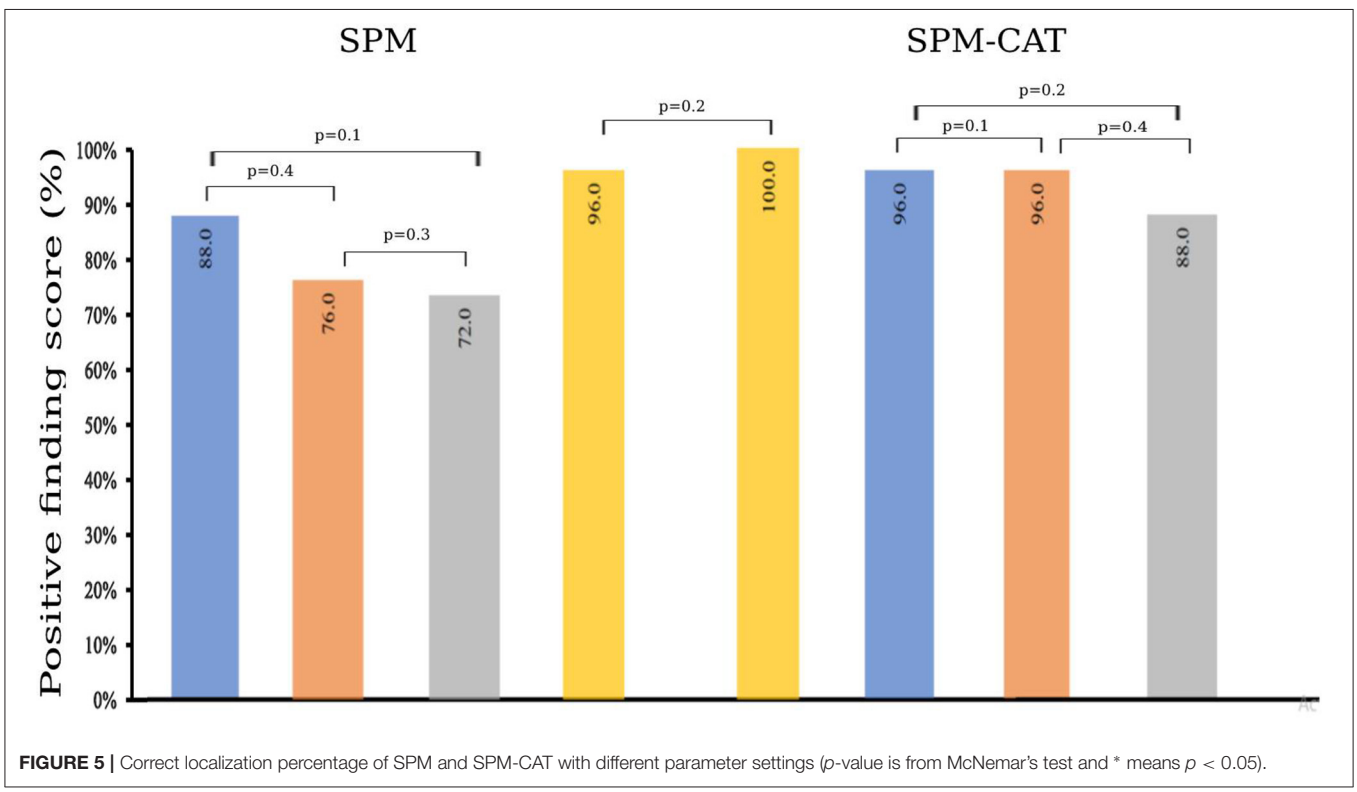

FIGURE 5 | Correct localization percentage of SPM and SPM-CAT with different parameter settings (*p*-value is from McNemar's test and * means $p < 0.05$).

TABLE 5 | Concordance between the identified EZ by SPM and SPM-CAT and the postsurgical EZ.

	Settings	Kappa index (*k*)	$CI_{95\%}$
SPM	$p < 0.0002, k > 25$	0.04	0.2, 0.3
	$p < 0.001, k > 100$	0.1	0.1, 0.4
	$p < 0.005, k > 200$	0.5	0.3, 0.7
	Overall	0.22	0.06, 0.4
SPM-CAT	$p < 0.0002, k > 25$	0.5	0.3, 0.7
	$p < 0.001, k > 100$	0.3	0.1, 0.6
	$p < 0.005, k > 200$	0.3	0.07, 0.5
	Overall	0.5	0.3, 0.7

precise surgical planning. The technique seemed to distinguish subtle lesions not appreciated by MRI or PET alone that turned out to be CD upon histopathological analysis.

As a functional neuroimaging method, PET can provide complementary information for patients who have normal MRI findings and require further intracranial investigation prior to surgery. Halac et al. performed a study to distinguish the compatibility of specific characteristics of FDG-PET analyses of FCD subgroups with MRI and clinical findings of the patients in these subgroups (7). Their study revealed that FDG-PET had demonstrated high sensitivity to hypo-metabolism in patients with refractory epilepsy and who had no findings in MRI results (MRI negative).

FDG-PET imaging plays an important role in the localization of epileptic foci. Tang et al. performed an investigation on kinetic parameters for epileptic foci identification (24). They assessed the correlation of parameters asymmetry indexes (ASYM) between dynamic and static FDG-PET to understand the hypo metabolism pathophysiology within intractable epilepsy. Dynamic FDG-PET provided an effective and complementary measure for epileptogenic zone detection in the small cohort for the authors and suggested that inter-ictal epilepsy was more impacted by glucose phosphorylation than by capillary influx.

FDG-PET functional imaging is likewise applied for localization of SOZ in epilepsy surgery. Elkins et al. present a gray-matter segmentation method for functional neuroimaging to localize SOZ in epilepsy surgery (25). They suggested that F-FDG-PET segmentation significantly increases the number of cases where an iEEG SOZ is correctly identified, often detecting an anatomically specific SOZ at the subgyral level.

Voxel-Based Analysis

Accurately localizing epileptogenic zones remains challenging for medical scientists, and visual assessment is insufficient for most cases. Consistent and objective analysis methods must be employed to accurately localize the EZ.

This study proposes a VBM analysis to diagnose and localize the epileptogenic zone of 25 patients. Our assessment procedures followed a standard VBM pipeline as described in (13, 23). Our methodology consisted of comparing SPM to its toolbox CAT12 (SPM-CAT) associated with different parameter settings. The idea of using SPM and CAT12 toolbox to investigate refractory epilepsy is based on the need to improve visual analysis by accurately localizing the lesions zone and determining which VBM approach is best suited to make such analysis.

VBM demonstrated its effectiveness as a valuable method to investigate refractory epilepsy patients, as SPM and CAT12 have been widely used for this purpose. Mayoral et al. performed a study where the utility of SPM in PET-negative epilepsies was explicitly addressed (16). They demonstrated the usefulness of SPM with optimized thresholding in a series of 55 patients who underwent an FDG-PET study evaluated upon visual inspection, where 20 of 55 patients who had PET-negative studies had lesional MRI. The highest rate of positive and correctly localizing studies with SPM was obtained when the least restrictive threshold in *p*-value and the largest minimum cluster size were used. According to their study, SPM appeared to be offset by decreased specificity. Thus, they suggest that patients be accurately selected, and that PET must be requested when MRI alone is not sufficient to locate the SOZ with maximum certainty.

VBM can also be used to analyze brain activity, in particular brain changes associated with TLE. Chaudhary et al. also performed the evaluation of the semantic verbal memory outcomes in pre-and post-surgery TLE patients using functional MRI and voxel morphometric methods (26). VBM was applied using the statistical parametric imaging (SPM12) and CAT12 toolbox. Their study reveals a significant reduction in gray matter volume in the left temporal lobe, postoperatively compared to prenursery and healthy control groups. In the post-surgery TLE group, neuropsychological scores were reduced in specific PGI domains, such as visuospatial, working memory, and executive functioning.

SPM or SPM-CAT for Positive Finding and Correctly Localizing EZ

The experiment in the present study provides novel insight into the relationship between SPM and SPM-CAT. Satisfactory results were obtained in terms of successful EZ localization. SPM and SPM-CAT achieved a positive localization percentage score of 96.0 and 100.0%, respectively. However, for individual parameter settings, a significant difference is observed. For both methods, the highest score was achieved with setting 1 ($p < 0.0002$, $k > 25$), while a lower score was achieved with ($p < 0.005$, $k > 200$). For a correct localization percentage, an overall score of 28.0 and 64.0% was achieved by SPM and SPM-CAT, respectively. For individual parameters settings, the highest score of 56.0% was achieved with setting 1 ($p < 0.0002$, $k > 25$) of SPM-CAT. However, this scenario was carried out slightly higher than the second scenario with a score of 48.0 and 20% achieved by other parameter settings ($p < 0.001$, $k > 100$, and $p < 0.005$, $k > 200$) for SPM-CAT. In contrast, SPM has achieved the same score of 20.0% for all three-parameter settings.

In our study, EZ is correctly localized by using SPM in only five out of 25 patients; for 10 out of the 25 patients, different positive regions are identified while changing the parameter settings of SPM. Such result highlights the motivation of our study, i.e., to explore an appropriate analysis method of EZ localization for better curative solution. Moreover, it has been

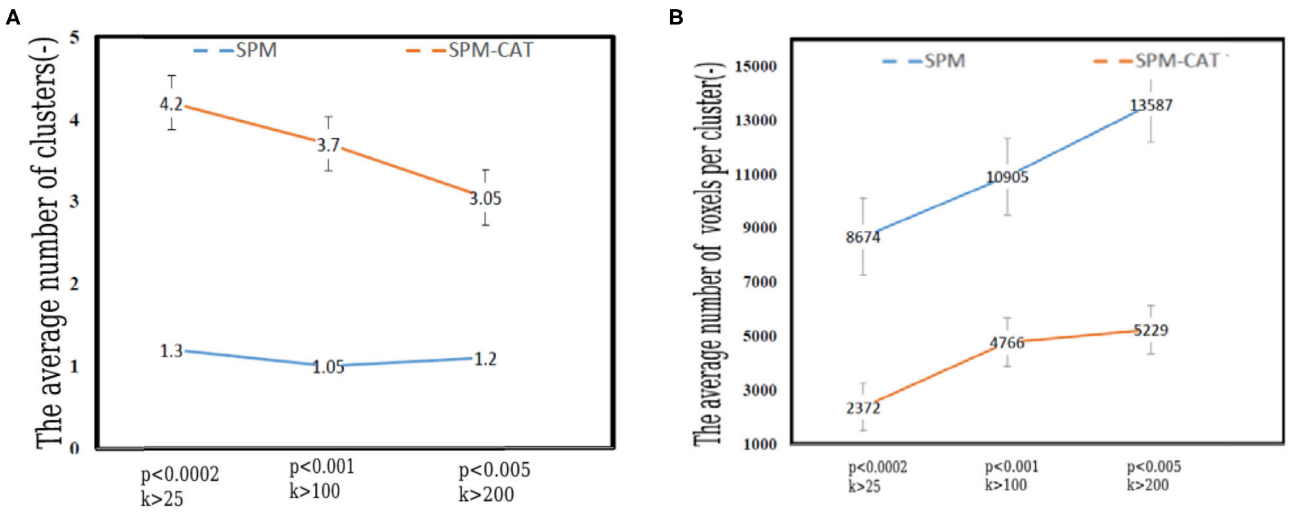

FIGURE 6 | Number and volume of clusters identified by SPM and SPM-CAT with different parameter settings. **(A)** The average number of clusters. **(B)** The average volume of per cluster (number of voxels).

well-known that only PET image analysis cannot accurately localize EZ for surgery, pre-operative SEEG and intraoperative ECoG must be used as the golden standard.

SPM-CAT shows higher sensitivity associated with the best performance and more correlation to the confirmed EZ according to the postsurgical follow-up. The main differences between these two VBM approaches might come from the pre-processing steps, where both approaches use different segmentations. SPM bases the image segmentation on tissue probability maps (TPM), which represents the prior probability of an image unit (voxel) being either gray or white matter or non-brain tissue (12). CAT12 uses TPM to normalize the image, perform an initial skull-stripping, and initialize the segmentation to update the estimation models for brain tissue classification and accounting for partial volume effects (27). Tavares et al. compared two segmentation pipelines (the SPM12 toolbox and an SPM12 add-on, the CAT12 toolbox) of structural brain MRI to investigate Alzheimer's disease (28). The authors suggested that SPM12 and CAT12 brain volume measure differences are tissue-dependent. The following steps are very relevant, in that (1) SPM12 volume estimates are strongly correlated with CAT12 volume estimates, while the absolute differences between pipelines are tissue specific; (2) pipeline choice modulates the effect of age on all volume measures and of diagnosis on hippocampi GM volumes computed from 3 T data; and (3) the pipeline has no effect on the accuracy of any brain volume measure detecting AD diagnosis.

CAT12 is a relatively novel tool that is computationally less expensive than SPM owing to its parallel processing algorithms. It enables more facilities in processing VBM and other processing methods. Farokhian et al. compared GM and WM abnormality results, obtained by VBM analysis using CAT12 via the current version of SPM12, with the results obtained by VBM analysis using the VBM8 toolbox implemented in the older software SPM8 (14). Their findings were consistent with the literature and pathology-based knowledge of VBM analysis using the TLE.

Comparing the performance of SPM-CAT to a previous study in (27), the PET-analysis obtained 66.7% (20/30) of correct localizations, which is comparable to our results (56.0%). Further, using CAT12, regional tissue volumes can be estimated in different regions based on the probabilistic atlases. However, further analysis must be conducted to confirm and improve this approach. The excellent performance achieved by the parameter setting 1 ($p < 0.0002$, $k > 25$) might come from the cluster's size, including the minimum size of the metabolic zone.

To measure the distance between the point of maximum VBM alteration and the center point of the surgically removed tissue can give more precise evaluation of the concordance between PET and surgery. However, the coordinates of center point of the surgically removed tissue are unknown for two reasons. First, this information is not recorded in the pre-operative plan and the surgically removed tissue might be changed according to measurement of the pre-operative SEEG and intraoperative ECoG. Second, it is difficult to localize the center point of the surgically removed tissue from the post-operative MRI images due to the potential deformation of brain. In the future, more advanced methods will be required and developed.

Limitations and Future Works

The generalizability of the results has several limitations. Although the VBM automated approach has distinct advantages over conventional region-of-interest-based methods, it has certain limitations due to the source images' imperfect spatial normalization, segmentation, and smoothing. Volume differences in regions where none occur, such as gray matter changes in brain regions that should be white or gray matter, may result from systemic misclassification of structures (29). This limitation is common to SPM and SPM-CAT, while both

techniques apply VBM. Further research is needed to assess this error; other methods such as surface-based morphometry (SBM) or tensor-based morphometry (TBM) can be explored to solve some of these issues. In the near future, multi-modality MRI including diffusion-weighted imaging and resting-state functional MRI (rs-fMRI) will be used to identify the potential regions and connections related to epileptogenic zone (30–32).

Another limitation of VBM analysis is about hypo-metabolic selection criteria. A common practice is to select the area with the largest volume identified by SPM and SPM-CAT as the EZ. One or more areas of reduced metabolism in PET could be caused by some reasons other than epilepsy, such as other neurological lesions, antiepileptic therapy, or functional alterations secondary to epilepsy (e.g., cognitive disorders). The identified clusters (or areas) caused by neurological lesions visible in MRI images can be excluded. However, all the patients in our study were MRI-negative. For hypo-metabolic clusters caused by other reasons, no good identification method is available. This limitation is mostly common to VBM applications; most previous studies have noticed this problem but they employed the same procedure as we did. Meanwhile, for the similar reason given above, as it is a very common procedure, the positive finding score defined in our study might be overestimated.

CONCLUSION

SPM and SPM-CAT with different parameter settings can be employed to objectively detect the hypo-metabolic areas in FDG-FET images for refractory epilepsy patients. SPM and SPM-CAT have achieved the same overall positive finding score. However, according to different parameter settings, the positive finding score was different. SPM-CAT has achieved a higher positive finding score than that of SPM for each setting, which makes SPM-CAT more efficient than SPM in localizing EZ for refractory epilepsy by quantitative analysis of FDG-PET images. Moderate agreement is found between the confirmed EZ and the pre-surgical EZ identified by SPM-CAT. SPM-CAT with the setting of $p < 0.0002$ and $k > 25$ might perform as an objective complementary tool for the visual assessment of EZ localization.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of the requirement of the Ethics Committee of Shengjing Hospital of China Medical University (Shenyang, China). Requests to access the datasets should be directed to Han Li, leoincmu@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shengjing Hospital of China Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

EB performed experiments and analyzed the data along with SQ and CJ. SQ, DH, and HL conceived the study, presented the results, and wrote the manuscript along with EB. SH and LW collected and analyzed the data. SQ and LW supervised the algorithm development and analyzed the data. All authors read and approved the final manuscript.

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CASE REPORT
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Magnetoencephalography STOUT Method Adapted to Radiofrequency Thermocoagulation for MR-Negative Insular Epilepsy: A Case Report

Kaiqiang Ma[1], Guoming Luan[1,2,3], Xiongfei Wang[1,2,3], Shen Luo[4,5], Lang Qin[4], Pengfei Teng[1], Yuguang Guan[1], Meng Zhao[1], Jing Wang[6], Mengyang Wang[6] and Jia-Hong Gao[4,5,7]*

[1] Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, China, [2] Beijing Key Laboratory of Epilepsy, Epilepsy Center, Sanbo Brain Hospital, Capital Medical University, Beijing, China, [3] Beijing Institute for Brain Disorders, Beijing, China, [4] Center for MRI Research, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China, [5] Beijing City Key Laboratory for Medical Physics and Engineering, Institute of Heavy Ion Physics, School of Physics, Peking University, Beijing, China, [6] Department of Neurology, Sanbo Brain Hospital, Capital Medical University, Beijing, China, [7] McGovern Institute for Brain Research, Peking University, Beijing, China

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Emma Losito, Hôpital Necker-Enfants Malades, APHP, France

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Tommaso Tufo, Catholic University of the Sacred Heart, Rome, Italy

***Correspondence:**
Guoming Luan
luangm@ccmu.edu.cn

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Epilepsy is one of the most challenging neurologic diseases confronted by human society. Approximately 30–40% of the worldwide epilepsy patients are diagnosed with drug-resistant epilepsy and require pre-surgery evaluation. Magnetoencephalography (MEG) is a unique technology that provides optimal spatial-temporal resolution and has become a powerful non-invasive imaging modality that can localize the interictal spikes and guide the implantation of intracranial electrodes. Currently, the most widely used MEG source estimation method for clinical applications is equivalent current dipoles (ECD). However, ECD has difficulties in precisely locating deep sources such as insular lobe. In contrast to ECD, another MEG source estimation method named spatio-temporal unifying tomography (STOUT) with spatial sparsity has particular advantages in locating deep sources. In this case study, we recruited a 5 year-old female patient with insular lobe epilepsy and her seizure recurred in 1 year after receiving the radiofrequency thermocoagulation (RF-TC) therapy. The STOUT method was adopted to locate deep sources for identifying the epileptic foci in epilepsy evaluation. MEG STOUT method strongly supported a stereo-electroencephalographic (SEEG)-guided RF-TC operation, and the patient reported a satisfactory therapeutic effect. This case raises the possibility that STOUT method can be used particularly for the localization of deep sources, and successfully conducted RF-TC under the guidance of MEG STOUT results.

Keywords: magnetoencephalography, STOUT, radiofrequency thermocoagulation, stereo-electroencephalography, insular epilepsy

INTRODUCTION

There has been an increasing interest in insular epilepsy since it was first described 70 years ago (1). The manifestation of insular seizure varies since the deeply located insular lobe is functionally connected to most brain areas (2). The diversity of clinical semiology of insular epilepsy, especially the magnetic resonance imaging (MRI)-negative insular epilepsy, often mischaracterizes the epileptogenic zone and leads to the failure of treatment (3).

More and more insular epilepsy patients are diagnosed as the stereo-electroencephalographic (SEEG) has been developed as a particularly effective tool for identifying seizure onset zone (4–6). Common therapies for insular epilepsy include insular cortex resections, bipolar electro-coagulation, and radiofrequency thermocoagulation (RF-TC). In contrast to insular cortex resections and bipolar electro-coagulation, RF-TC as a minimally invasion technique takes advantages of the already implanted SEEG electrodes and has quite few complications (7). However, due to the limited scope of RF-TC (8), the success rate of RF-TC for insular epilepsy has never been close to that of resection surgery and it is just regarded as a palliative treatment. As the success of RF-TC for hypothalamic hamartomas (HH), periventricular nodular heterotopias (PNH), and small focal cortical dysplasias (FCD) depends on high-resolution MRI, it should expect that the success rate of RF-TC for insular epilepsy will be increased when ablations are performed based on the scope of a given epileptogenic lesion.

In this paper, a case of recurrent insular epilepsy after RF-TC is reported. As a unique technology, magnetoencephalography (MEG) can provide optimal spatial-temporal resolution and localize the interictal spikes and guide the implantation of intracranial electrodes. Given the equivalent current dipoles (ECD), the most widely used MEG source estimation method, often fail to locate deep sources, we adopted spatio-temporal unifying tomography (STOUT) to delineate the scope of epileptogenic lesions within insular region. Guided by the results generated with STOUT, the patient received RF-TC operation and has now already achieved seizure free.

CASE PRESENTATION

A 5 year-old right-handed girl with no family history was re-admitted to our epilepsy center because the seizures recurred 1 year after first ablation. When she was 3 years old, the patient was admitted to our hospital for first evaluation as a 5-month history of seizures. The form of seizures was a loss of consciousness followed by her head and eyes turned to the right and then tonic–clonic seizure of right limbs. Seizures were not controlled after taking at least three anti-seizure medications (oxcarbazepine, sodium valproate, and lacosamide), and the frequency of seizures gradually increased to about 7–10 times per day.

Epilepsy evaluation included MRI, video-electroencephalographic (VEEG) recordings, MEG recording (with ECD source estimation), and 18F-fluorodeoxyglucose positron emission tomography (18F-FDG–PET) scan. The VEEG recorded several seizures without heart rate abnormalities, and results of VEEG are displayed in **Figure 1A**. The MRI showed no obvious abnormalities (**Figure 1D**), which was evaluated by a neuroradiologist and neurosurgeon. Large hypometabolic regions surrounding left sylvian fissure can be seen on PET. After evaluation, a case of focal epilepsy surrounding left sylvian fissure was considered. To validate the seizure onset zone, 12 intracranial electrodes surrounding left sylvian fissure were stereotaxically implanted and their positions are shown in **Figure 1E**. SEEG electrodes (5–18 contacts, diameter: 0.8 mm; length: 2 mm; 1.5 mm apart) were manufactured by Alcis, Besancon, France. The SEEG monitoring continued for 2 days during which 13 seizures were recorded, and the results of SEEG are displayed in **Figures 1B,C**. The epileptogenic zone was located in the third insular short gyrus, the insular long gyrus, and the parietal opercula.

According to SEEG results, RF-TC therapy targeting the ictal site was designed (J1-6, G1-2, M1-6, N1-7). RF-TC with an output power (3.5 W) and ablation time (120 s) resulted in successful thermo-conduction. RF-TC generator system was R-2000b (Beiqi, Beijing, China).

While seizures ceased in 1 month after ablation, the patient regained seizures in about a year, and the antiepileptic medication was taken at the original dose. This time, the patient was again admitted to our hospital for further evaluation. The VEEG monitor recorded for 24 h, and six seizures occurred. The MRI showed no obvious abnormalities. The hypometabolic regions surrounding left sylvian fissure can be seen on PET and is more localized than the previous one. MEG ECD showed that the epileptogenic zone was located in the right posterior cingulate cortex (**Figure 2A**). Taken together these results, we diagnosed that the epileptogenic zone should be located in insula and insulo-opercular areas. Eight intracranial electrodes densely covering the insula and insulo-opercular were implanted, and their positions are shown in **Figure 2C**. Wearing SEEGs, the patient was monitored for 2 days, and 10 seizures were captured. The semiology was stiffening of right limb followed by left limb complex movement, apnea, and laryngeal myoclonus. **Figure 3A** shows that SEEGs for all the inter-ictal discharges were located in the insular and insulo-opercular cortex (N1-6, O2-7, P2-4, R1-3, V2-4, Q5-9, K1-2/7-8, M1-3/6-8). The onset zone also originated from the insular and insulo-opercular cortex (Q3-9, R1-8, N2-8, V2-4, P2-4) with spike–waves in fast activities (**Figure 3B**).

RF-TC therapy (Q2-10, R1-9, N1-9, V1-5, P1-5) targeting onset zone was designed and conducted with an output power (3.5 W) and ablation time (120 s), after which the patients were monitored wearing SEEGs for 2 days and four seizures were captured. The semiology of seizures changed to an aura of abdominal discomfort, and then decreased body activity, apnea, and tonic clonus of the proximal right limb. **Figure 3C** shows that SEEGs for the inter-ictal discharges were located in the insula (N2-4/6-9, V1-3). The onset zone originated from the insular and insulo-opercular cortex (N7-9/2-3, Q7-10, V2-6, R2-4) with spike-waves in fast activities (**Figure 3D**).

Since the scope of ablation guided by SEEG was obviously insufficient, new guiding strategies for RF-TC shall be developed. As a result, MEG STOUT was adopted to further clarify the location of epileptogenic zone. The resting-state MEG date was record (0.1–300 z pass filter, 1-kHz sample rate) for 90 min after sleep deprivation using 306-channel VectorviewTM MEG system. After recording, the date was processed as follows: First, denoising operation to reduce environmental noise. Second, registering the MEG date with the MRI coordinate systems and marking interictal spikes. The spike selection criteria has been described extensively by Mohamed et al. (9). Briefly, spikes were marked on MEG by an expert epileptologist, who then selected those showing a clear dipolar magnetic field;

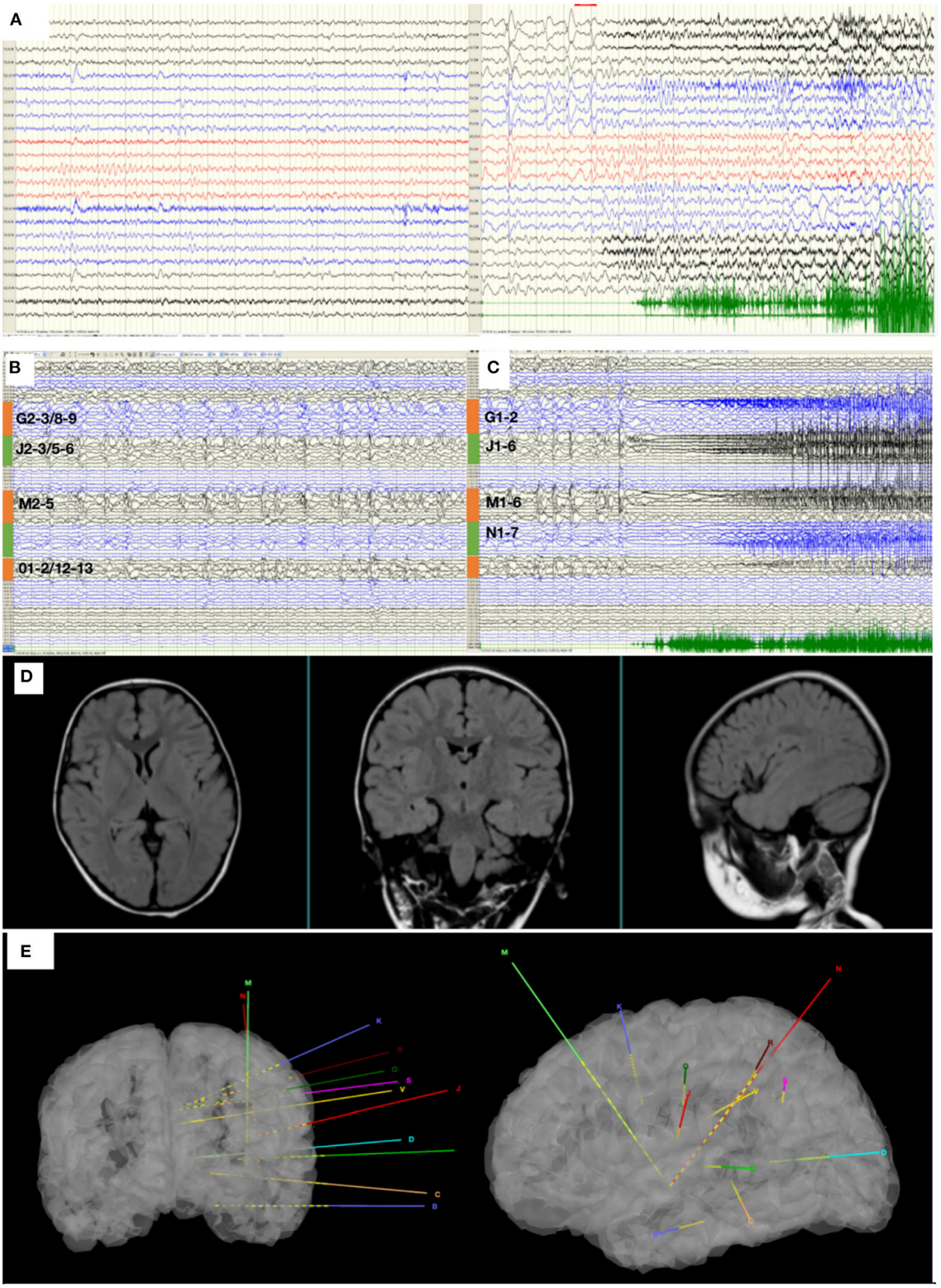

FIGURE 1 | (A) The interictal and ictal scalp VEEG. Scalp VEEG showed seizure onset with stiffening of right limb, apnea, salivation, waving of left limb. **(B)** SEEG showed all the inter-ictal discharges were located in insular-opercular cortex (J2-3/5-6, M2-5, G2-3/8-9, 01-2/12-13). **(C)** SEEG showed that the seizures onset zones originated from the insular-opercular cortex (J1-6, G1-2, M1-6, N1-7) with spike-wave in fast activities. The Semiology is stiffening of right limb, apnea, salivation, waving of left limb. **(D)** MRI images of the patient before the first intracranial electrode implantation. **(E)** The position of twelve electrodes.

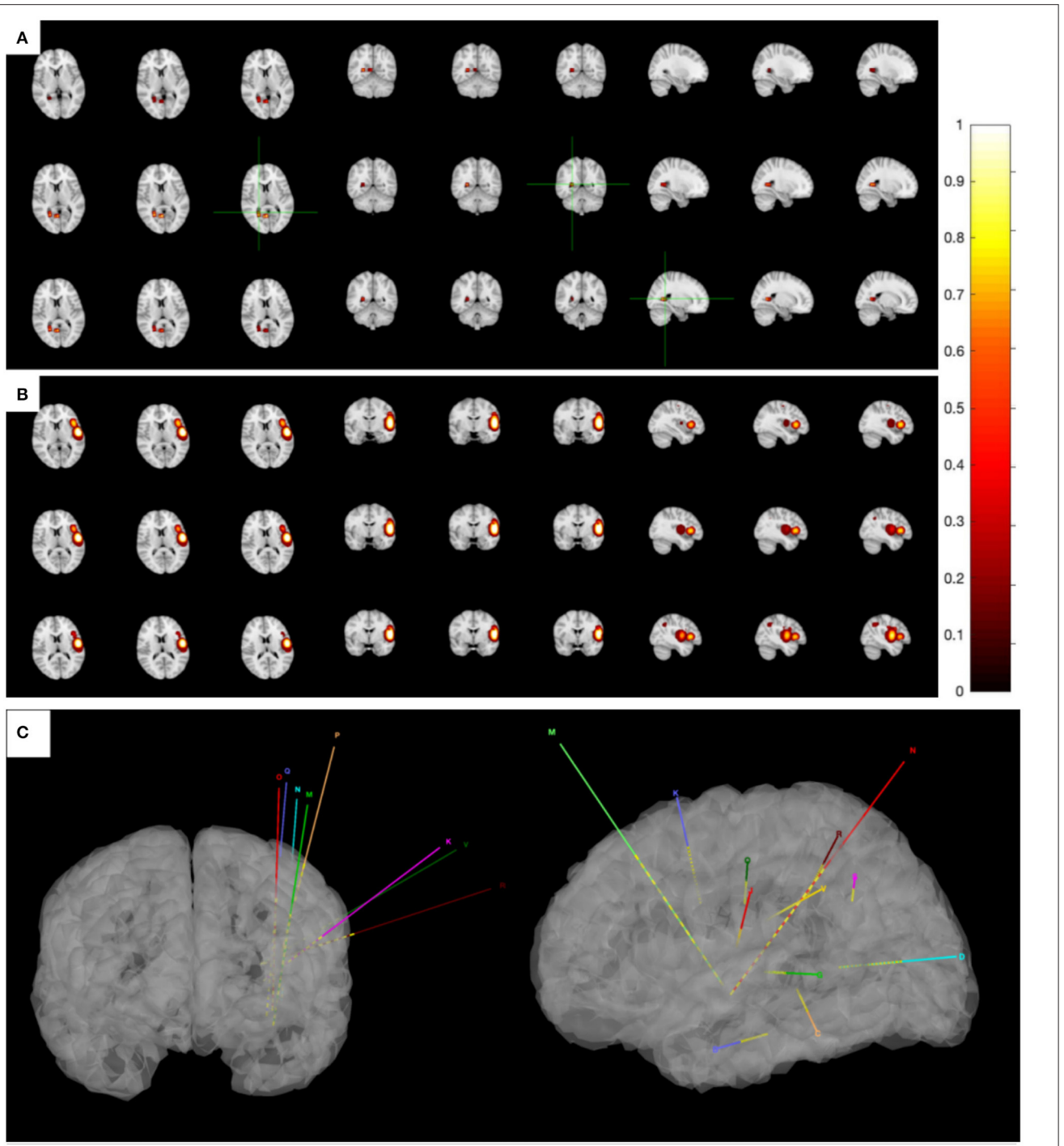

FIGURE 2 | (A) The MEG ECD method delineated epileptic zone at right posterior cingulate cortex. **(B)** The MEG STOUT method delineated epileptic zone at the left insular long gyrus of island and the parietal opercula. Thirteen spikes were marked in this patient and Source localization was conducted using ECD and STOUT on each spike within a −100 to 100 ms time window around the peak spike signal. All results displayed over the corticalsur face are thresholded at 50% of the maximum amplitude. As ECD method assumes that a small number of focal sources exist that can be equivalent to a few current dipoles in the brain, the result of MEG ECD method is localized to right posterior cingulate cortex. And the STOUT method is localized to the left insular long gyrus of island and the parietal opercula through localization bias compensation. **(C)** The position of eight intracranial electrodes.

this criterion ensures selected spikes have focal generators. Thirteen spikes were marked in this patient. Third, the STOUT solution was performed for datesets. Source localization was conducted using ECD and STOUT on each spike within a −100 to 100 ms time window around the peak spike signal, when the noise covariance estimation selected a 2,000 ms time

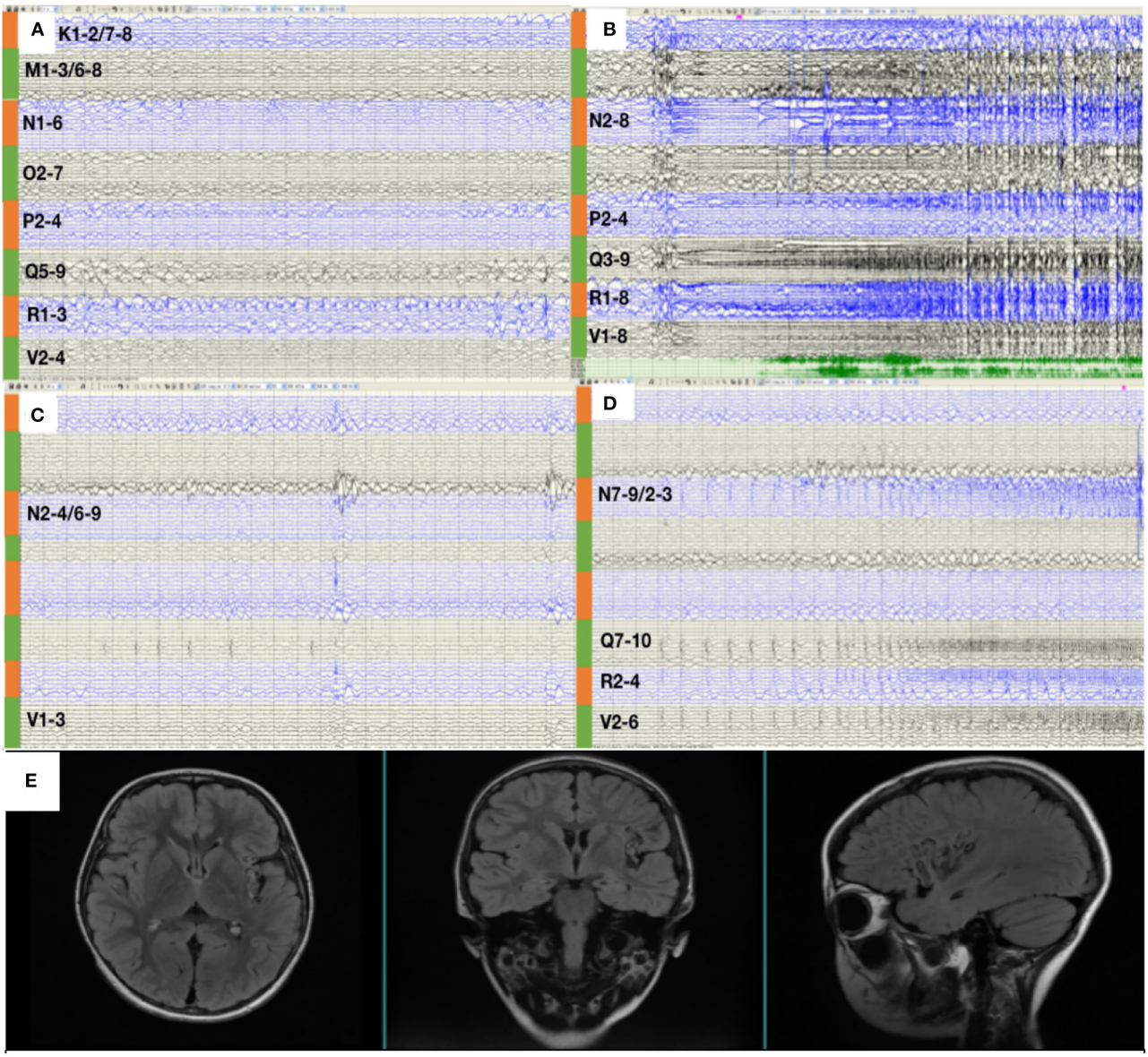

FIGURE 3 | (A) SEEG showed that all the inter-ictal discharges were located in the insular and insular-opercular cortex (N1-6, 02-7, P2-4, R1-3, V2-4, Q5-9, K1-2/7-8, M1-3/6-8). **(B)** The onset zone also originated from the insular and insular-opercular cortex (Q3-9, R1-8, N2-8, V2-4, P2-4) with spike—waves in fast activities. **(C)** SEEGs for the inter-ictal discharges were located in the insula (N2-4/6-9,V1-3). **(D)** The onset zone originated from the insular and insular-opercular cortex (N7-9/2-3, Q7-10, V2-6, R2-4) with spike—waves in fast activities. **(E)** Images 1 year after RF-TC showed a satisfying ablation.

window as baseline. The MEG STOUT method delineates the epileptic zone in the insular long gyrus, and the parietal opercula (**Figure 2B**) covered the epileptogenic zone determined by the original SEEG. We compared the STOUT source localization with the epileptogenic zone identified by SEEG and found the STOUT source localization can completely cover the lesions of ablation. Also, the epileptogenic zone mainly located in the insular long gyrus of island and the parietal opercula. The insufficient ablation of insular long gyrus and the parietal opercula seizures led to the dissatisfied therapeutic effect. According to the STOUT source localization, RF-TC (V5-7, V4-N8, V4-N9, V5-N8, V5-N9, V3-Q8, V3-Q9, V4-Q8, V4-Q9, R2-Q6, R3-Q6, R4-Q6, R2-Q7, R3-Q7, R3-Q8) treatment was performed again. The RF-TC was performed between two adjacent contacts of the different electrodes to achieve full ablation, after which a 24 h SEEG records showed no inter-ictal discharges. Of note, seizures ceased right after the ablation. Post-ablation complications for this patient included clumsy speech and limp, but these complications recovered within half a month. No intelligence decline was observed, and the

TABLE 1 | Patient's clinical data of each attack or therapy.

Attack or therapy	1	2	3	4	5
Time from disease onset	onset	+5 months	+18months	+24months	+24months
Age (years)	3	3.5	4.5	5	5
Semiology	Loss of consciousness, head and eyes turned to the right and then tonic-clonic seizure of right limbs	Stiffening of right limb, apnea, salivation, waving of left limb	Stiffening of right limb, left limb complex movement, apnea, laryngeal myoclonus	Stiffening of right limb, left limb complex movement, apnea, laryngeal myoclonus	Abdominal discomfort, decreased body activity, apnea, tonic clonus of the proximal right limb
Medicine	Oxcarbazepine	Oxcarbazepine, sodium valproate, Lacosamide	Oxcarbazepine, Sodium valproate, Lacosamide	Oxcarbazepine, sodium valproate, Lacosamide	Oxcarbazepine, sodium valproate, Lacosamide
Therapy	Medicine	Medicine+RF-TC	Medicine	Medicine+RF-TC	Medicine+RF-TC guided by STOUT
Clinical response to therapy	Relief	Seizures ceased in 1 month after ablation	Recur	Relief	Seizure free

parent was satisfied with the treatment. After the ablation, three anti-seizure medications (oxcarbazepine, sodium valproate, and lacosamide) were given as the postoperative antiepileptic drug. At the 1 year follow-up, there was no sign of relapse and VEEG showed no inter-ictal discharges. MRI image of the patient showed a satisfying ablation and was shown in **Figure 3E**. The timeline with relevant data from the episode of care is shown in **Table 1**.

DISCUSSION

SEEG was proposed by Talairach et al. (10). As a minimal invasive method, it offers a unique means of accurately mapping the epileptogenic network in pre-surgical evaluations of epilepsy. Moreover, SEEG-guided RF-TC, which ablates epileptogenic zone directly through the recording electrodes according to SEEGs evidence, is considered as a minimally invasive treatment with notable preservation of neurocognitive functions. SEEG-guided RF-TC is considered as a palliative approach, and its principle often referred to selectively destroying epileptogenic zone or the critical nodes of epileptogenic networks (7). MR-positive epileptic foci including HH, PNH, and FCD type II (11) demonstrated satisfactory results after ablation. For MR-negative lesions, especially MR-negative insular lesions, the ablation effect is not satisfactory. It has been reported that only 11% of the patients were persistently seizure-free and 41% were responders (12). So STOUT method was used to clarify the scope of the epileptogenic zone.

As a non-invasive measure, MEG has high value for epilepsy patients' pre-surgical evaluation (13), with the ECD method being a standard method for MEG to locate interictal epileptiform discharges (14). Moreover, MEG can assist intracranial electrode placement planning (15–17). The ability of ECD method to delineate the epileptic zone is very limited due to (1) difficulties in localizing extended sources and (2) an error in the sensitivity of the dipole to the deep location (18). In this insular epilepsy case, the deep source location with MEG ECD was inaccurate.

STOUT method as a minimum L1-norm solution has spatial sparsity (19), which is different from the minimum L2 norm estimation, a distributed source imaging technology that leads to the low spatial resolution of the reconstructed image and the overestimated area of the active region boundary. STOUT approach combines the main advantages of Sparse Basis Field Expansions (S-FLEX) (20) and Time–Frequency Mixed-Norm Estimates (TF MxNE) (21). S-FLEX expresses current density as a linear combination (20), which is locally smooth but space-constrained spatial basis function. TF MxNE decomposes the current density into the time basis function and the corresponding coefficient. Similarly, as a combination of S-FLEX and TF-MxNE, STOUT expresses the current density as a linear combination of spatio-temporal basis functions.

To compensate for localization bias, STOUT adopts a diagonal weight matrix

$$\Psi(\mathrm{i},\mathrm{i}) = \sqrt{\left(||\mathrm{L_x}\left(\cdot,\mathrm{i}\right)||_2^2 + ||\mathrm{L_y}\left(\cdot,\mathrm{i}\right)||_2^2 + ||\mathrm{L_z}\left(\cdot,\mathrm{i}\right)||_2^2\right)^{\zeta}}.$$

Parameters determine the intensity of depth compensation. When $\zeta = 0$, there is no depth bias compensation, while $\zeta = 1$ leads to full compensation. Therefore, the accuracy of deep source localization is greatly improved. For reference, MEG STOUT method was used to locate the deep source in this case, assisting in delineating the epileptogenic zone. Compared with the other two source estimation methods, the accuracy of the STOUT method in clinical used was described by Zheng et al. (22).

In this article, we used MEG STOUT to locate the deep source of the insula. Compared with the first ablation location, post-surgery outcomes verified that the STOUT location was accurate, and the RF-TC guided by MEG STOUT achieved satisfactory treatment results. Still, the accuracy of MEG STOUT method needs to be verified by large samples in

clinical applications. Conclusively, the importance of this case is that we gave MEG STOUT method as a potentially optimal solution to locate deep sources, which can effectively assist RF-TC by accurately locating the epileptogenic zone. By continuously improving the accuracy of MEG source positioning methods, in the future, it may be possible to achieve precise positioning of epileptogenic zone through non-invasive methods.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Sanbo Brain Hospital, Capital Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

KM collected the patient information, conceptualized and designed the study, performed the SEEG-guided RF-TC, and drafted the manuscript. SL, LQ, XW, and PT conducted the computational calculations. MW and JW performed the clinical data analyses. GL, YG, and MZ conducted the electrode implantation. MW and JG critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Treatment Guidelines for Rare, Early-Onset, Treatment-Resistant Epileptic Conditions: A Literature Review on Dravet Syndrome, Lennox-Gastaut Syndrome and CDKL5 Deficiency Disorder

Richard F. Chin[1], Ana Mingorance[2,3], Benjamin Ruban-Fell[4], Isabelle Newell[4], Jenni Evans[5], Kishan Vyas[6], Charlotte Nortvedt[6] and Sam Amin[7]*

[1] Royal Hospital for Sick Children, Edinburgh, United Kingdom, [2] The Loulou Foundation, London, United Kingdom, [3] Dracaena Consulting, Madrid, Spain, [4] Costello Medical, London, United Kingdom, [5] Costello Medical, Cambridge, United Kingdom, [6] GW Pharma Ltd., London, United Kingdom, [7] Bristol Royal Hospital for Children, Bristol, United Kingdom

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Emma Losito, APHP, France

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***Correspondence:**
Richard F. Chin
r.chin@ed.ac.uk

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Background: Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS) and CDKL5 deficiency disorder (CDD) are rare epileptic conditions, characterised by drug-resistant seizures. Seizure management in these patients requires careful therapy selection. This targeted literature review (TLR) aimed to collate and synthesise information from country-specific and international treatment guidelines for DS, LGS and CDD.

Methods: A TLR was performed between 25th January and 11th March 2021. Online rare diseases and guideline databases were manually searched in addition to websites of national health technology assessment bodies for the following countries: Australia, Canada, France, Germany, Israel, Italy, Japan, Spain, Switzerland, UK and US, as defined by pre-specified eligibility criteria. Search terms, developed for each condition, were translated into local languages where appropriate. Descriptive analyses were performed to examine the geographical distribution of included guidelines; methodologies used to develop guidelines; cross-referencing of treatment recommendations made within other guidelines; patterns of treatment recommendations. An author map was created using R version 3.5.1, to visualise the extent of collaboration between authors.

Results: Forty total guidelines were included, of which 29, 34 and 0 contained recommendations for DS, LGS and CDD, respectively (some provided recommendations for ≥1 condition). Most were country-specific, with guideline authors predominantly publishing in regional groups. Five guidelines were classified as "International" and displayed connections between author groups in the US, UK, France and Italy. Reported guideline development processes were lacking [43% (17 guidelines) had unclear/absent literature review methodologies] and those reported were variable, including both systematic and targeted literature reviews. Use of expert consultation was also variable. A high degree of heterogeneity was observed in the availability of treatment recommendations across disorders, with 271 and 190 recommendations

for LGS and DS, respectively, and contradictory positive and negative treatment recommendations for several drugs in each indication [35% (11/31) and 22% (6/27) in LGS and DS, respectively].

Conclusions: This review highlights the need for further high-quality international consensus-based treatment guidelines for LGS, DS, and particularly for CDD (for which no treatment guidelines were identified). Supra-national consensus guidance based on findings from a wider geographical range may improve resource allocation and establish an improved world-wide standard of care.

Keywords: epilepsy, treatment, literature review, rare disorders, guidelines, CDKL5 deficiency disorder, Dravet syndrome, Lennox-Gastaut syndrome

INTRODUCTION

Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are severe, treatment-resistant developmental epileptic encephalopathies (DEEs), in which seizure activity is associated with general cerebral dysfunction (1). CDKL5 deficiency disorder (CDD) is a more recently-described DEE caused by mutations in the *CDKL5* gene (2–4). Despite their distinct aetiologies, these disorders all feature the onset of seizures in early childhood, as well as severe cognitive and behavioural impairments (1, 5, 6). It is important to manage seizures carefully to avoid injuries, disability, and reduce the risk of life-threatening complications, such as sudden unexpected death in epilepsy (SUDEP) and status epilepticus (SE) (7, 8).

Management of epileptic seizures requires careful therapy selection to optimise seizure control and improve a patient's quality of life (QoL) (9), balanced against significant side effects that are associated with many pharmacological treatments. The three main forms of treatment available are anti-seizure medications (ASMs), dietary modification (typically the ketogenic diet), and surgical intervention (4, 5, 7), with preventative ASMs remaining the mainstay of epilepsy treatment (10).

The management of seizures in patients with DS, LGS and CDD is particularly challenging as the seizures are frequently treatment-resistant (requiring the use of two or more appropriately chosen ASMs), and patients often fail to achieve complete seizure control (4, 7, 9, 11). In addition, therapy with specific mechanisms of action may be required for certain seizure types, and individual responses to these drugs can be variable (5). In some cases, ASMs may also become less effective over time and can even worsen seizure control (5). Physicians must also consider that seizure patterns and progression of these disorders may change over time (9).

Due to the challenges associated with the selection of appropriate ASMs to manage seizures in patients with DS, LGS and CDD, the development and use of treatment guidelines helps to optimise management of these conditions and align best practises and care in both national and international contexts (12). Additionally, the content of such guidelines may be used to inform health technology assessment (HTA) recommendations and play a decisive role in treatment licencing (13, 14). It is therefore widely accepted that treatment guidelines should be developed using robust methods of evidence generation, such as systematic literature reviews (SLRs) and rigorous forms of expert consensus (12). In addition, expert collaboration and the co-ordinated development of guidelines prevent the duplication of efforts and allow the generation of high-quality recommendations, based on learnings from across the globe (15, 16). Whilst these are the ideal considerations, they are not always met, particularly for rare diseases.

Treatment guidelines for rare diseases are often scarce, geography-specific, and are of varying quality largely due to a paucity of high certainty evidence (17, 18). Physicians, support groups and carers of people with rare diseases often need to keep updated with developments in the field; however, clinicians and families may not have the time to collate and analyse available data, and therefore require guidelines to ensure patients receive optimal care (19). In a user satisfaction survey undertaken by the Orphanet website (an online resource which aims to provide high-quality information on rare diseases to a variety of stakeholders), respondents were reported as being interested in accessing more clinical guidelines and review articles than were already available, as well as expanding access to resources from a wider range of countries, highlighting the continued need for robust treatment guidelines (20).

The objective of this targeted literature review (TLR) was to perform a descriptive analysis of available treatment guidelines for the management of DS, LGS and CDD. More specifically, we aimed to:

1. Determine the availability of country-specific and international treatment guidelines for DS, LGS and CDD;
2. Describe the methodology used to develop individual existing guidelines;
3. Assess the extent of collaboration between authors through the identification of shared authors between the included guidelines; and
4. Report the frequency and patterns of existing treatment recommendations for DS, LGS and CDD.

METHODS

Search Strategy

A TLR was performed between 25th January and 11th March 2021; online information sources were manually searched in

accordance with pre-specified search criteria, to identify relevant treatment guidelines. The search strategies used for each information source, and the dates of searches are summarised in **Supplementary Table 1.**

The search strategy included searches of the following sources: Google, Guideline Central, Orphanet, National Organisation for Rare Disorders (NORD), American Academy of Neurology (AAN), American Epilepsy Society (AES) and International League Against Epilepsy (ILAE). Websites of national HTA bodies for the following countries were also searched: Australia, Canada, France, Germany, Israel, Italy, Japan, Spain, Switzerland, United Kingdom (UK), and United States (US).

Each database was queried with search terms appropriate for its search functionality (e.g., Boolean operators were used where possible) and the specificity of the database (e.g., whether it was a repository of treatment guidelines, in which case search terms for "guidelines" were unnecessary); searches were filtered for guidelines where possible. Search terms included combinations of free-text and terms for each of the indications of interest. These terms were translated into the relevant language where applicable.

Review Process

Each record identified through the searches was screened for eligibility according to criteria defined using a PICOS (Population, Intervention, Comparators, Outcomes, Study design) approach, as presented in **Table 1**. Briefly, eligible publications were guidelines or guidance reporting routine pharmacological management of seizures in patients with DS, LGS or CDD in the countries of interest described previously. Eligible publications were classified as "International" if they were developed either for multiple countries or did not specify to which countries they pertained. Guidance or guidelines were defined as publications which were informed by rigorous methods, such as an SLR, had multiple authors or explicitly stated that certain treatments were "recommended". In addition to guidelines produced by HTA bodies, the review also captured technology appraisal guidance following any conducted technology assessments. Search results were screened by a single reviewer. Where the applicability of the inclusion criteria was unclear, the record was assessed by a second reviewer. Where possible, reviewers who were either fluent or had a high level of proficiency in a relevant language were responsible for the identification, screening and extraction of any guideline documents not published in the English language. For languages in which reviewers were not proficient, the online translation software, DeepL®, was used.

Data Extraction and Analyses

Guidelines presenting relevant data were extracted into a pre-defined extraction grid. Information extracted for each guideline included: publication date and planned revision date; the organisation that developed the guideline; author names and author affiliations; the methodology used for the development of guidelines, including use of literature reviews and expert consultation; population(s) addressed; pharmacological recommendations by treatment stage and seizure subtype and references to other guidelines, HTA assessments/regulatory body decisions and compiled literature sources (including SLRs, meta-analyses and electronic databases).

Descriptive analyses were performed in Microsoft Excel® to examine: the distribution of identified guidelines across the

TABLE 1 | Eligibility criteria.

Modified PICOS domain	Inclusion criteria	Exclusion criteria
Population	Patients with the following epileptic conditions: • Dravet syndrome • Lennox-Gastaut syndrome • CDKL5 deficiency disorder	Conditions other than those listed
Intervention	Any	None
Outcomes	The document must have discussed the management of the conditions of interest in terms of pharmacological treatment pathways for routine seizure control	• Documents that did not discuss the management in terms of pharmacological treatment pathways • Emergency medication and surgical guidelines
Publication type	Guidelines or guidance documents	Publications other than guidelines
Other considerations	Specifically produced for use in: • EU5 countries (UK, Germany, Spain, Italy, France) • Japan • Australia • Switzerland • Israel • US • Canada International guidelines (i.e., guidelines produced for multiple countries that included or potentially included the countries of interest, or guidelines that did not specify which countries they pertained to)	Produced specifically for use in countries that were not of interest

EU, European Union; PICOS, Population, Intervention, Comparators, Outcomes, Study design; UK, United Kingdom; US, United States.

countries of interest; the methodologies used to develop the treatment guidelines; and the cross-referencing of treatment recommendations made within other guidelines.

The authors involved in developing each of the guidelines identified in this study (including guidelines for both DS and LGS) were mapped into a network, using R version 3.5.1 to visualise whether authors were contributing to >1 guideline and if so, to measure the extent of collaboration between these authors, both on a national and international level.

In order to assess the patterns of positive and negative pharmacological treatment recommendations for each indication, further descriptive analyses were performed. A positive recommendation was defined as an individual ASM that was recommended for use in a specific indication, irrespective of the line of treatment (e.g., first-line) or whether the treatment was adjunctive; whilst a negative recommendation was defined as an individual ASM treatment that was highlighted as a potential option by a guideline but whose use was recommended against (for any reason) in a specific indication, irrespective of the line of treatment or whether the treatment was adjunctive.

RESULTS

Characteristics of Included Guidelines

A total of 40 eligible records were included in the review (**Figure 1**), with publication dates ranging between November 2005 and January 2021. More detailed information regarding each of the guidelines is presented in **Supplementary Table 2**. The majority of guidelines were country-specific (with recommendations intended for patients in a specific country); however, five guidelines were classified as "International" (**Figure 2**). The countries with the highest number of identified guidelines were France (7; 18%), Spain (7; 18%), Japan (5; 13%) and the UK (5; 13%). No national guidelines were identified for use in Israel or Switzerland. Only three guidelines were identified that developed recommendations specifically for DS or LGS (one in LGS from Germany, one in LGS from an international author group and one in DS from an international author group). The remaining guidelines including recommendations for DS or LGS were identified within broader epilepsy guidelines. Several guidelines were specifically developed for regions within one of the countries of interest (13% [5/40]). Out of these, two UK guidelines were created for use in Scotland, an Italian guideline was developed for the region of Tuscany and two of the seven Spanish guidelines identified were created specifically for the region of Andalusia. None of the guidelines identified were for use in the US at the state level.

Evidence Base and Methodology for Guideline Development

Of the 40 guidelines identified, 10 (25%) did not specify whether literature reviews were used to inform guideline development. An additional seven guidelines (18%) explicitly stated that a literature review was not used as part of the development process. The remaining guidance documents involved either systematic [22% (9/40)] or targeted [15% (6/40)] literature searches, or a combination of these [20% (8/40)]; (**Figure 3**). Details on expert consultation were not reported by 12/40 guidelines (30%); three guidelines (8%) explicitly did not include any form of expert consultation. Only three guidelines (7%) involved a Delphi panel to inform guidance, while seven guidelines (17%) were based on formal consensus group exercises; the remaining 15 guidelines (38%) utilised other forms of expert consultation, such as working groups or targeted expert interviews (**Figure 4**). Although 20/40 (50%) of guidelines reported the use of a combined development approach consisting of a literature review and expert consultation, only one of the guidelines explicitly used an SLR and Delphi panel in combination.

A review of cross-referencing between the included guidelines and other published guidance/literature reviews revealed that citations within the identified guidelines mainly referenced other treatment guidelines (53/103; 51%) or other compiled literature sources (33; 32%), with the majority of the latter consisting

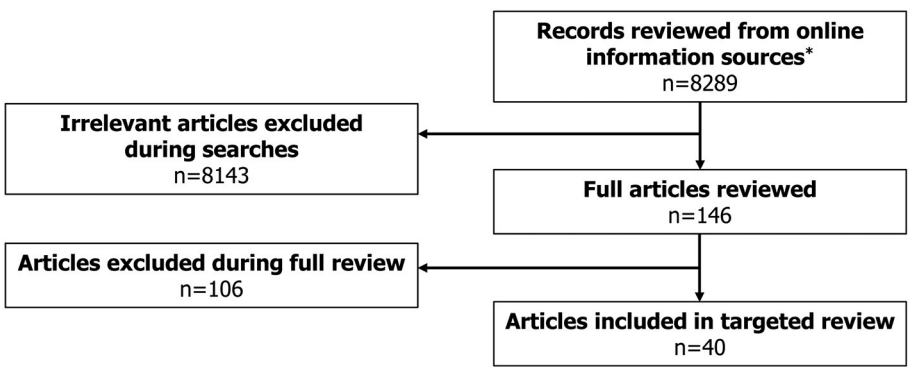

FIGURE 1 | Literature review flowchart. *Online information sources included: Guideline Central, National Organization for Rare Disorders (NORD), American Academy of Neurology (AAN), American Epilepsy Society (AES), International League Against Epilepsy (ILAE), Orphanet, Google, National Institute for Health and Care Excellence (NICE), Pharmaceutical Benefits Scheme (PBS), Canadian Agency for Drugs and Technologies in Health (CADTH), Ministerio de Sanidad, Consumo y Bienestar Social (MSCBS), Agenzia Italiana del Farmaco (AIFA), Haute Autorité de Santé (HAS), Gemeinsamer Bundesausschuss (G-BA), Bundesamt für Gesundheit (BAG), State of Israel – Ministry of Health, Ministry of Health, Labour and Welfare (MHLW).

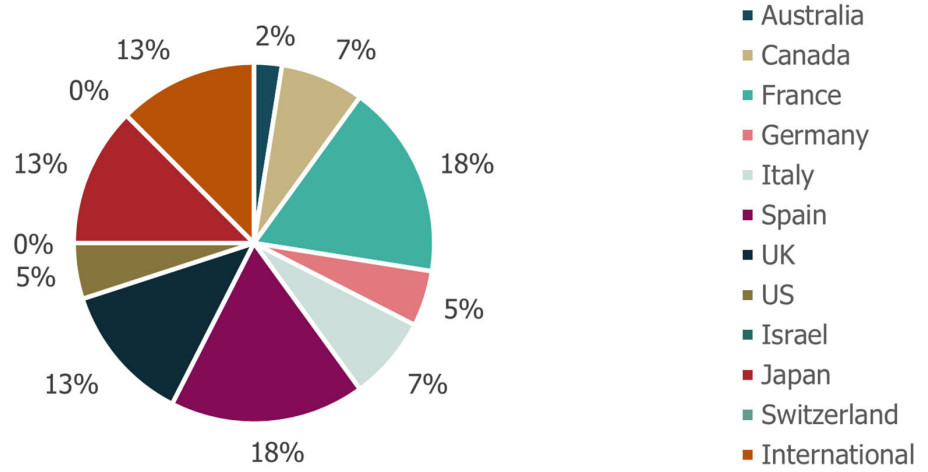

FIGURE 2 | Geographies of identified guidelines. *No guidelines were identified for use in Israel or Switzerland. The geography of guideline use refers to the country for which that the guidance was specifically developed.

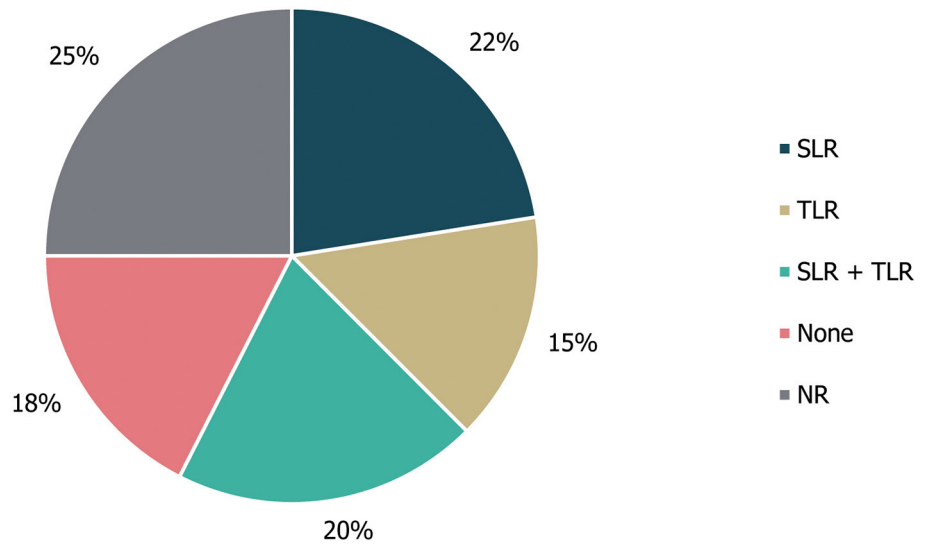

FIGURE 3 | Types of literature review performed to inform guideline development. "None" refers to guidelines in which a literature review was explicitly not used; NR, not reported; SLR, systematic literature review; TLR, targeted literature review.

of SLRs included in the Cochrane Database of Systematic Reviews (20/33; **Figure 5**). Citations also referenced 15 (15%) regulatory body recommendations, two of which were made to HTA body recommendations. The three documents most frequently referenced (ten, six and seven times, respectively) were the UK's National Institute for Health and Care Excellence (NICE)'s guidance on the diagnosis and management of epilepsies (CG137) (21), an SLR from the Cochrane Database of Systematic Reviews on the treatment of infantile spasms (22) and a systematic literature review from the Cochrane Database of Systematic Reviews on the treatment of Lennox-Gastaut syndrome (23, 24).

Extent of Author Collaboration

In the author map, which was developed to investigate the extent of national and international levels of collaboration by visualising a network of the authors involved in developing each of the guidelines identified in this study (including guidelines developed for both DS and LGS), connections were identified between international treatment guidelines and US, UK, French and Italian guideline author groups as well as between Canadian and Spanish guideline author groups. Other regional guidelines displayed only occasional connections between author groups within the region in question (these were mostly found to be within the Japanese region; **Figure 6**).

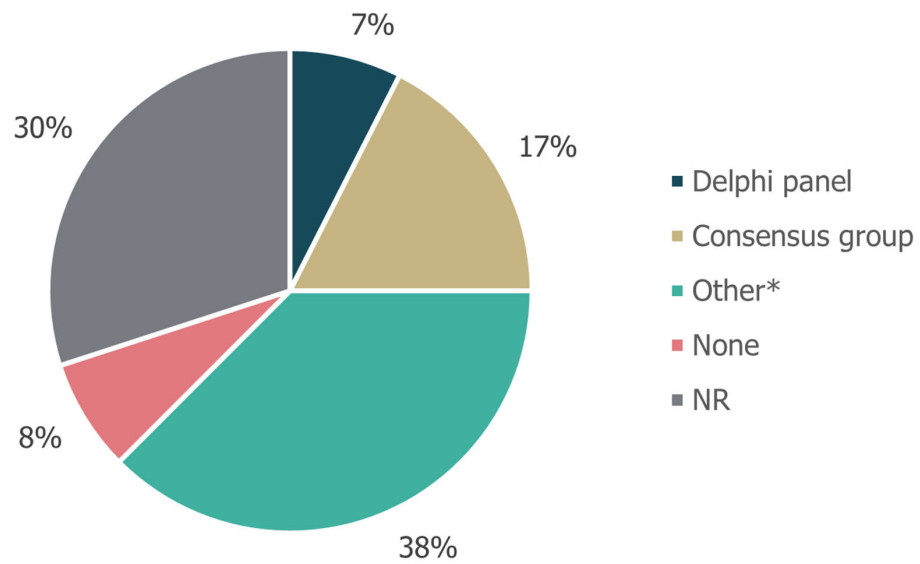

FIGURE 4 | Types of expert consultation performed to inform guideline development. "None" refers to guidelines in which expert consultation was explicitly not used; NR, not reported. *Other refers to working groups or targeted expert interviews.

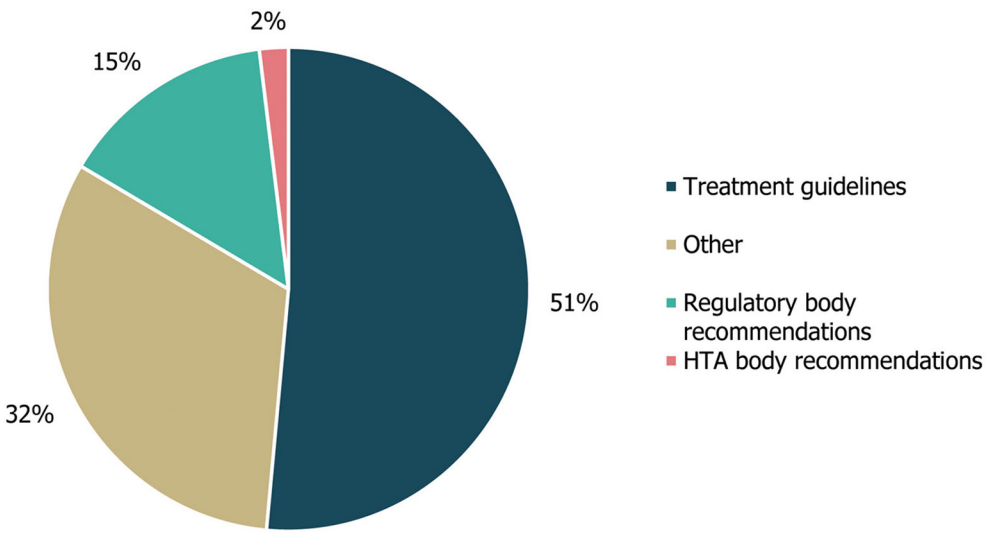

FIGURE 5 | Guideline cross-referencing to other treatment guidelines and regulatory/HTA recommendations. Cross-referencing refers to the number of different treatment guidelines, regulatory body recommendations, HTA body recommendations or other references that were cited within the guidelines identified in this study, either in the body of the guideline text or in accompanying reference lists. "Other" references included a Cochrane systematic literature review, an information website, a narrative review and a consensus conference report. HTA, health technology assessment.

Treatment Recommendations for Dravet Syndrome

In the 29 guidelines identified for DS, a total of 190 individual treatment recommendations were made (irrespective of the line of treatment; **Figure 7**). Of these treatment recommendations, similar proportions were positive (53%; 101/190) and negative (47%; 89/190). Most of the recommended treatments (21/27) received either exclusively negative or positive recommendations, with only stiripentol, cannabidiol, phenobarbital, acetazolamide, bromide, and lamotrigine having received both (**Figure 7**). Out of the 27 treatments, 11 received exclusively positive recommendations for use in DS, of which sodium valproate,

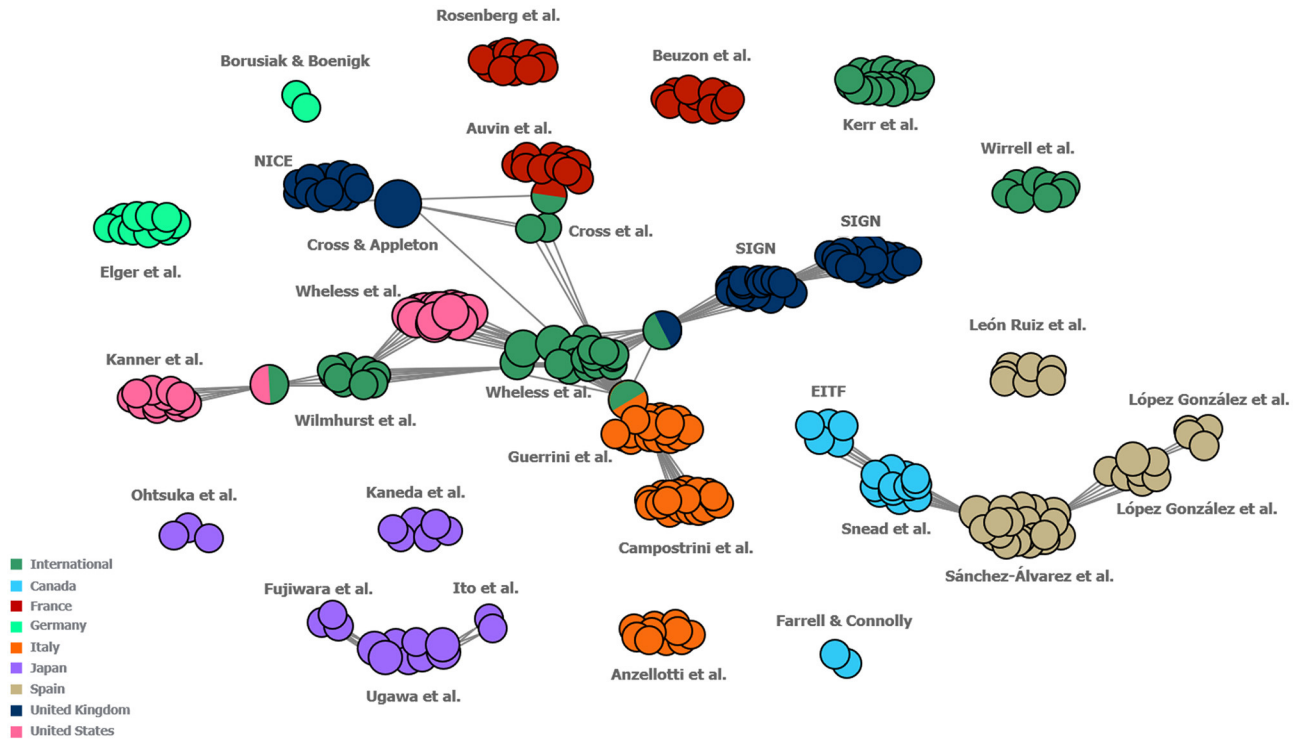

FIGURE 6 | Map of collaboration between the author groups of included guidelines. Each individual circle represents one author of a guideline. Each "cluster" represents the group of authors that developed one guideline. Each cluster is labelled with the names of its respective first author(s). Guidelines which share one or more authors between them are connected by grey lines, with single circles between guideline clusters representing the individuals who authored both guidelines in question. Guidelines were classified as "International" if they were developed either for multiple countries or did not specify to which countries they pertained. Guidelines for which author names were not reported have not been included in this figure. EITF, Epilepsy Implementation Task Force; NICE, National Institute for Health and Clinical Excellence; SIGN, Scottish Intercollegiate Guidelines Network.

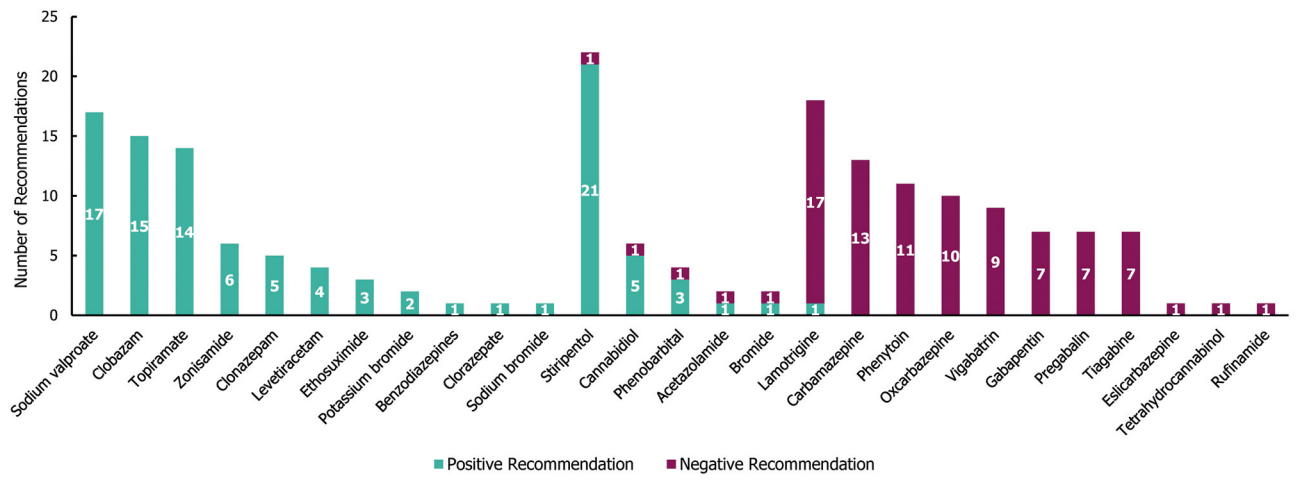

FIGURE 7 | Treatment recommendations for Dravet syndrome. *N* = 190 (101 positive and 89 negative recommendations) from 29 guidelines. Positive recommendation: use of an individual ASM that was recommended for use in a specific indication, irrespective of the line of treatment (e.g., first line) or whether the treatment was adjunctive; Negative recommendation: an individual ASM treatment that was highlighted as a potential option by a guideline but whose use was recommended against (for any reason) in a specific indication, irrespective of the line of treatment or whether the treatment was adjunctive.

clobazam and topiramate had the highest number (≥14 each). However, stiripentol had the highest number of positive recommendations (21), as well as one negative recommendation. Of these, only stiripentol and cannabidiol have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of seizures in Dravet syndrome; both drugs received a negative recommendation due to not being licenced in the region of interest at the time of guideline publication (25–28). A number of treatments (10/27) received exclusively negative recommendations for use in DS, of which carbamazepine, phenytoin, oxcarbazepine and vigabatrin had the highest number (≥9 each).

Out of the 101 total positive treatment recommendations for DS, 37 (37%) were recommended for a specific line of treatment (18 for first-line, 19 for second line; see **Supplementary Table 3**). Sodium valproate received the highest number of positive first-line recommendations (ten), followed by topiramate (five) and stiripentol (two; approved only as an add-on therapy to sodium valproate and clobazam) (29). Clobazam received the highest number of positive second-line recommendations (four). There were only three seizure type-specific recommendations for DS, two of which were positive recommendations for the use of stiripentol in tonic-clonic seizures, and one was a negative recommendation for the use of lamotrigine in myoclonic seizures.

Treatment Recommendations for Lennox-Gastaut Syndrome

In the 34 guidelines identified for LGS, a total of 271 individual treatment recommendations were made irrespective of line of treatment (**Figure 8**). Of these 271 individual recommendations, 205 (76%) were positive and 66 (24%) were negative. Nearly two-thirds of the drugs that were recommended (65% [20/31]) received either exclusively negative or positive (1 and 19 drugs, respectively) recommendations for LGS. However, 35% (11/31) of drugs received both negative and positive recommendations. Of the 19 drugs that received positive recommendations for use in patients with LGS; lamotrigine, topiramate and rufinamide received the most (with ≥27 positive recommendations each, and no negative recommendations; **Figure 8**). These three drugs have been specifically approved for the treatment of epilepsy in LGS (30–32) in addition to felbamate (13 positive and one negative recommendation), clobazam (17 positive recommendations) and cannabidiol (5 positive and one negative recommendation) (28, 33, 34). Vigabatrin was the only drug with exclusively negative recommendations for the treatment of LGS (nine in total). Carbamazepine and gabapentin received the highest number of individual negative recommendations (receiving 12 and 13 negative recommendations across the guidelines, respectively).

Out of the 205 positive treatment recommendations, 63 (31%) were recommended for a specific treatment line for LGS (**Supplementary Table 4**). Sodium valproate received the highest number of positive recommendations as a first-line therapy (14), whereas lamotrigine received the highest number of positive recommendations as a second-line therapy (9). All negative recommendations for a specific line of treatment (6/66 [9%]) were associated with second-line treatment recommendations (with carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine and vigabatrin receiving one each). Additionally, there were 40 seizure type-specific recommendations for LGS (35 positive, 5 negative), which covered a wide range of seizure types, including absence, atonic, atypical absence, crisis episode, generalised, myoclonic, tonic, tonic-atonic and tonic-clonic (although most seizure-type specific recommendations were only made once among the guidelines). The two most frequent seizure type-specific recommendations (each receiving 3) were positive recommendations for ethosuximide in atypical absence seizures and topiramate in atonic seizures.

Treatment Recommendations for CDKL5 Deficiency Disorder

Although there are publications that describe treatment response to specific drugs or diets in patients with CDD (35), no treatment guidelines for the management of routine seizures in CDD were identified.

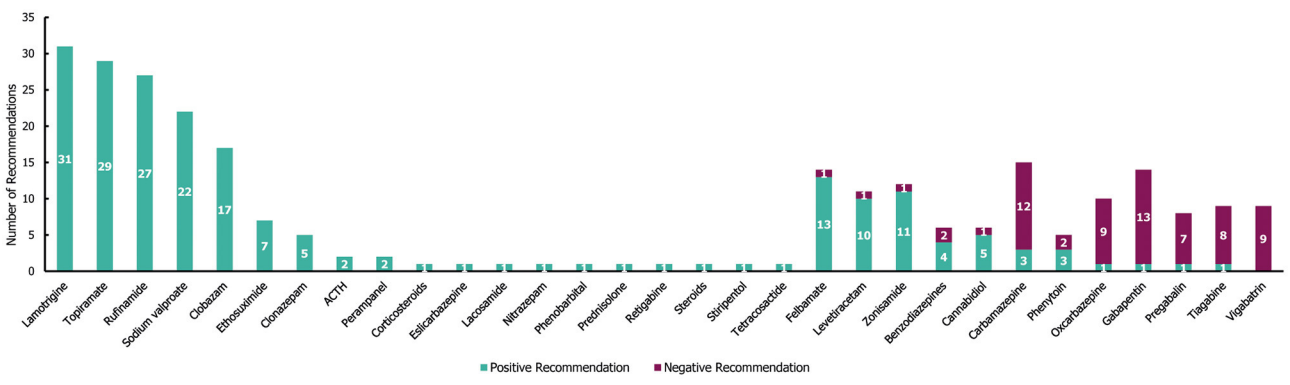

FIGURE 8 | Treatment recommendations for Lennox-Gastaut syndrome. *N* = 271 (205 positive and 66 negative treatment recommendations) from 34 guidelines. Positive recommendation: use of an individual ASM treatment that was recommended for use in a specific indication, irrespective of the line of treatment (e.g., first line) or whether the treatment was adjunctive; negative recommendation: an individual ASM treatment that was highlighted as a potential option by a guideline but whose use was recommended against (for any reason) in a specific indication, irrespective of the line of treatment, or whether the treatment was adjunctive.

DISCUSSION

This review provides a comprehensive overview of available guidelines and their treatment recommendations for DS, LGS and CDD in 11 countries across Europe, North America and Asia Pacific. The main findings were: whilst there were guidelines for DS and LGS, none were identified for CDD; there were relatively few international treatment guidelines, and in particular, very few that specialised specifically in DS or LGS (most recommendations for DS or LGS were identified within broader epilepsy guidelines); a wide variety of methodologies were used in guideline development; there was limited collaboration between author groups outside of Europe and North America; and a lack of homogeneous treatment recommendations. Most guidelines were country-specific (five guidelines were classified as "International;" two and three of which reported recommendations for DS and LGS, respectively), and five guidelines were specifically developed for a particular region within a given country, which may be reflective of differing drug availabilities in a given country or region.

Key links were identified between the author groups of two international guidelines (36, 37) and guidelines from the US (38), UK (SIGN) (39), Italy (40), and France (41). Additionally, a separate link was observed between the author groups of two Canadian guidelines (42, 43) and Spanish groups (44). This suggests a reasonably well-defined network between North America and Europe, whilst highlighting a lack of collaboration between the author groups in North America, Europe and Japan. Although several of the guidelines were apparently developed in regional groups, with no connections to other guideline author groups identified in the author map (particularly those developed for Germany and Japan), there were no major divergences observed in the recommendations across the geographies. Unsurprisingly, there was a lack of guidelines developed specifically for either LGS or DS (3), and of these, all were developed by international author groups (45–47). Despite the general consensus observed among the included guidelines, bringing together national expert groups and corresponding pooling of clinical expertise, for example via supra-national bodies, could still be beneficial for the development of internationally valid and relevant guidance specifically for these conditions, and in particular, for CDD. For rare conditions with limited high-quality clinical trial data, international consensus recommendations from clinical experts offer a globally accepted standard of care, to which clinicians worldwide can refer (48). This is of particular benefit in regions where no national guidance is available.

For example, in 2013, the International League Against Epilepsy (ILAE) developed a report investigating the efficacy of ASMs as monotherapies for untreated epilepsy (49). Similar international guidance for treatment of DS, LGS and CDD could provide much needed guidance in a global context, accepting that implementation would depend on local infrastructure, resource availability or the healthcare systems in place (50).

The current TLR highlighted the wide variety of methodologies used to develop treatment guidelines. Just over half of the guidelines specified their development process in relation to literature reviews [58% (23/40)] and approximately two-thirds specified some type of expert consultation [65% (25/40)] but reporting of methodology overall was unclear or absent in many instances, and only one guideline used a combination of an SLR and Delphi panel, which is considered to be the "gold standard" of guideline development. SLRs are considered to be the most robust methodology for evidence synthesis, and Delphi panels are recommended for use in healthcare settings as a reliable means of determining consensus for defined clinical problems (51–53). A lack of the combined approach of an SLR and Delphi panel for guideline development highlights a need for standardisation in guideline development and reporting, for which tools to facilitate the improvement of guideline reporting are currently available (e.g., the AGREE checklist) (54). The frequent references that were made by both UK and non-UK guidelines to recommendations by NICE and Cochrane reviews (21–23) that are widely recognised as using rigorous and high-quality development processes (23, 24), may demonstrate the perceived value of guidelines or reviews with robust methodologies regardless of their intended geographical region of influence. Similarly, only one guideline made reference to the ILAE website, which is an international resource for current and emerging standards and best practise in epilepsy and has collaborated with organisations such as AAN, NICE, and the World Health Organization to outline evidence-based clinical practise guideline development (55).

There were a large number of treatment recommendations made for DS (190) and LGS (271), while no individual treatment recommendations were made for CDD. We infer that these findings reflect the lack of high level evidence for preferred treatments, and the refractory nature of the seizures in each of the three syndromes (4, 7, 56). Further, our results also highlight a lack of treatment guidelines in diseases of more recent clinical description and that have no licenced medications, such as CDD (6). Consequently, there is an urgent need to develop up-to-date treatment guidelines for CDD (4, 57). A lag between completion/publication of clinical research and the incorporation of their key findings into disease specific guidelines is expected, and this is reflected in the absence of identified guidelines for DS that include recommendations for the drug fenfluramine, which is the latest treatment approved for this indication (58, 59). However with the recent emergence of novel treatments for DS, LGS and CDD (3, 59–61), and for other diseases in general, it is hoped that this lag will become as short as possible.

Interestingly, there was continued recommendation for use of older drugs, such as sodium valproate, for treating seizures in DS and LGS. The consistent recommendation of more traditionally used ASMs may indicate a limited pool of available treatment options and the corresponding need for new and effective treatments that target the specific aetiologies of each disorder (62). In addition, many of the treatments that were widely recommended in the review have no licence available for the indications of interest and are instead more generally indicated for the management of seizures. While stiripentol and cannabidiol have been approved by the FDA and EMA as orphan products for the treatment of DS (25–28), other medications that received a high number of positive recommendations for DS are either licenced more generally for the treatment of

epilepsy (e.g., sodium valproate) or for specific seizure types (e.g., topiramate) (7, 25, 26, 63, 64). Similarly, whilst topiramate, lamotrigine, felbamate, rufinamide, clobazam and cannabidiol have been approved by the FDA for use in LGS (28, 30–34), a number of other medications that received positive recommendations for LGS were licenced for all forms of epilepsy (e.g., sodium valproate), or for specific seizure types (e.g., zonisamide) (56, 63, 65).

Due to the targeted nature of the review, some limitations were present; eligibility of all records in the analysis was assessed by a single reviewer, with a second adjudicating the decision of whether a guideline was eligible to include when the applicability of the inclusion criteria was unclear. This approach differs slightly from the dual review technique adopted in systematic literature reviews (66). Additionally, this TLR searched less standard sources than those typically seen in a systematic review (e.g., Embase, MEDLINE/PubMed), for example through the use of Google, as well as medical society and guideline developer websites. Given that not all guidelines are published in traditional medical journals, or necessarily in the English language, this approach ensured a focus on sources that specifically orientated towards, indexing guidelines to minimise the risk of missing local guidelines. While less standard for a literature review, these sources were able to return a large number of highly specific records and provided a multinational overview of the available guidelines and their treatment recommendations in the absence of previously conducted analyses. Additionally, the study aimed to provide an overview in a broad sample of countries likely to be highly influential in the development of treatment guidelines. As such, with the focus on Australia, Canada, France, Germany, Israel, Italy, Japan, Spain, Switzerland, the UK and the US only, the results may not fully represent the international landscape of treatment guidelines for DS, LGS and CDD.

The scope of this review was also limited to treatment guidelines for the routine management of seizures with individual ASMs and was not designed to capture publications including guidance on combination therapies, whether a combination of ASMs or ASMs and/or dietary modification and/or surgery, non-pharmacological therapies or rescue therapies used in treating seizures in acute situations. In addition, the review does not capture treatment guidelines published after February 2021 or those that are currently in development. As treatment guidelines are updated after advancements in clinical care and drug approval have been made (67), the individual recommendations in this review should be interpreted in the context and date that they were made (all identified papers were published between November 2005 and January 2021).

The results of this review suggest the need for further high-quality international consensus-based guidance, influenced by a more diverse range of geographical regions, for the treatment of DS, LGS, and especially for CDD (for which no treatment guidelines could be identified). Following recent approvals for these indications, there is a need to reduce the delay between completion of clinical research and the incorporation of their key findings into disease specific guidelines. In addition, the presence of contradictory positive and negative treatment recommendations for many different drugs in each indication, highlights the need for clarification and consensus on evidence-based first- and second-line drugs to treat each disorder. Supra-national consensus guidance would support the development of local treatment guidance, may improve resource allocation and establish an improved international standard of care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

BR-F, IN, JE, and KV: substantial contributions to study conception and design. RC, AM, BR-F, IN, JE, KV, CN, and SA: substantial contributions to analysis and interpretation of the data, drafting the article or revising it critically for important intellectual content, and final approval of the version of the article to be published. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.734612/full#supplementary-material

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Magnetic Resonance-Guided Laser Interstitial Thermal Therapy (MR-gLiTT) in Pediatric Epilepsy Surgery: State of the Art and Presentation of Giannina Gaslini Children's Hospital (Genoa, Italy) Series

Alessandro Consales[1]*, *Erica Cognolato*[2,3], *Mattia Pacetti*[1,2], *Maria Margherita Mancardi*[3], *Domenico Tortora*[4], *Giuseppe Di Perna*[5], *Gianluca Piatelli*[1] and *Lino Nobili*[2,3]

[1] Unit of Neurosurgery, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Giannina Gaslini, Genoa, Italy, [2] DINOGMI, University of Genoa, Genoa, Italy, [3] Unit of Child Neuropsychiatry, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Giannina Gaslini, Genoa, Italy, [4] Unit of Neuroradiology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Giannina Gaslini, Genoa, Italy, [5] Unit of Neurosurgery, Azienda Ospedaliera Universitaria (AOU) Città della Scienza e della Salute, University of Turin, Turin, Italy

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Edited by:
Valentina Chiesa,
Santi Paolo e Carlo Hospital, Italy

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Sandipan Pati,
University of Texas Health Science Center at Houston, United States
Emanuele Bartolini,
Azienda USL Toscana Centro, Italy

***Correspondence:**
Alessandro Consales
alessandroconsales@gaslini.org

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Magnetic resonance-guided laser interstitial thermal therapy (MR-gLiTT) is a novel minimally invasive treatment approach for drug-resistant focal epilepsy and brain tumors. Using thermal ablation induced by a laser diode implanted intracranially in a stereotactic manner, the technique is highly effective and safe, reducing the risk associated with more traditional open surgical approaches that could lead to increased neurological morbidity. Indications for MR-gLiTT in pediatric epilepsy surgery include hypothalamic hamartoma, tuberous sclerosis complex, cavernoma-related epilepsy, SEEG-guided seizure onset zone ablation, corpus callosotomy, periventricular nodular heterotopia, mesial temporal lobe epilepsy, and insular epilepsy. We review the available literature on the topic and present our series of patients with drug-resistant epilepsy treated by MR-gLiTT. Our experience, represented by six cases of hypothalamic hamartomas, one case of tuberous sclerosis, and one case of dysembryoplastic neuroepithelial tumor, helps to confirm that MR-gLiTT is a highly safe and effective procedure for several epilepsy conditions in children.

Keywords: epilepsy surgery, pediatric, laser, magnetic resonance, interstitial, MR-gLiTT

INTRODUCTION

Magnetic resonance-guided laser interstitial thermal therapy (MR-gLiTT) is a novel and very promising minimally invasive therapeutic approach in the field of neurosurgery. The two major indications for this type of neurosurgical treatment are drug-resistant focal epilepsy and brain tumors (1). LiTT uses heat to generate ablation by light absorption of tissue (2). The physical principle of LiTT is based on the denaturation of tissue proteins, which starts if a temperature above 50°C is applied for a few seconds (3). The use of lasers is not entirely new in neurosurgery. The real novelty of LiTT is that it is a stereotactic method that involves the use of a laser diode

implanted intracranially, so it does not require a craniotomy but simply a very small hole in the skull. Another distinguishing feature, compared with techniques that employ the same physical principle as LiTT (e.g., radiofrequency thermocoagulation), is that LiTT is not only spatially driven by MR but it is continuously controlled by it, due to the fact that all components of the LiTT equipment are MR-compatible (4). Each type of tissue has an energy absorption coefficient, called proton resonance frequency (PRF) (5). Pathological brain tissue possesses a higher PRF. This promotes ablation of abnormal tissue, the target of treatment, while normal tissue is spared. This allows the formation of a transition zone of approximately 1 mm between the ablation zone and normal brain tissue, which is monitored in near real time by MR thermometry (6, 7). MR-gLiTT uses synchronized T1-weighted images. Once the laser is activated, the hydrogen bonds decrease in the area of ablation. This determines an increase in tissue penetrability. MR thermography measures temperature differences by subtracting thermal fast-spoiled gradient-recalled phase images obtained after administration of thermal energy from a reference fast-spoiled gradient-recalled phase image obtained at body temperature before any energy pulse is delivered; therefore, accuracy on baseline temperature is critical to the software's ability to predict the ablation damage (8). The thermal mapping is updated every 3, 6, and 8 s for single, biplanar, and triplanar viewing, respectively (9).

There are two LiTT systems available on the market: the Visualase system (Medtronic, Minneapolis, MN, USA) and the NeuroBlate system (Monteris Medical Inc., Plymouth, MN, USA), the latter only marketed in North America so far. Both systems use color-coded thermal maps superimposed on MR and have a software that, using the Arrhenius equation that estimates cell death based on the temperature and time dependence of protein denaturation processes, represents areas of irreversible damage (7). The estimated zone of tissue necrosis is shown in near real time as an orange zone with the Visualase system and as yellow, blue, and white lines with the NeuroBlate system.

MRgLiTT has been licensed for use in Europe in spring 2018.

In this paper, we report on the state of the art on the use of MRgLiTT in pediatric epilepsy surgery. Moreover, we present the case series of patients with focal epilepsy associated with lesions treated by MRgLiTT at Giannina Gaslini Children's Hospital in Genoa (Italy).

PRINCIPAL INDICATIONS IN PEDIATRIC EPILEPSY SURGERY

Hypothalamic Hamartoma (HH)

Hypothalamic hamartomas (HHs) are rare, tumor-like, and non-progressive malformative lesions that occur during fetal development from ventral hypothalamus (10). Although there is great interindividual variability in the clinical picture, symptoms generally occur during childhood or adolescence and are mainly characterized by endocrinological disorders (especially precocious puberty), epilepsy, and cognitive–behavioral disorders, according to their anatomical location (11). Epilepsy usually occurs during the first year of life and is characterized by gelastic or, less frequently, dacrystic seizures. Several classifications have been proposed for HHs with the aim to guide the best surgical approach and to predict seizure and functional outcome after surgery; among these, the classification of Delalande remains the most widely adopted at present (12). These classifications play a less relevant role in MR-gLiTT, which can also be planned in multiple steps for particularly voluminous lesions (13). Treatment of HH-associated epilepsy using LiTT is providing extremely encouraging results, both when evaluated in absolute terms and in comparison with other treatment options (e.g., open surgery, endoscopic, radiosurgery) (1, 14). In a recent review, seizure control achieved by LiTT in patients with a follow-up of at least 1 year was 87% in patients with gelastic seizures and 60% in patients with other type of seizures (15). These data, in themselves very good, are even more relevant when compared with the other forms of treatment mentioned above, taken as a whole. In these forms, in fact, with follow-up of comparable duration, the share of patients who are seizure-free is about one-third (14, 16). LiTT can be used both as a first treatment of HH and in cases already treated unsuccessfully with other methods. In this regard, it is important to note, for LiTT as for other treatment options, that disconnection of the hamartoma from the epileptogenic network, rather than its ablation or resection, is often sufficient to achieve seizure freedom (17).

Complications with LiTT are often transient but can be severe. In their recent series of 18 patients, Xu et al. (18) reported a 39% (7/18) incidence of new neurological deficits (including hemiparesis and visual disturbances) and an 11% (2/18) incidence of short-term memory problems as immediate complications. At the last follow-up, many patients with initial neurologic deficits had improved, with 22% (4/18) having persistent deficits but only 1 (6%) having functional impact. Hypothyroidism was the only long-term endocrine deficit (11%, 2/18). Over time, some patients (22%, 4/18) reported new subjective problems with short-term memory, weight gain, or increased appetite. Memory problems can be caused by a mono- or bilateral involvement of the mammillothalamic tract which, as it is known anatomically, is part of the Papez circuit connecting the mammillary body to the anterior thalamic nucleus, although some authors believe that mnestic dysfunctions occur more frequently in patients who have already undergone other types of epilepsy surgery (19). Other adverse events include intracranial hemorrhage and electrolyte imbalance (15). However, since LiTT is a technology that has yet to be widely deployed in the neurosurgical field, a learning curve factor must also be considered. On the other hand, the same complications described for LiTT can occur, even when the known therapeutic alternatives are used, at rates $>30\%$ (17).

Tuberous Sclerosis Complex (TSC)

TSC is a neurocutaneous syndrome that variably involves the brain, skin, kidney, heart, and lungs. Epilepsy is the most common clinical manifestation of TSC, occurring in approximately 90% of cases (20). Epileptogenesis has been theorized to result from different morphological and molecular abnormalities observed in the cortical tubers and the perituberal cortex (21). The cortical tubers are often multifocal and located within deep brain structures. The anatomical features of these

lesions make LiTT a valid therapeutic option because, through this technique, it is possible to treat multiple epileptogenic lesions without the need to perform multiple craniotomies. Tovar-Spinoza and colleagues reported on seven patients with TS and drug-resistant epilepsy who underwent LiTT of cortical tubers. Two patients had a single procedure, and five patients had staged procedures. All of the patients had a meaningful reduction in seizure frequency, and more than 70% experienced a reduction in antiepileptic medications. Three of the four patients who presented with neuropsychiatric symptoms had some improvement in these domains after laser ablation, although the authors did not have data from formal neuropsychological evaluation to support their observations. No perioperative complications were noted. The authors stated that laser ablation represents a minimally invasive alternative to resective epilepsy surgery and is an effective treatment for refractory epilepsy due to cortical tubers (22).

Cavernoma-Related Epilepsy

Cavernomas are mulberry-like vascular malformations often found in brain and spinal cord. Brain cavernomas can determine irritation (epilepsy) or deficiency symptoms (23). LiTT has increasingly been offered as an alternative minimally invasive treatment for cavernoma-related epilepsy (24, 25). The published case histories are currently quite small in number. However, the very satisfactory epileptological outcome reported in the aforementioned case reports, coupled with excellent overall clinical conditions [e.g., Engel class I in 80% of patients and zero adverse events reported by McCraken et al. (25)], makes it important to continue studying the use of LiTT in the treatment of cavernoma-related epilepsy.

SEEG-Guided Seizure Onset Zone Ablation

The SEEG is a method of Functional and Stereotactic Neurosurgery that allows an invasive EEG study in order to identify the seizure onset zone (SOZ) in cases where non-invasive diagnostic studies have not produced good anatomo-electro-clinical correlations (26). More recently, it has also been used as a possible therapeutic weapon, for example in radiofrequency thermocoagulation of heterotopic cortical nodules (27). A topic closely related to SEEG studies is that of MR-negative epilepsies, which are a crucial field of investigation in Epilepsy Surgery. When, in MR-negative epilepsies a SOZ is identified and delineated by SEEG, ablation of the SOZ by LiTT can be considered in selected cases (1). Of course, further studies will be needed to define the potential role of a SEEG-guided LiTT in the thermoablative treatment of a SOZ.

Corpus Callosotomy

Huang et al. recently published a retrospective study of a case series of six patients (three children and three adults) who underwent callosotomy using LiTT. Engel outcomes for completion corpus callosotomy by LiTT were similar to reported outcomes of open completion callosotomy, with seizure reduction primarily observed in adult patients (28). As with other new indications for LiTT, future in-depth studies will be needed for callosotomy using LiTT.

Periventricular Nodular Heterotopia

Periventricular nodular heterotopias (PNHs) are malformations of cortical development characterized by disorganized but histologically normal aggregates of neuronal and glial cells. They are often associated with drug-resistant epilepsy (29). The anatomic electro-clinical characteristics of PNHs have prompted consideration in the relevant literature of a number of minimally invasive approaches, such as stereotactic radiosurgery and stereotaxy-guided radiofrequency lesioning. Moreover, the possibility of treating these malformations, after adequate epileptological diagnostic procedure, by a minimally invasive surgical approach such as LiTT, especially when they are located in high functional areas, has already been described (30). While data concerning seizure outcome within the pediatric population are still somewhat limited, results in the adult population are very good, with seizure freedom up to 100% and no adverse events after LiTT treatment (1). These data are very striking, as epilepsy involving a PNH can be multifocal, with complex and distributed epileptogenic networks. However, focal resections/ablations can be successful if the role of the PNH within the epileptogenic network is understood. It is therefore more than reasonable to assume that as Epilepsy Surgery centers will increase their experience with LiTT, the trend of LiTT treatment outcomes of PNHs will be the same or even more positive within the pediatric population.

Mesial Temporal Lobe Epilepsy

Treatment of mesial temporal lobe epilepsy (MTLE) by means of LiTT has been addressed by some studies concerning the adult population (31, 32). It can be reasonably assumed that this was for epidemiological reasons related to this type of epilepsy. Nevertheless, the technical considerations can be considered applicable to the pediatric population as well. In MTLE, the percentage of patients seizure-free after LiTT is lower than in cases treated with open surgery (about 50%) (8). It can be speculated that this is partly due to the particular complexity of the epileptogenic network in MTLE, which may consequently lead to partial or complete error in identifying the target of LiTT. However, it is important to note that LiTT treatment can be repeated, even multiple times, and that it does not preclude further treatment, surgical or otherwise (33).

Insular Epilepsy

Insular epilepsy is another potentially interesting area of application of LiTT in pediatric epilepsy surgery (34). The insula is indeed a deep encephalic structure with a rich and complex vasculature (35). Therefore, an open surgical approach to the insula, in addition to requiring considerable technical expertise, may be burdened by significant ischemic complications. Perry et al. (36) described 20 pediatric patients with insular epilepsy who underwent 24 LiTT procedures. After a mean follow-up of 20.4 months after their last treatment, 10 patients (50%) were in Engel Class I, 1 (5%) in Engel Class II, 5 (25%) in Engel Class III, and 4 (20%) in Engel Class IV at the last follow-up. Patients were discharged within 24 h of the procedure in more than 60% of cases. Transient complications were registered after seven (29%) procedures: mild hemiparesis in six cases

(all patients experienced complete resolution or had minimal residual dysfunction by 6 months), and expressive language dysfunction in another one (resolved by 3 months). More recently, another recent study by Hale et al. (37) compared LiTT and surgical resection of at least some portion of the insular cortex, concluding that both surgical resection and LiTT are valid management options in the treatment of medically refractory insular/opercular epilepsy in children. At present, therefore, and pending further and more in-depth studies, LiTT can certainly be considered an effective and low-risk alternative to open surgery for insular epilepsy.

Other Epileptogenic Lesions

Focal cortical dysplasias and dysembryoplastic neuroepithelial tumors (DNETs) are the most frequent causes of drug-resistant epilepsy in children (38). Nevertheless, the literature data on the use of LiTT in the treatment of these diseases are still scarce and patchy, when compared with other epileptogenic conditions, such as HH (30, 39–41). Other conditions associated with drug-resistant epilepsy, the treatment of which by LiTT has been sporadically reported to date, are Rasmussen's encephalitis and parasitic lesion (30, 39).

MR-gLiTT IN PEDIATRIC EPILEPSY SURGERY: OUTLINES OF TECHNICAL PRINCIPLES

The use of MR-gLiTT in Epilepsy Surgery requires the placement, through a micro-hole drill, of a laser fiber within an intracranial lesion target using stereotactic methods (frameless, robotic, or frame-based). A skull anchoring system is mounted on a steel rod and is screwed into the microhole at the calculated angle, forming a solid anchor point for insertion of the laser fiber. The laser probe is then positioned through the above system until it reaches the intracranial target. Heat delivery is monitored in near real time by MR thermography, as explained above, until the desired ablation is achieved; multiple heat deliveries may be required during the single procedure, and repositioning of the laser probe may be necessary (2).

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Patient demographics, preoperative seizure frequency, seizure semiology, and postoperative outcomes are listed in **Table 1**.

Overall, the age of the patients ranged from 11 months to 15 years. The mean age at surgery was 6 years (73 months). Six of eight (75%) patients were male. Pathologies were represented by HH in six patients, TSC in one case, and DNET (residual lesion) in another one. Precocious puberty was present in three patients with HH (pt nr. 1, 7, 8); two of them received pharmacological treatment before surgical intervention.

Patients were studied with prolonged video-EEG monitoring and brain MRI.

Preoperative seizure frequencies ranged from 1 event per month to more than 40 per day. Seizure types were gelastic and dacrystic seizure in the six HH patients, five of them presented with additional seizure types (two focal seizures with impaired awareness—patient nr. 1 and 4—and one with spasms—pt. nr. 2). In patient nr 7 and 8, we could not assess the level of awareness impairment during the seizure (young age in pt 7, intellectual disability in pt 8). Patients affected with DNET and TSC presented with focal seizures with preserved awareness.

In the HH cases, the EEG data, together with anatomical localization of the hamartoma, were used to decide the side of the entry point of the laser fiber on the skull.

The trajectories of the laser fiber were designed using the following principles. For the HH cases, the target point of the laser probe was placed at a point between the lateral two-thirds and the mesial third of the maximum diameter of the lesion, measured on coronal and axial planes. Then, the intralesional target point was shifted slightly in a caudal and dorsal direction in the sagittal plane to maximize heat dissipation by the "heat sinks," represented by the basal arachnoid cisterns and blood vessels. The trajectories of the laser probe were planned in order to avoid structures that could potentially be damaged mechanically or by the heat developed by the laser, such as cerebral blood vessels, optic tracts and/or optic chiasm, mammillothalamic tracts, and fornices. The laser system used (Medtronic Visualase^{TM}) made it possible to monitor in almost real time the temperature variations reached at certain points, in order to avoid damage to the perilesional nervous structures, automatically stopping laser delivery in the event of an increase in temperature beyond a previously set level (usually 45°C; see also **Figure 1**). In the patient with TSC, we performed a double ablation of two cortical tubers, during a single therapeutic session, using two laser fibers, monitoring temperature increments to protect ipsilateral optical radiation. In the case of treatment of residual parietal DNET, we paid special attention to avoid dangerous temperature increases at the level of the corticospinal tract. Postoperative outcomes after laser ablation, as characterized by the Engel Epilepsy Surgery Outcome Scale, ranged from class I to class IV.

Three of the eight patients (two HH, one DNET) were completely seizure-free after the procedure.

One patient (HH) experienced two focal episodes in the 2 months after the procedure; to date, he is seizure-free with only one anti-seizure medication (ASM).

Two patients with HH experienced rare, non-disabling seizures after the procedure (classified as Engel Ib). One patient with HH (#7) showed no seizure improvement (it is worth noting that the patient presented with a large HH).

In the TSC patient with drug-resistant epilepsy associated with multiple cortical tubers, a significant reduction in seizure frequency (from two to three episodes per day to <1 episode per week) was achieved, along with an improvement in his behavioral hyperactivity.

Postoperatively, no patients experienced new neurological morbidity or endocrine dysfunction, with two of them experiencing acute postoperative seizures (APOS). The mean hospital stay was 6 days, and 100% of patients regained normal preoperative motility and activity on the second day after the procedure. In three patients, neurodevelopmental assessment (Vineland scales) before and after the surgical procedure (at 6 months in one patient, at 12 months in 2 patients) showed improvement in cognitive and social behavior.

TABLE 1 | Clinical features and outcome of Giannina Gaslini Children's Hospital series.

Pt	Sex	Lesion type	Age epilepsy onset	Epilepsy duration (m)	Age at surgery	Seizure frequency	Semiology	EEG pre LITT	ASM tried *(n)*	Co-morbidity	Lesion size (mm)	Localization	Side	Laser probe placement system	APOS	Compl.	Last F.U. (months from procedure)	Seizure outcome (engel class)
#1	M	HH	8 m	99	8 y 11 m	2–3/w	Gelastic seizure, focal w/ impaired awareness seizure	**Interictal**: right CT spikes **Ictal**: bilateral rhythmic SpWs	1	ID, PP	20 × 18 × 14	Tuber, E.V.	M	Frameless, Medtronic Vertek™	No	No	11	I b
#2	M	HH	6 m	15	1 y 9 m	30–40/d	Gelastic seizure, spasms	**Interictal**: bilateral CT SIWs **Ictal**: uninformative	3	DD, rest tremor	12 × 13 × 13	Tuber/mammillary body, I.V.	L	Frameless, Medtronic Vertek™	No	No	11	Ib
#3	M	HH	7 m	20	2 y 3 m	3–4/d	Gelastic and dacrystic seizures	**Interictal**: bilateral SIWs (left>right) **Ictal:** no seizures recorded	1	Language Delay	18 × 11 × 18	Tuber, I.V/E.V.	L	Medtronic Stealth Autoguide™	No	No	6	Ia
# 4	M	HH	36 m	48	7 y	0–10/d	Gelastic, focal with impaired awareness	**Interictal**: right FT SIWs and SpWs **Ictal**: right FT SpWs	2	Language delay, ID	12 × 10	Tuber, I.V.	R	Medtronic Stealth Autoguide™	No	No	2	I b
#5	M	TS (2)	10 m	60	6 y 8 m	1–10/d	Focal with preserved awareness	**Interictal**: right T SIWs **Ictal**: Right T EEG flattening followed by ISWs	6	ASD	8 × 6, 13 × 10	Temporal lobe neocortex	R	Frameless, Medtronic Vertek™	Yes	No	2	II b
#6	F	DNET	60 m	120	15 y 5 m	1/m	Focal with preserved awareness	**Interictal**: Left, CP sharp waves	2	Cardiac malf., hypothyroidism	13 × 10,5 × 14	Parietal	L	Medtronic Stealth Autoguide™	Yes	No	1	Ia
#7	F	HH	0 d	12	11 m	1–10/d	Gelastic, motor focal	**Interictal**: left, fronto-centro-parietal spike-waves **Ictal**: left EEG flattening	3	PP	47 × 30 × 27	Tuber,/mamillary body I.V./E.V. Sellar/parasellar	M	Medtronic Stealth Autoguide™	No		0	IV
#8	M	HH	0,2 m	42	4 y 3 m	1–5/d	Gelastic, motor focal	**Interictal**: Posterior bilateral SpWs (right>left) **Ictal**: diffuse EEG flattening	3	ID, PP	20 × 23 × 24	Tuber,/mamillary body I.V/E.V.	R	Medtronic Stealth Autoguide™	Yes	No	0	Ia

HH, Hypothalamic Hamartoma; DNET, dysembryoplastic neuroepithelial tumor; TS Tuberous Sclerosis; Compl., complications; ASM, anti-seizure medications; ID, Intellectual Disability; DD, developemental Delay; PP, Precocious Puberty; ASD, autism spectrum disorder; APOS, acute postoperative seizures; E.V., extra-ventricular; I.V, intra-ventricular CT, centro-temporal; FT, fronto-temporal; T, temporal; M, median; L, left; Cardiac malf., cardiac malformation; SpWs, spike-waves; SIWs, slow waves.

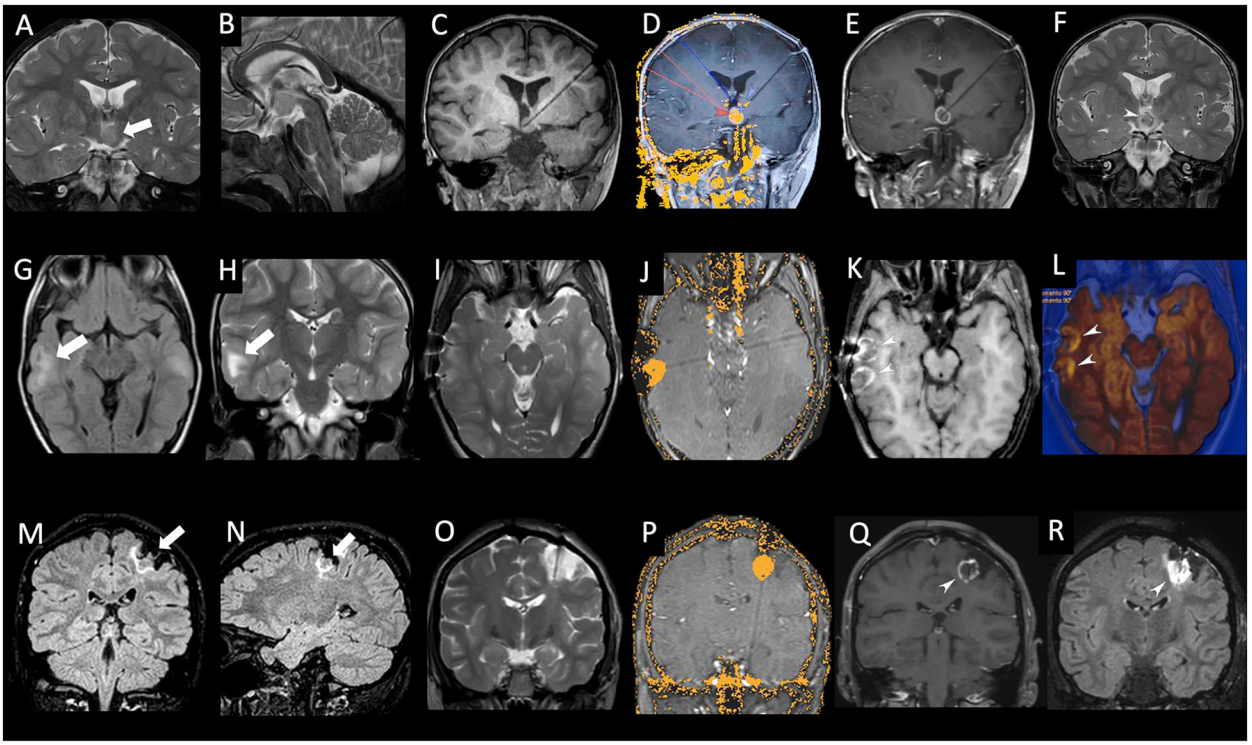

FIGURE 1 | (A–F): Patient #2 (see **Table 1**), male, 2 years old. Coronal **(A)** and sagittal **(B)** T2-weighted images showing the intraventricular hypothalamic hamartoma localized on the left side (thick white arrow). Coronal T1-weighted image **(C)** acquired after stereotactic placement of a laser cannula within the hamartoma. Real-time MR thermogram overlaid on background T1-weighted image **(D)** exhibiting the irreversible damage map (yellow area within the hamartoma). Note the low-limit threshold, set at 48°C (blue arrowhead), placed on the left mammillothalamic tract, and the high limit-thresholds, set at 90°C (red arrowhead) at the tip of laser catheter and within the hamartoma. Coronal post-contrast T1-weighted image **(E)** performed at the end of laser ablation showing central necrosis of ablated hamartoma with peripheral contrast enhancement. Coronal T2-weighted image **(F)** performed 48 h after laser ablation confirming necrosis of ablated hamartoma (white arrowhead). **(G–L):** Patient #5 (see **Table 1**), male, 6 years old with tuberous sclerosis. Axial FLAIR **(G)** and coronal T2-weighted **(H)** image showing two cortical tubers in the right temporal lobe (white arrow). Axial T2-weighted image **(I)** acquired after stereotactic placement of two laser cannulas within the cortical tubers. Real-time MR thermogram overlaid on background T1-weighted image **(J)** exhibiting the irreversible damage map (yellow area within the tuber). Axial post-contrast T1-weighted image **(K)** performed at the end of laser ablation showing central necrosis of ablated tubers with peripheral contrast enhancement. Axial diffusion weighted image **(L)** overlaid on the axial T2-weighted image, performed at the end of laser ablation confirming necrosis of ablated tubers with peripheral restricted diffusion (white arrowheads). **(M–R):** Patient #6 (see **Table 1**), female, 15 years old. Coronal **(M)** and sagittal **(N)** FLAIR images showing relapsing DNET localized in the left post-central gyrus (thick white arrows). Coronal T2-weighted image **(O)** acquired after stereotactic placement of a laser cannula within the lesion. Real-time MR thermogram overlaid on the background T1-weighted image **(P)** exhibiting the irreversible damage map (yellow area within the hamartoma). Coronal post-contrast T1-weighted **(Q)** and FLAIR image **(R)** performed at the end of laser ablation showing central necrosis of ablated lesion with peripheral contrast enhancement (white arrowhead).

Although follow-up is overall very short (in two cases is shorter than 3 months) and the number of patients is still quite small, our data are globally consistent with those reported in literature, showing that the high majority of HH patients become seizure free after the procedure (15, 17). Only one patient with a large HH has not shown an improvement after the intervention.

In our opinion, besides from seizure outcome, the most striking aspect of the procedure is the regain of habitual motility and functioning in such a short time compared to traditional surgery, with a reduced hospital stay and convalescence time (mean hospital stay 6 days vs. 12 days).

The relevance of the technique is also fundamental in treatment of multiple tubers as in TSC cases: such a minimally invasive procedure could potentially make it possible to perform multiple surgeries on multiple tubers, something that is not advisable with a classical open technique.

DISCUSSION/GENERAL CONSIDERATIONS/CONCLUSION

Although the evidence on the therapeutic results of LiTT in the pediatric setting is still limited in terms of both quantity and scientific quality, there is no doubt that, at least in perspective, it may represent a first line of minimally invasive treatment of diseases associated with drug-resistant epilepsy. This consideration is particularly pertinent for those brain lesions difficult to access with the methods of traditional surgery. The overall complication rate is considered more than acceptable compared to traditional surgical techniques, the epileptological outcome obtained with LiTT is commonly evaluated as good. It remains to be clarified what will be the real economic costs of this innovative technique on the various health systems. Carefully designed scientific studies will in any case have to

take into account not only the currently high costs of this new technology but also the indirect cost savings through a shorter duration of hospitalizations, cost savings on ASMs, and medium- and long-term follow-up. Ultimately, although future prospective, multicenter studies will better define the role of LiTT in neurosurgery, it is more than reasonable to believe that, with increasing ease of use and a more robust demonstration of efficacy, LiTT will rapidly become an extremely attractive therapeutic method for the treatment of many conditions associated with drug-resistant epilepsy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participant's legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AC: ideation, data collection and analysis, writing and critical revision of the paper. EC, MP, and DT: data collection and critical revision of the paper. MM, GD, and GP: critical revision of the paper. LN: data analysis and critical revision of the paper. All authors contributed to the article and approved the submitted version.

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Treatment Outcome and Risk Factors of Adult Newly Diagnosed Epilepsy: A Prospective Hospital-Based Study in Northeast China

Nan Li[1], *Jing Li*[1], *Yanyan Chen*[1,2], *Chaojia Chu*[1] *and Weihong Lin*[1]*

[1] *Department of Neurology, The First Hospital of Jilin University, Changchun, China,* [2] *Department of Neuroelectrophysiology, Changchun Six Hospital, Changchun, China*

Objective: The study was conducted to summarize the treatment outcomes of newly diagnosed epilepsy (NDE) and analyse the risk factors for refractory epilepsy (RE) in Northeast China.

Methods: A total of 466 adult patients with NDE were consecutively enrolled in this programme. Clinical data were collected at baseline and each follow-up. Several scales concerning recognition and mood were also completed at the first visit.

Results: Seizure-free status was achieved by 52% ($n = 244$) of the patients; however, 15% ($n = 68$) manifested RE. A total of 286 (61%) patients continued with the first ASM as monotherapy, among which 186 (40%) patients became seizure-free. Fifteen (22%) patients with RE became seizure-free following ASM adjustment and 34 patients (14%) had breakthrough seizures after being classified as seizure-free. One patient developed RE after attaining seizure-free status. Breakthrough seizures during the first expected interictal interval [Odds ratio (OR) = 5.81, 95% CI: 2.70–12.50], high seizure frequency at baseline (OR = 1.24, 95% CI: 1.04–1.49), younger age of onset (OR = 1.42, 95% CI: 1.12–1.79), and male sex (OR = 2.64, 95% CI: 1.26–5.53) were risk factors for RE.

Significance: Treatment outcomes of the majority of NDE cases are good. New risk factors could help physicians more promptly and accurately identify patients who are likely to develop RE. Seizure-free state is not long enough to commence the withdrawal of ASMs. RE is not permanent and seizure-free may be achieved subsequently by appropriate drug adjustment.

Keywords: drug resistant epilepsy, antiseizure medication, risk factors, adult, newly diagnosed epilepsy

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Daichi Sone,
University College London, United Kingdom

***Correspondence:**
Weihong Lin
linwh@jlu.edu.cn

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INTRODUCTION

Epilepsy is a serious neurological disorder that affects more than 70 million people worldwide, ranging from neonates to older adults (1). In China, the number of patients with epilepsy was ∼10 million in 2015 (2). Pharmacotherapy is the first choice for controlling epileptic seizures, and the majority of them could be controlled by currently available antiseizure medication (ASM). Refractory epilepsy (RE) is one of the most serious conditions, which affects 30–40% of people with epilepsy (3, 4). After years of multi-drug treatment with limited efficacy, patients with RE face great financial burden and mental pressure that seriously affect

their quality of life. In this situation, making a precise diagnosis of RE is critical and would give a chance for appropriate subsequent treatments, such as neurostimulation and surgery. In previous studies (5–7), the diagnostic criteria for RE were inconsistent; thus, it is difficult to compare the conclusions across them. To set up explicit and practical criteria, the International League Against Epilepsy (ILAE) published a new definition of RE (8). That is, the minimum criteria for defining RE, ensuring that less time was wasted in inappropriate pharmacological therapy, thereby improving patient care. However, the definition has not been widely applied to the epidemiologic studies. Finding risk factors according to the new definition could help the physicians more promptly and accurately identify patients who are likely to develop RE.

This study consecutively enrolled patients with newly diagnosed epilepsy (NDE) at the Epilepsy Diagnosis and Treatment Center of the First Hospital of Jilin University, which is one of the biggest general hospitals in Jilin province, China. We summarized the treatment outcomes of NDE and analyzed the risk factors of RE in Northeast China.

MATERIALS AND METHODS

Patient Recruitment

Patients visiting the Epilepsy Diagnosis and Treatment Center of the First Hospital of Jilin University were screened, and the adult patients who were newly diagnosed with epilepsy were consecutively enrolled in this programme between June 2015 and November 2019, and followed up until December 2020.

The definitions of epilepsy, the classification of seizure, and epileptic syndrome conformed to the diagnostic criteria published by ILAE (9–11). RE is defined as the failure of two tolerated and appropriate ASMs (whether monotherapy or in combination) to achieve sustained seizure-free state (8). The 50% defined daily dose (50% DDD) is considered as the "adequate dose" of each ASM (12). When patients are free from all seizures, including aura, for three times the interictal interval or 1 year (whichever is longer), they can be classified as seizure-free (8, 13). If the two abovementioned definitions cannot be satisfied, the outcome is designated as undetermined. The definition of a patient with NDE used in this study is a person with confirmed epilepsy who had not been diagnosed specifically with epilepsy or treated with ASMs previously.

Study Procedure

At their first visit, all the participants underwent a thorough clinical and laboratory investigation, including a 24-h video electroencephalogram (EEG) and 3.0-T high-resolution brain magnetic resonance imaging (MRI). The patients were administered an ASM following the 2012 guidelines of the National Institute for Health and Clinical Excellence (14), starting at a low dose. If the patients with NDE agreed to participate in the programme and signed an informed consent form, a baseline file was completed, which contained demographic, symptomatic and etiologic data, as well as the results of a systematic physical examination, an EEG, and an MRI. The symptomatic data were collected by interviews with the patients or the witnesses to seizure. Participants were then asked to complete a series of scales, including the Montreal cognitive assessment (MOCA), the Generalized Anxiety Disorder 7-item Scale (GAD-7), and the Chinese version of the Neurological Disorders Depression Inventory for Epilepsy (c-NDDI-E), to estimate their cognitive function and mood.

The patients enrolled in the programme were called back for a follow-up visit for treatment adjustments at 1, 3, and 6 months following the treatment and every 6 months thereafter. In cases of seizure recurrence between scheduled appointments, the patient could visit the specialist epilepsy clinics. The second ASM was considered when the first one was ineffective or the patient had intolerable side effects. At every scheduled visit, a follow-up file was completed for all patients, which recorded the patients' seizure types and frequency, the doses of the ASMs administered, and any adverse effects. If a face-to-face visit was inconvenient, the follow-up file would be completed by physicians based on the interviews with patients or caregivers by telephone. Instances of patients withdrawing the ASMs without medical advice were defined as poor compliance. Patients were excluded if the follow-up periods were <12 months. The ASMs were gradually reduced and stopped if the patients had no breakthrough seizure for at least 3 years and the repeated EEG was normal.

Statistical Analyses

Student's *t*-test, analysis of variance (ANOVA), Pearson's chi-squared test, the rank-sum test, and Fisher's exact test were used to compare continuous and categorical variables. A survival (Kaplan-Meier) analysis was often used to visually summarize time-to-event data and Log-rank was used to estimate the difference between the groups. Cox regression model analysis was applied to identify the risk factors for retention of the first ASM. Logistic regression was used to analyse the risk factors of RE.

Values for continuous variables are expressed as mean ± standard deviation (SD), and values for categorical variables are expressed as frequencies (%). All *p*-values were from two-tailed tests. $P < 0.05$ was considered to indicate statistical significance. The data were inputted by EpiData software (The EpiData Association, Odense, Denmark) and were subsequently analyzed using SPSS for Windows, Version 24.0 (SPSS Inc., Chicago, IL, USA).

Ethical Approval

The protocol for this study was approved by the Ethics Committee of the First Hospital of Jilin University [the approval number: 2017-326] and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Each enrolled patient provided a signed informed consent form before the study began.

RESULT

Demographic Information

A total of 6,636 people with epilepsy (PWE) who visited the Epilepsy Diagnosis and Treatment Center of the First Hospital of Jilin University were screened, and 466 patients were diagnosed as NDE and enrolled in the programme. The demographic

TABLE 1 | Demographic data of the patients with newly diagnosed epilepsy, *N* (%) or mean ± standard deviation.

Variable	Total at start ($n = 466$)	Refractory epilepsy ($n = 68$)	Seizure free ($n = 244$)	*P*-value[d]
Gender				0.142
Male	283 (61)	46 (68)	141 (58)	
Female	183 (39)	22 (32)	103 (42)	
Age of onset, y	31.2 ± 18.5	27.4 ± 16.7	31.4 ± 18.3	0.093
Duration of disease, y	3.91 ± 7.69	4.75 ± 8.75	3.42 ± 7.10	0.280
Baseline frequency of seizure per month, median (interquartile range)	1.00 (2.52)	2.75 (14.0)	1.00 (1.50)	<0.001
Lower average income (<160 USD/month)	61 (13)	14 (21)	27 (11)	0.040
Types of seizure				0.089
Focal	418 (90)	66 (97)	215 (88)	
Generalized	43 (9.2)	2 (2.9)	26 (11)	
Unknown	5 (1.1)	0 (0.0)	3 (1.2)	
History of status epilepticus	21 (4.5)	5 (7.4)	8 (3.3)	0.137
Etiology				0.212
Structural	96 (21)	19 (28)	41 (17)	
Genetic	1 (0.2)	0 (0.0)	1 (0.4)	
Infectious	9 (1.9)	1 (1.5)	5 (2.0)	
Immune	1 (0.2)	0 (0.0)	0 (0.0)	
Unknown	359 (77)	48 (71)	197 (80)	
Family history of epilepsy	49 (11)	11 (16)	24 (9.8)	0.143
History of febrile seizure	44 (9.4)	7 (10.3)	23 (9.4)	0.671
MOCA[a+], score	24.1 ± 4.62	24.1 ± 4.58	24.6 ± 4.24	0.482
GAD-7[b], score	4.62 ± 4.38	5.35 ± 4.76	4.58 ± 4.05	0.428
c-NDDI-E[c], score	8.09 ± 3.19	8.34 ± 3.34	7.90 ± 3.02	0.444

[a]*MOCA, Montreal cognitive assessment.*
[b]*GAD-7, Generalized Anxiety Disorder 7-item Scale.*
[c]*c-NDDI-E, Chinese version of the Neurological Disorders Depression Inventory for Epilepsy.*
[d]*The p-value between the refractory group and seizure-free group.*

information is shown in **Table 1**. The median follow-up time was 24 (range, 12–48) months. After treatment adjustments based on the responses to ASMs, 52% ($n = 244$) of the patients achieved seizure-free status; however, 15% ($n = 68$) were diagnosed as RE. The others (33%, $n = 154$) were undetermined (**Figure 1**). The median duration of treatment before arriving at RE and seizure-free status were 12 (range, 3–36) months and 12 (range, 12–36) months, respectively. About 74% ($n = 50$) of the patients required at least 12 months before being diagnosed with RE.

Comparing the demographic data between the RE group and the seizure-free group, patients with RE were inclined to having a lower average income ($Z = -1.764$, $p = 0.078$) and younger age of onset ($Z = -1.679$, $p = 0.093$). The baseline seizure frequency in the RE group was more than that in the seizure-free group ($Z = -3.911$, $p < 0.001$).

Response to the First ASM

The first ASMs administrated to the patients are shown in **Table 2**. The focal seizure was the most common type of seizure and oxcarbazepine was the most commonly used ASM. A total of 370 (79%) patients remained on the first ASM at the last follow-up and 286 (61%) patients remained on the first ASM as monotherapy, among which 186 (40%) patients achieved seizure-free status. Among those who did not reach seizure-free status with the first ASM, 174 patients were treated with monotherapy (100 remaining on the first ASM with increased dosage and 74 switching to another monotherapy) and 102 patients with multiple therapy at the last visit; among these patients, 24% ($n = 68$) developed RE and 21% ($n = 58$) were seizure-free. For those who reached seizure-free status with the first ASM, the maintenance doses are shown in **Table 2**. The median maintenance doses were no more than 50% DDD except for oxcarbazepine. At the 12- and 24-month follow-up, lamotrigine (88 and 82%), levetiracetam (82 and 82%), and oxcarbazepine (84 and 83%) had a higher probability of retention, and topiramate had the lowest probability of retention (56 and 56%, respectively). Carbamazepine, phenobarbital, and other ASM (pregabalin and gabapentin) were excluded from the comparison due to the limited number of patients. The probability of retention of the first ASM is shown in **Figure 2**. There was a significant difference between the probability of the different types of ASMs ($\chi^2 = 17.807$, $p = 0.001$). A total of 183 (39%) patients reduced the dose of the first ASM due to adverse effects, among whom 96 patients withdrew the

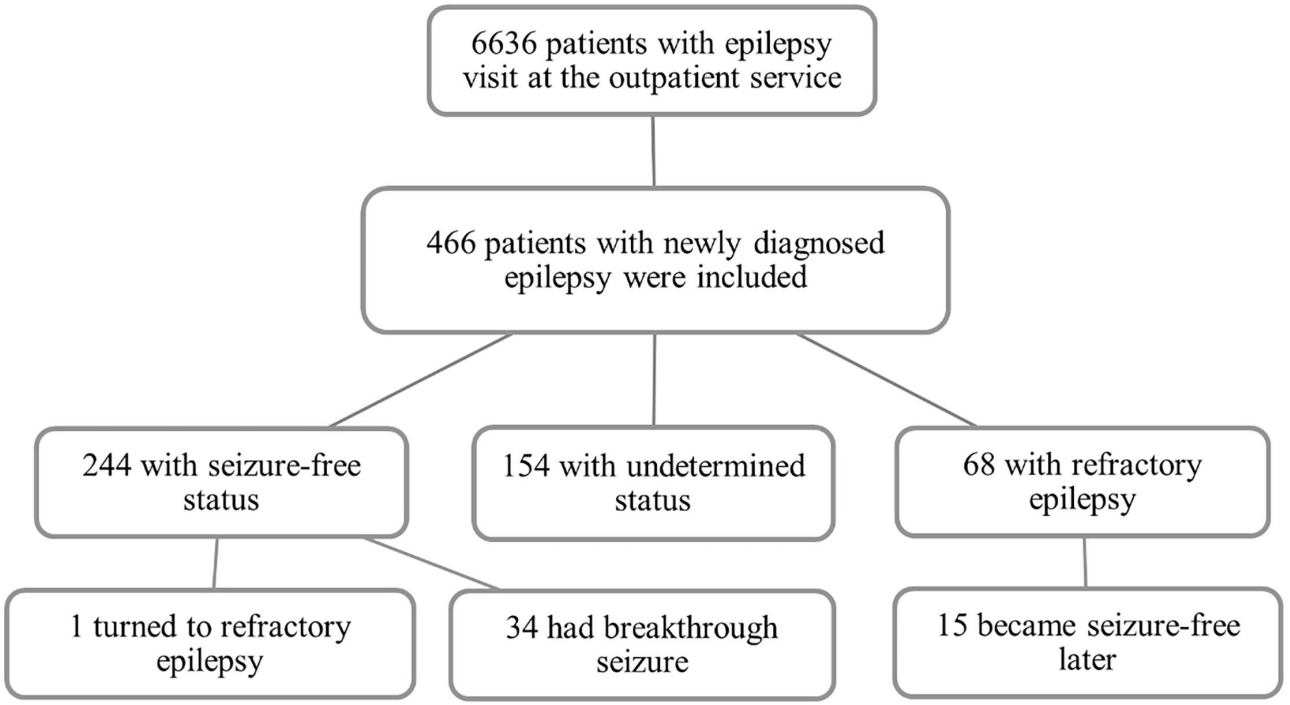

FIGURE 1 | Flow diagram of the study.

first ASM. The causes of withdrawal or dose-reduction are shown in **Table 3**. The objective adverse effects were drowsiness, ataxia, dizziness, headache, memory decline, irritability, weight gain or loss, palpitation, and gastrointestinal complaints, among others.

Cox regression was used to analyse the influencing factors of the retention of the first ASM. Considering the types of the first ASM, gender, age of onset, average income, disease duration, seizure frequency, and types of seizure at baseline as independent variables in the Cox regression model analysis of the first ASM retention, the hazard ratio (HR) of withdrawal of valproic acid and topiramate were 2.31 [95% confidence intervals (CI): 1.35–3.93] and 2.93 (95% CI: 1.38–6.20), respectively, compared to that of oxcarbazepine.

Risk Factors of Refractory Epilepsy

At the last visit, 4 (0.9%) patients were receiving no ASM, and 360 (77%), 81 (17%), 18 (4%), and 3 (0.6%) patients were receiving one, two, three, and four ASMs, respectively. The ratio of seizure-free patients was 0.4% (no ASM, $n = 1$), 91% (one ASM, $n = 223$), 7.4% (two ASMs, $n = 18$), and 0.8% (three ASMs, $n = 2$), respectively. During the treatment, 83 (18%) patients had ever withdrawn the ASMs without medical advice but the ASMs were re-administered at the nearest follow-up. Approximately 24% ($n = 16$) of the patients in the RE group and 16% ($n = 38$) in the seizure-free group had poor compliance, and no significant difference was found ($\chi^2 = 2.352$, $p > 0.05$). Breakthrough seizures during the first expected interictal interval following ASM treatment were compared between the RE (77%, $n = 52$) and seizure-free group (26%, $n = 63$), and there was a significant difference ($\chi^2 = 58.622, p < 0.01$).

Fifteen (22%) patients who had been diagnosed with RE reached seizure-free status following ASM adjustment (they were still classified to RE in the statistics described above). Among them, six, eight, and one patient(s) were treated with one, two, and three ASM(s), respectively. No significant difference in the demographic data was found between the patients with RE who achieved seizure-free status and patients who had not ($p > 0.05$). Finding alternative effective ASMs and increasing doses of the ASM in use were methods to achieve seizure-free status. Thirty-four patients (14%) had breakthrough seizures after being classified as seizure-free. The time of relapse was 6 to 36 months (median 6 months) (**Figure 3**). No significant difference in the demographic data or poor compliance was found between patients with seizure relapse and those without ($p > 0.05$). One patient developed RE after identifying as seizure-free.

Logistic regression was applied to analyse the risk factors of RE, and gender, age of onset, average income, disease duration, seizure frequency and types of seizure at baseline, history of status epilepticus, etiology, compliance, and breakthrough seizures during the first expected interictal interval were set as independent variables (**Table 4**). Breakthrough seizures during the first expected interictal interval (OR = 5.66, 95% CI: 3.05–10.51) and higher seizure frequency (increased every 5 times/month) (OR = 1.20, 95% CI: 1.02–1.41) were risk factors. When the scores of MOCA, GAD-7, and c-NDDI-E were

TABLE 2 | Doses of the first antiseizure medication (ASM) for patients who reached seizure-free status with the first ASM.

	At baseline, *n* (%)	As the only monotherapy, *n* (%)	Seizure-free, *n* (%)	Median, mg/d	Maximum, mg/d	Minimum, mg/d
Valproic acid	52 (11)	20 (7.0)	14 (70)	500.0	750	400
Carbamazepine	8 (1.7)	4 (1.4)	2 (50)	500.0	800	200
Oxcarbazepine	279 (60)	186 (65)	122 (66)	600.0	1,200	240
Topiramate	19 (4.1)	5 (1.7)	2 (40)	100.0	125	50
Levetiracetam	78 (16.7)	52 (18)	37 (71)	750.0	1,250	375
Phenobarbital	4 (0.9)	3 (1.0)	1 (33)	–	–	–
Lamotrigine	24 (5.2)	17 (6.0)	8 (47)	112.5	150	100
Others[a]	2 (0.4)	1 (0.3)	0 (0.0)	–	–	–

[a] *"Others" refers to pregabalin and gabapentin.*

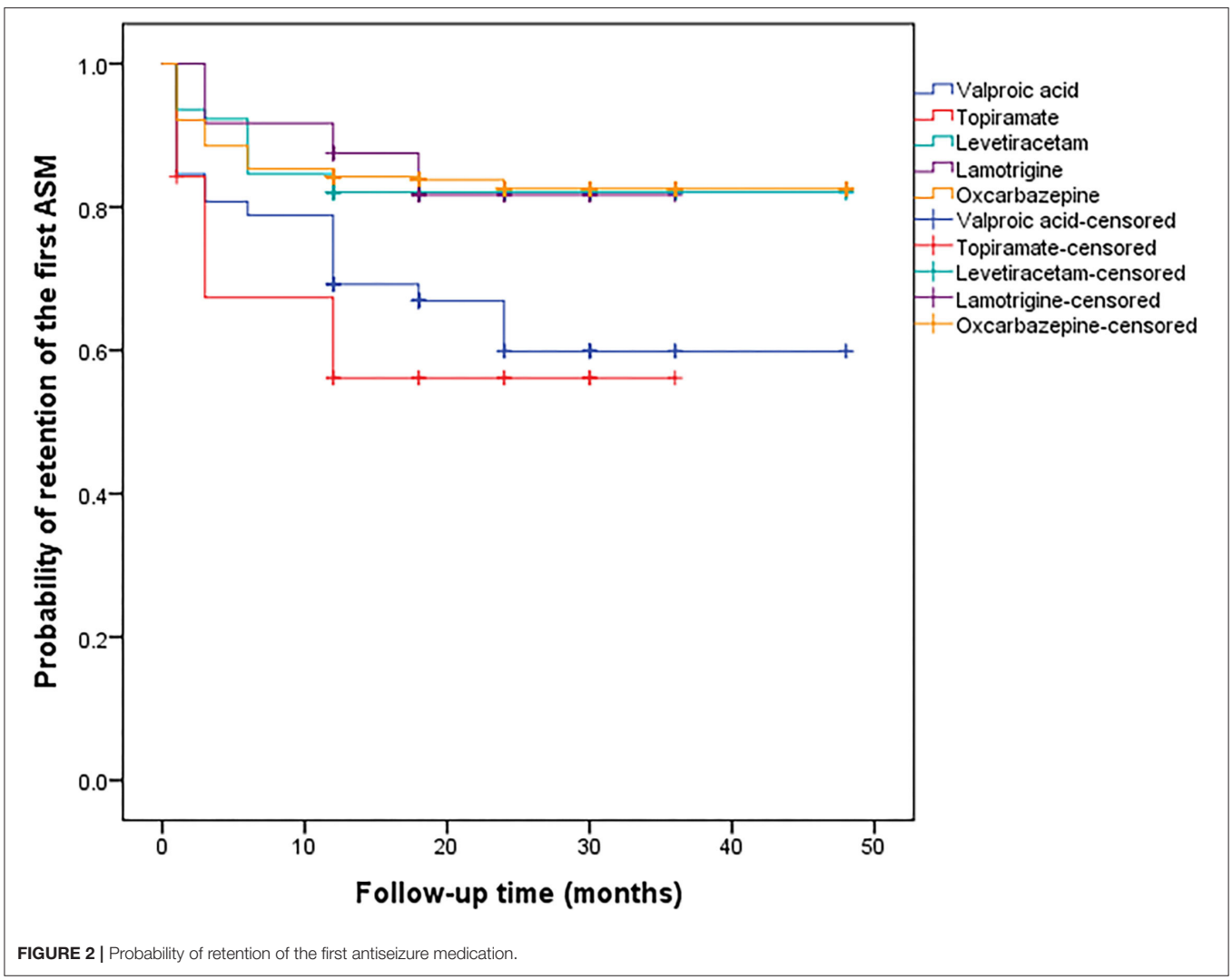

FIGURE 2 | Probability of retention of the first antiseizure medication.

adjusted in the analysis, men were more likely to develop RE than women [Odds ratio (OR) = 2.66, 95% CI: 1.26–5.62], and a younger age of onset (decrease of every 10 years) (OR = 1.42, 95% CI: 1.12–1.79) was also a risk factor of RE. Meanwhile, the ORs of breakthrough seizure during the first expected interictal interval and higher seizure frequency were 5.53 (95% CI: 2.57–11.92) and 1.22 (95% CI: 1.02–1.46), respectively (**Table 4**).

TABLE 3 | Causes of withdrawal or dose-reduction of the first antiseizure medication, *n* (%).

	Allergy	Ineffective	Liver damage	Other objective adverse effects	Poor compliance	Seizure-free for 3 y
Valproic acid	3 (9.4)	9 (28)	4 (13)	9 (28)	8 (19)	1 (3.1)
Carbamazepine	0 (0.0)	0 (0.0)	1 (25)	1 (25)	2 (50)	0 (0.0)
Oxcarbazepine	19 (19)	16 (16)	24 (25)	28 (29)	10 (10)	1 (1.0)
Topiramate	3 (21)	2 (14)	0 (0.0)	6 (43)	3 (21)	0 (0.0)
Levetiracetam	1 (3.8)	7 (26)	7 (26)	9 (33)	2 (7.4)	1 (3.7)
Phenobarbital	0 (0.0)	1 (50)	1 (50)	0 (0.0)	0 (0.0)	0 (0.0)
Lamotrigine	1 (17)	3 (50)	1 (17)	0 (0.0)	1 (17)	0 (0.0)
Others[a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)

[a] *"Others" refers to pregabalin and gabapentin.*

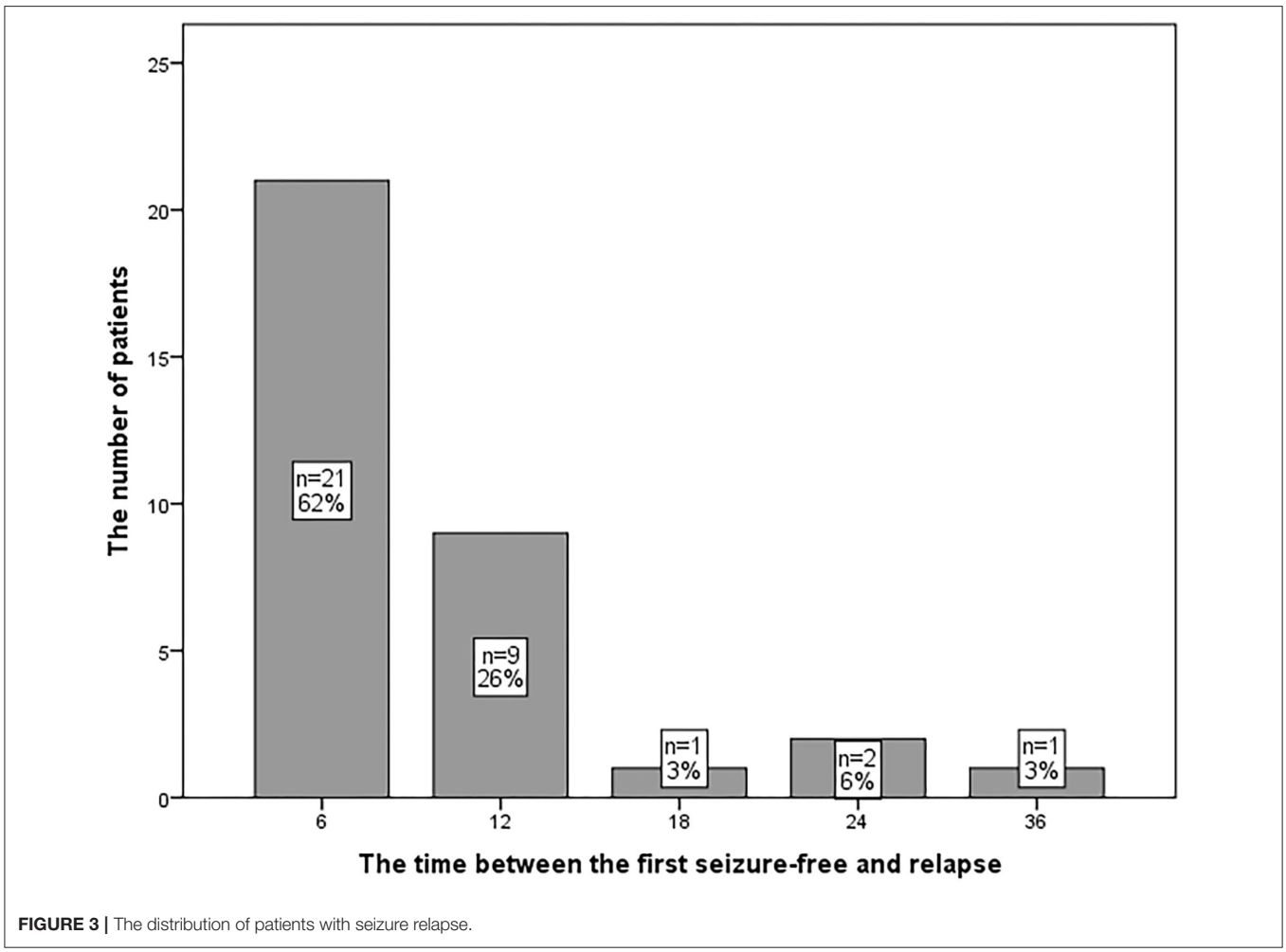

FIGURE 3 | The distribution of patients with seizure relapse.

DISCUSSION

ILAE published a new definition of RE in 2010 to set up explicit and practical criteria. Based on this definition, we conducted the first prospective study on treatment outcome of NDE in Northeast China, and we identified the risk factors of RE according to the new definition, which can help physicians more quickly and accurately identify patients that are likely to develop RE.

Nearly half of the adult patients with NDE became seizure-free in our study and 91% of them were treated with monotherapy. This proportion is lower than that in previous studies (15, 16), but the criteria in these studies were relatively lenient compared to the ILAE criteria (no seizures for at least the previous year). Forty

TABLE 4 | The logistic regression analysis for risk factors of refractory epilepsy in newly diagnosed epilepsy.

	Variables	*p*-value	OR	95% CI	
				Lower	Upper
Before adjusted by scales	Breakthrough seizures during the first expected interictal interval	<0.001	5.66	3.05	10.51
	Higher seizure frequency (increased every 5 times/month)	0.033	1.20	1.02	1.41
After adjusted by scales	Breakthrough seizures during the first expected interictal interval	<0.001	5.53	2.57	11.92
	Higher seizure frequency (increased every 5 times/month)	0.033	1.22	1.02	1.46
	Male gender	0.010	2.66	1.26	5.62
	Younger age of onset (decrease of every 10 years)	0.003	1.42	1.12	1.79

percent of the patients achieved seizure-free status with the first monotherapy and the median maintenance doses were no more than 50% DDD except for oxcarbazepine. This is consistent with the conclusion of previous studies that responsiveness may be identified with exposure to low ASM doses (12, 17). Most of the seizure-free statuses were obtained by monotherapy. Although Chi et al. found that combination therapy could increase the ratio of seizure-free patients compared to monotherapy (18), the latter is more acceptable for PWE in our clinic for fear of adverse effects. Dash et al. also found that reduction of the numbers of ASM may not aggravate seizures but decrease the side effects (19). Hence, combination therapy was always applied during the period of switching to another ASM or when the monotherapy did not work in our experience.

The probability of retention and the efficacy of levetiracetam and oxcarbazepine were satisfactory as the monotherapy, and liver damage and other objective adverse effects were the main causes of withdrawal. As a traditional ASM, valproic acid had relatively lower retention but it was also very efficient. Lamotrigine had a high likelihood of retention but did not perform as well as the other drugs. Neither the retention nor the efficacy of topiramate were satisfactory, and objective adverse effects were the main cause of withdrawal. In some studies with children, lamotrigine had better retention than oxcarbazepine (20) and topiramate (21). For older adults, carbamazepine is more likely to cause withdrawal symptoms than lamotrigine, levetiracetam, and valproic acid (22). Levetiracetam, on the other hand, has better efficacy than that of lamotrigine (23). Levetiracetam and oxcarbazepine were the more favorable drugs in terms of better tolerance and efficacy in our study. Unfortunately, we could not analyse their retention in older adults due to the limited number of patients.

The incidence of RE in adult NDE in our study was 15%, which is similar to the result of the systematic review on NDE (17%) (24). Although the ILAE definition is the minimum criteria, it could take more than 1 year for the majority of the patients to identify as RE. Moreover, patients with RE were inclined to have lower income, which means that the pharmacotherapy with the possibility of poor effect would put a huge burden on this population. Timely diagnosis helps physicians and patients to consider other optimal treatments, such as resective or palliative surgery, neurostimulation (25, 26), and ketogenic diet (27).

Breakthrough seizures during the first expected interictal interval, high seizure frequency at baseline, younger age of onset, and the male sex were risk factors of RE in our study. Younger age at seizure onset and high initial seizure frequency were discussed as predictors of RE in previous studies (28–30). The breakthrough seizures during the first expected interictal interval reflect responses to the first ASM and the longitudinal data could be a more accurate predictor. Jiang et al. posited that more than two seizures in the first year after ASM initiation predicted less likelihood of achieving 2-year remission. Making the interictal interval as the observing time may be more suitable for each PWE with different seizure periods. Hughes et al. (31) found both the presence and number of post-breakthrough seizures indicated poor outcomes. Only one patient developed RE after achieving seizure-free status in our study, and others were undetermined for limited post-seizure follow-up; therefore we cannot reach the same conclusion. Previous research found that men were more susceptible to temporal lobe epilepsy-like seizures and seizure-related damage (32). Therefore, the severity of epilepsy and the degree of hemicranial volume loss were worse in men than that in women. The finding supports our conclusion that male sex was a risk factor of RE.

Nearly 14% of the patients with seizure-free status had seizure relapse and 88% of them had a relapse within 12 months. Hence, prolonging the period of ASM treatment and careful withdrawal should be emphasized, and the minimum period of ASM treatment should be 2 years of seizure-free status (33). Although diagnosing as RE, 22% of the patients achieved seizure-free status after changing to the alternative ASM regimen or increasing the doses of the ASMs in use, which is supported by a previous study (34). A patient with identified seizure-free status developed RE later in the course of her epilepsy. This is consistent with the patterns of previous research, and excessive expression of transporters for ASM removal and reduced drug-target sensitivity are the major probable theories (35). A new approach in anti-epilepsy rather than antiseizure treatment is necessary to reverse the unsatisfactory treatment scenario.

In conclusion, treatment outcomes of the majority of the NDE are good, and monotherapy could be efficient at a low dose. Levetiracetam and oxcarbazepine performed best in tolerance and efficacy. Breakthrough seizures during the first expected interictal interval, high seizure frequency at baseline, younger

age of onset, and male sex predicted RE. Achieving seizure-free status is not enough to start the withdrawal of ASMs. RE is not permanent and seizure-free may be achieved subsequently by appropriate drug adjustment.

LIMITATION

This was a single-center study and the findings might be difficult to extrapolate in the global settings. The follow-up period was not sufficient to determine RE for a part of patients. However, as our program is still going on, the follow-up time would be extended and the "undetermined" patients may achieve their outcome at the subsequent visits.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of The First Hospital of Jilin University [the approval number: 2017-326]. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

NL, JL, CC, and YC are responsible for including participants, data entry, and following up. WL is the designer of this project. All authors contributed to the article and approved the submitted version.

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Sodium Valproate Combined With Topiramate vs. Sodium Valproate Alone for Refractory Epilepsy: A Systematic Review and Meta-Analysis

Zhen-Ye Ji[1†], *Yi-Qian Huang*[2†] *and Wen-Zhen He*[2*]

[1] *The Second Department of Neurology, First Affiliated Hospital of Shantou University Medical College, Shantou, China,*
[2] *Department of Internal Neurology, First Affiliated Hospital of Shantou University Medical College, Shantou, China*

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Giuseppe Didato,
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Marche Polytechnic University, Italy

****Correspondence:***
Wen-Zhen He
wenzhen_he@163.com

†These authors have contributed equally to this work and share first authorship

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Background: Among antiepileptic drugs (AEDs), sodium valproate alone or in the combination of topiramate (TPM) for treating refractory epilepsy was controversial. This meta-analysis aimed to systematically evaluate the clinical effects of these two regimens in this population.

Methods: Relevant studies up to August 2021 were identified through systematic searches of CNKI, Wanfang, PubMed, and Embase databases. We assessed the effectiveness and the frequency of absence seizures, atonic seizures, and tonic–clonic seizures. The included literature's risk of bias was evaluated using the Cochrane Collaboration's Risk of Bias tool. Sensitivity analysis was conducted to confirm the results' stability. STATA 15.0 was utilized for all pooled analyses in the included studies.

Results: Totally 10 articles were determined for our meta-analysis, involving 976 patients with epilepsy in total (combined group, $n = 488$; monotherapy group, $n = 488$). The results of this meta-analysis indicated that the total effective rate of sodium valproate combined with TPM was higher than that of sodium valproate alone (random-effect model: $OR = 3.52$; 95% CI 1.47 to 8.47; $p < 0.001$; $I^2 = 73.8\%$). The frequency of absence seizures in the combined group was lower (fixed-effect model: WMD = −6.02; 95% CI −6.50 to −5.54; $I^2 = 0.0\%$) than that in the monotherapy group, with a statistical difference ($p < 0.05$). The combined group had lower frequency of atonic seizures (WMD = −4.56, 95% CI −6.02 to −3.10; $I^2 = 82.6\%$) and lower frequency of tonic–clonic seizures (WMD = −3.32; 95% CI −4.75 to −1.89; $I^2 = 96.4\%$). In addition, the distinct difference of adverse events was non-existent between two groups.

Conclusions: Sodium valproate combined with TPM was more effective than sodium valproate alone for epilepsy therapy. This meta-analysis provides feasibility data for a larger-scale study on AED therapy of refractory epilepsy and may contribute to better therapy strategies for epilepsy clinically.

Keywords: topiramate (Topamax), sodium valproate, epilepsy, refractory epilepsy, antiepileptic drugs (AEDs)

INTRODUCTION

Epilepsy is a chronic brain disorder characterized by long-term prone epileptic seizures (1, 2). It is a complex disease with multiple risk factors and a strong genetic tendency rather than a single expression and etiology, which affects over 70 million people globally and ∼80% of cases occur in developing countries (1). The number of available antiepileptic drugs (AEDs) designed to inhibit seizure occurrence has increased substantially over the decades (3). However, about a third of patients is still hindered by drug resistance (4), which is regarded as "drug-resistant" or "refractory" (5). In addition, the risk of death, psychiatric, and also adverse effects from AEDs increased remarkably in 20–30% of patients with refractory epilepsy (6). Therefore, it is very crucial to find a new effective therapy strategy of AEDs clinically.

Pharmacotherapy paradigms in epilepsy are constantly evolving. The monotherapy or multitherapy for AEDs has been a controversial topic over the last few decades. Monotherapy with AEDs is the primary initial cure for epilepsy (7). Globally, sodium valproate is one of the most generally used AEDs (8) for monotherapy treatment, which is usually regarded as a routine drug choice in adults and children with intractable epilepsy due to its broad-spectrum mechanism of action and antiepileptic activity (9). However, one study indicated that drug-resistant epilepsy patients have seizures that cannot be controlled by a single drug and requires a combination of two agents (8, 10). Therefore, AED combination therapy is becoming popular once more, with up to 30–40% of children using this treatment strategy. Ferrendelli pointed out that the era of "rational multitherapy" had begun (11). When the initial monotherapy fails, drug-resistant epilepsy almost always requires multidrug therapy, but the issue of the best cure is still debatable (12).

Topiramate (TPM) is a promising new AED as monotherapy or adjunctive therapy for generalized tonic–clonic seizures or partial seizures in adults and children (13, 14). This new AED has few distinct interactions with other drugs in clinic, which is effective when utilized in combination with other AEDs. Furthermore, oral TPM is quickly absorbed by epilepsy patients, with about 80% relative bioavailability (14). Studies have shown that TPM has the advantages of a five-fold mechanism of action, high seizure-free rate and effective rate in combination therapy, less drug interaction, and good tolerance. Therefore, it is recommended for combination therapy by domestic and foreign guidelines (15–19). Zhang reported that sodium valproate and TPM can be quickly absorbed, in which the combination therapy of the two drugs has certain advantages (20).

However, there may be safety issues during combination therapy, such as unwanted drug interactions. For example, Cheung et al. described a case report that valproate combined with TPM-induced hyperammonemic encephalopathy syndrome for a 15-year-old boy (21). Moreover, the efficacy and safety of the two therapeutic strategies are rarely evaluated in these studies. Here, we conducted a meta-analysis to estimate the clinical efficacy of sodium valproate combined with TPM vs. sodium valproate alone in refractory epilepsy therapy and to provide more guidance for the treatment of AEDs in the future.

METHODS

Search Strategy

For this meta-analysis, two researchers independently, comprehensively, and systematically searched the literature in CNKI, Wanfang, PubMed,and also Embase databases. The literature search was limited to full-length articles published up to August 2021 in Chinese and in English. The keywords used in the search were "Topiramate OR Topamax OR TPM" and "Sodium Valproate" and "epilepsy" and "Refractory epilepsy OR Intractable epilepsy." Two reviewers independently evaluated the qualified articles, and divergence was resolved *via* discussion, and if necessary, arbitrated by the third reviewer. Two authors independently assessed the searched studies based on the selection criteria, manually checking the retrieved articles' reference lists to determine additional relevant studies. Differences were resolved through discussion until the consensus was reached.

Selection Criteria

Studies included in our meta-analysis were required to satisfy the following criteria: (1) be related to AED therapy for refractory epilepsy (no restriction to the type of refractory epilepsy); (2) the intervention of the experimental group was sodium valproate combined with TPM, and the intervention of the control group was sodium valproate; (3) the main outcomes in the study included effectiveness, absence seizures, atonic seizures, tonic–clonic seizures, and adverse events.

Studies were excluded from this analysis if they were (1) repeated articles; (2) summary of the meeting, comments, letters, existing systematic reviews, and meta-analysis; (3) study on TPM combined with other drugs.

Data Extraction and Quality Assessment

The information from all qualified articles that met the inclusion criteria was extracted by two reviewers independently. Meanwhile, the risk of bias of the selected studies was evaluated to ensure the data's reliability. Any difference in the extracted data was resolved through discussion. If a disagreement still existed after the discussion, a third investigator was invited to evaluate these articles. The data extracted by the two

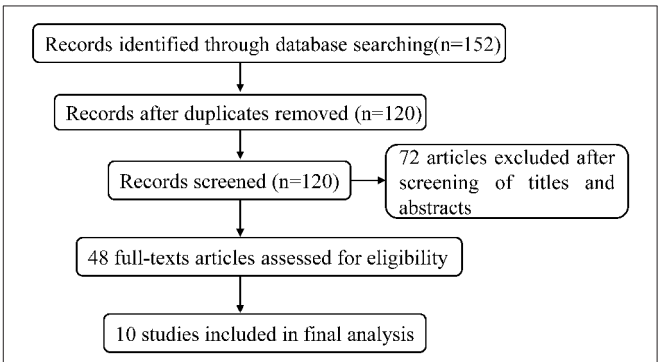

FIGURE 1 | The retrieval flow chart for the meta-analysis.

TABLE 1 | The baseline characteristics of the included studies.

References	Group	Intervention	Sample	Age	Outcomes
Chen et al. (22)	T + S	T: 300 mg, once/day; S: 15 mg/kg, once/day, 12 weeks	30	48.24 ± 1.27	(1), (5)
	S	S: 15 mg/kg, once/day, 12 weeks	30	48.34 ± 1.32	
Wang et al. (23)	T + S	T: adult, 25 mg, child, 0.5 mg, two times/day, 3 months; S: adult, 1 g, child, 30 mg, two times/day, 3 months	33	27.32 ± 13.81	(1), (2), (3), (4)
	S	S: adult, 1 g/day, child, 30 mg/day, 3 months	33	26.71 ± 14.55	
Qu (24)	T + S	T: 400 mg/day; S: 5–10 mg/kg/day, 1 week; after 1 week, 10–20 mg/kg/day	80	31.3 ± 5.7	(2), (3), (4)
	S	S: 5–10 mg/kg/day, 1 week; after 1 week, 10-20 mg/kg/day	80	31.2 ± 5.5	
Wlr et al. (25)	T + S	T: 100–150 mg/day; S: 0.2 g, once/day, 2 weeks; after 2 weeks, two times/day, maximum ≤ 1.2 g, 6 months	53	32.11 ± 2.36	(1), (2), (3), (4), (5)
	S	S: 0.2 g, once/day, 2 weeks; after 2 weeks, two times/day, maximum ≤1.2 g, 6 months	53	32.10 ± 2.35	
Li et al. (26)	T + S	T: 25–50 mg/day; S: 15 mg/kg, three times/day	50	45 ± 2.3	(1), (5)
	S	S: 15 mg/kg, three times/day	50	46±2.1	
Yan and Dai (27)	T + S	T: 100–150 mg/day; S: 0.2 g, once/day, 2 weeks; after 2 weeks, two times/day, maximum ≤ 1.2 g	62	37.6 ± 4.2	(1)
	S	S: 0.2 g, once/day, 2 weeks; after 2 weeks, two times/day, maximum ≤1.2 g	62	37.4 ± 4.3	
Peng et al. (28)	T + S	T: 100–150 mg, two times/day; S: 0.2 g, once/day, 2 weeks; after 2 weeks, two times/day, maximum ≤ 1.2 g	40	40.28 ± 7.36	(1)
	S	S: 0.2 g, once/day, 2 weeks; after 2 weeks, two times/day, maximum ≤ 1.2 g	40	40.59 ± 7.14	
Chen and Pan (29)	T + S	T: 300 mg/day; S: 15 mg/kg, once/day, 12 weeks	75	47.9 ± 6.8	(1), (5)
	S	S: 15 mg/kg, once/day, 12 weeks	75	48.7±6.9	
Liu (30)	T + S	T: adult, 25 mg, child, 0.5 mg, two times/day; S: adult, 500 mg, child, 15 mg, two times/day	15	36.7 ± 11.2	(1)
	S	S: adult, 500 mg, child, 15 mg, two times/day	15	37.7 ± 10.9	
Wang et al. (31)	T + S	T: 300 mg/day; S: 5–10 mg/kg, two times or three times/day, 12 weeks	50	–	(1), (5)
	S	S: 5–10 mg/kg, two times or three times/day, 12 weeks	50	–	

T, Topamax; S, sodium valproate; (1) effective rate; (2) absence seizure; (3) atonic seizures; (4) tonic–clonic seizure; (5) adverse events (headache, loss of appetite, and nausea).

researchers independently reading the full text of each eligible article, including the following information: the author's name, publication date, sample size, age, intervention measures, and also outcome measures.

The included studies' risk of bias was assessed using the Cochrane Collaboration's Risk of Bias tool, categorizing the study as "low risk" of bias, "high risk" of bias, or "unclear risk" of bias (32). The quality assessment was conducted by two reviewers independently; in case of disagreements, the third reviewer was consulted.

Outcome Measures

We assessed the rate of effectiveness and the frequency of absence seizures, atonic seizures, tonic–clonic seizures, and also adverse events. The main outcome for measuring efficacy was the total effective rate. The total effectiveness was defined as the improvement of symptoms and signs, mainly including sudden, recurrent loss of consciousness, body convulsing, and frothing at the mouth, and also a decrease of ≥50% in seizure frequency from baseline to posttreatment. The other outcome was the condition of patients who suffered from treatment-emergent adverse events (TEAEs). TEAE is an adverse event that occurred or became

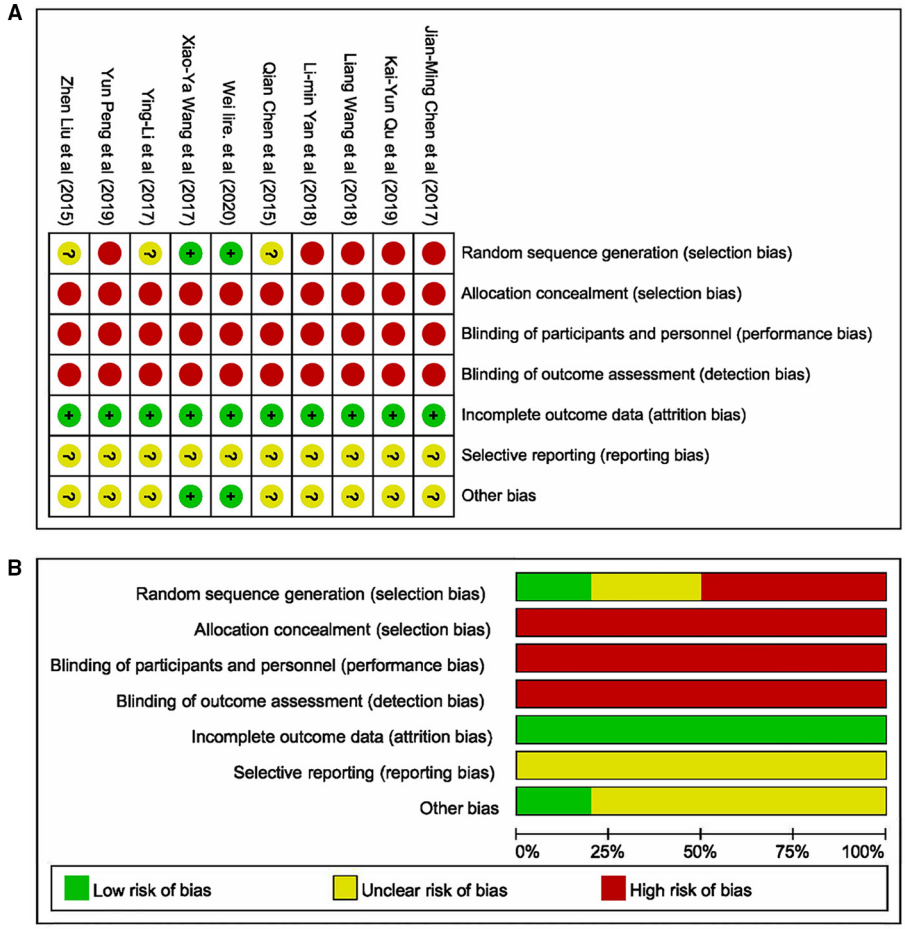

FIGURE 2 | Methodological quality of studies included in this meta-analysis. **(A)** Summary of the risk of bias in the included studies; **(B)** Risk of bias graph: the articles' risk of bias evaluation results.

worse in the treatment phase (33). TEAEs evaluated in our meta-analysis included headache, loss of appetite, and nausea.

Statistical Analysis

All analyses were conducted using STATA 15.0 software. The combined effect was assessed adopting weighted mean difference (WMD) and 95% CI or odds ratios (OR) value and 95% CI. The frequency of seizures was described by mean and standard deviation, and the pooled effect analysis in this meta-analysis was performed on the mean of seizures in each study. Statistical methods for combining the results of studies generally weight the influence of each study by the inverse of the variance for the estimated measure of effect. Based on the heterogeneity test results, the total effects were evaluated through random-effect or fixed-effect models (34, 35). Q-test and I^2-test were applied to assess the heterogeneity between studies. The fixed-effect model was used in case of $p > 0.1$, $I^2 \leq 50\%$; Otherwise, the random-effect model was used. Sensitivity analysis was used for estimating the results' stability. A funnel plot combined with Egger's test was used to assess publication bias (36, 37). The p-value < 0.05 indicates that the difference was statistically significant.

RESULTS

Literature Search and Study Characteristics

Overall, 152 articles were searched by the systematic search in total, of which 32 duplicates were excluded. After independently screening the title and abstract by two review authors, 72 irrelevant articles were removed, and 48 studies were selected for detailed full-text review. In the light of selection criteria, 38 articles were eliminated, and 10 were eventually included in our meta-analysis. The flow chart (**Figure 1**) described the process of literature retrieval and selection. The basic information of the included studies was summarized in **Table 1**. We identified a total of 976 patients with refractory epilepsy included in 10 reports of controlled studies (22–31) (**Table 1**). The cases of each study were selected and divided into a control group and an observation group. Sodium valproate was given to the control group, while the observation group was with the combination of TPM. The treatment effects were compared between two groups. All studies were randomized and nine studies reported the effective rate in groups of combined treatment vs. control groups (**Table 1**).

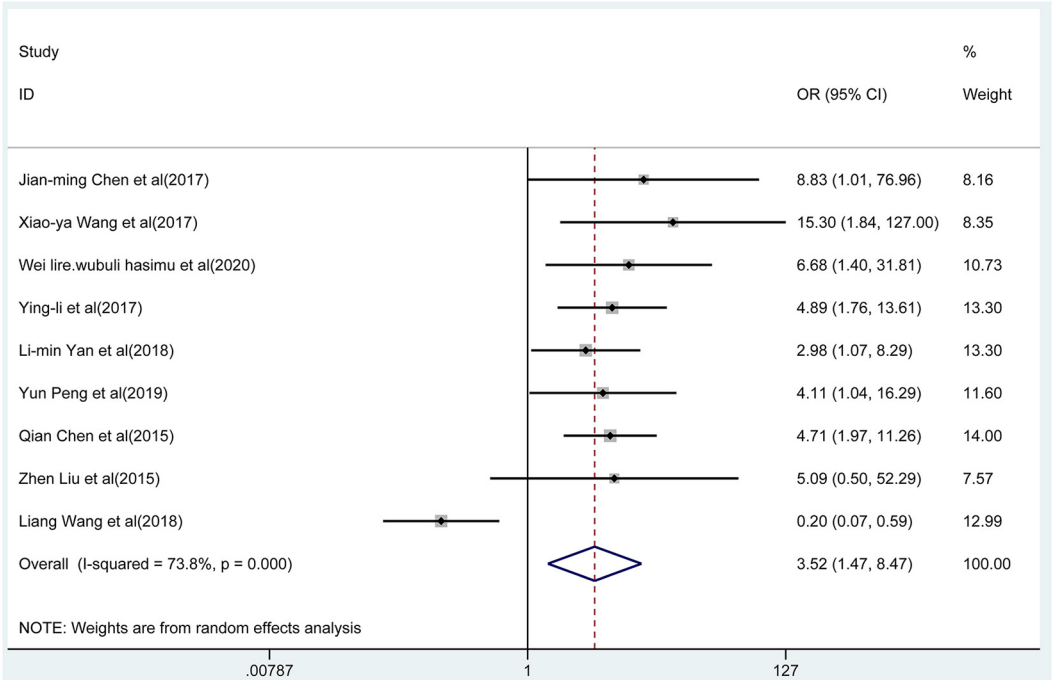

FIGURE 3 | Forest plot of the overall effectiveness of the combined group vs. monotherapy group.

Quality Assessment of Included Studies

The literature's risk bias estimation results were presented in **Figure 2**. As displayed in **Figure 2A**, two articles described the method of randomization. All studies did not describe stratified seclusion, and the corresponding risk was judged as the high risk; none of the included studies were blinded, which was a high risk. All research data were completed and without missing (**Figure 2B**). The included studies' selection bias was unknown, and other sources of biases were unknown.

Efficacy

Nine articles reported the total effective rate of the combined group and monotherapy group (**Figure 3**). The total effective rate of sodium valproate combined with TPM was higher than that of sodium valproate alone (random-effect model: $OR = 2.17$, 95% CI 1.47-8.47), and the difference was statistically significant ($p < 0.05$). By removing each qualified study in turn, we conducted the sensitivity analysis to evaluate the impact of each individual study on the pooled OR (**Figure 4A**). The estimated value of the total effect was within the range of 95% CI (1.47–8.47), which suggested the results were stable and reliable in this meta-analysis. The funnel plot was visually observed to estimate the publication bias, and no obvious asymmetry was found (**Figure 4B**). Moreover, the Egger's test was used for quantifying the publication bias, and the p-value was 0.09, indicating that the studies' biases were non-existent.

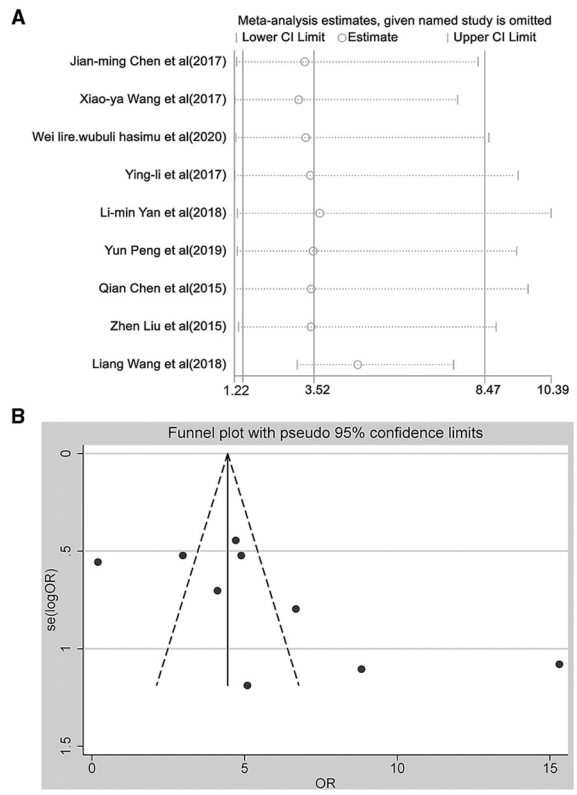

FIGURE 4 | Sensitivity analysis of results **(A)** and funnel plot of the publication bias **(B)**.

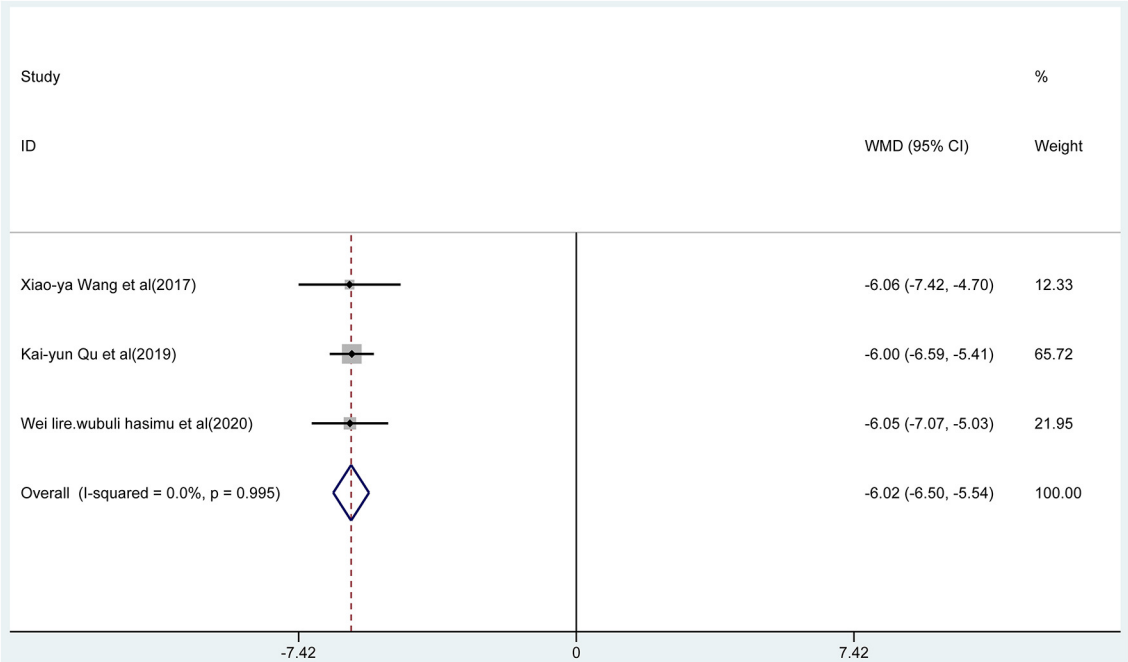

FIGURE 5 | The forest plot of absence seizures, the combined group vs. monotherapy group.

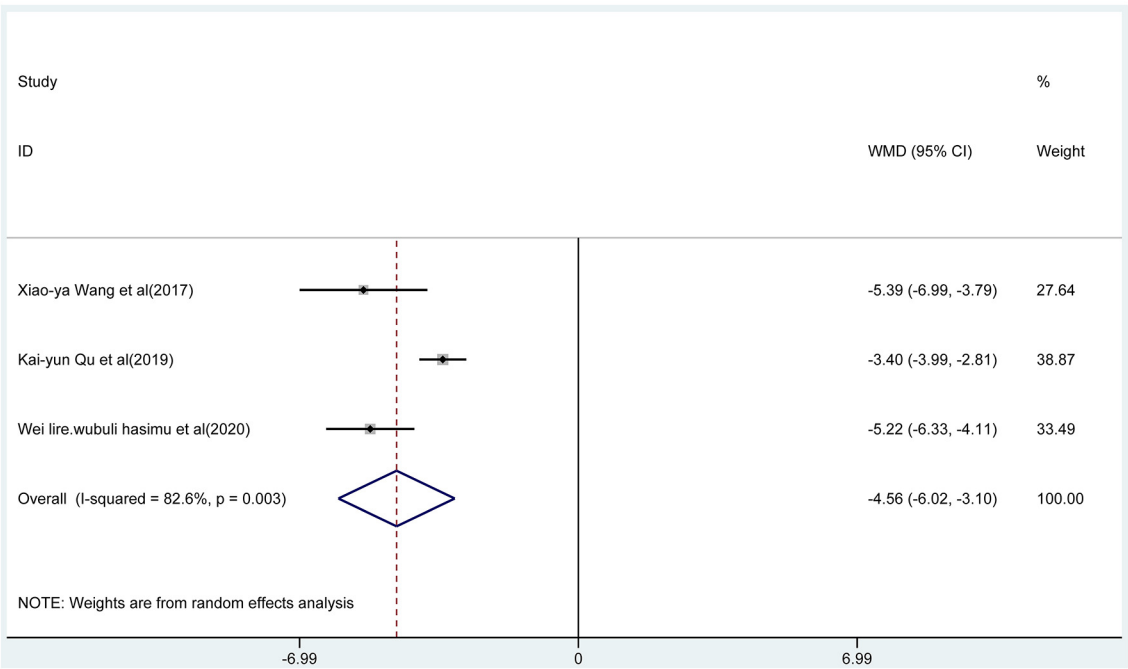

FIGURE 6 | The forest plot of atonic seizures, the combined group vs. monotherapy group.

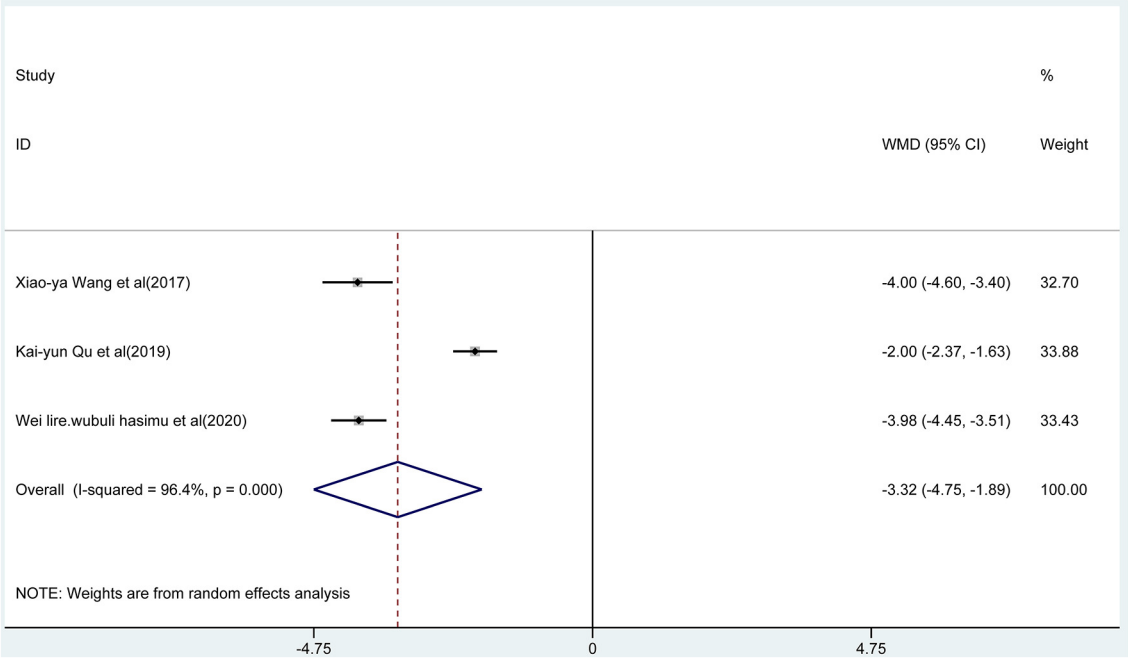

FIGURE 7 | The forest plot of tonic–clonic seizures, the combined group vs. monotherapy group.

Absence Seizures, Atonic Seizures, and Tonic–Clonic Seizures

Three articles reported the frequency of absence seizures, atonic seizures, and tonic–clonic seizures, respectively. The results showed that the frequency of absence seizures of sodium valproate combined with TPM was lower (fixed-effect model: WMD = −6.02; 95% CI −6.50 to −5.54; I^2 = 0.0%) than that of sodium valproate alone, with statistically significant difference ($p < 0.05$; **Figure 5**). Likewise, according to the random-effect model, the results showed that the frequency of atonic seizures (WMD = −4.56; 95% CI −6.02 to −3.10; I^2 = 82.6%; **Figure 6**) and tonic–clonic seizures (WMD = −3.32; 95% CI −4.75 to −1.89; I^2 = 96.4%; **Figure 7**) in the combined group was less than that in monotherapy group.

Adverse Events

We pooled data on adverse events mainly including headache, loss of appetite, and nausea. Five studies reported these adverse events with the two treatments, which were presented in **Figure 8**. According to the fixed-effect model, the results indicated that there was no significant difference in adverse events between the combined group and the monotherapy group (*OR* = 0.72, 95% CI 0.39-1.33; p = 0.297; I^2 = 0.0%, p = 0.981). In addition, the results of subgroup analysis indicated that there were no differences in the incidence of headache (p = 0.710), anorexia (p = 0.410), and nausea (p = 0.527) between the two groups.

DISCUSSION

Epilepsy is one of the most common neurological disorders, leading to a considerable incidence rate (38). In clinical practice, drugs are often used to control the condition of patients, thereby reducing the incidence of patients with intractable epilepsy and improving the quality of life and treatment effect (22). However, the patients with chronic intractable "drug-resistant" epilepsy cannot obtain the freedom of continuous seizures after a trial of two AEDs, thus requiring treatment with a combination of drugs (39). Herein, our meta-analysis indicated that sodium valproate in combination with TPM contributed to better control of seizures, which may be a good option for refractory epilepsy therapy. The choice of initial pharmacotherapy for epilepsy should be mainly guided by the evidence of efficacy and safety, so as to ensure that the ultimate goal is to keep seizure free without intolerable adverse events (40).

To date, many researchers have compared the efficacy of sodium valproate combined with TPM vs. sodium valproate alone for refractory epilepsy. Nevertheless, there is still a lack of systematic collection, classification, and assessment of these research data. In our study, 10 articles were screened strictly based on the selection criteria, and 976 patients with refractory epilepsy were included, with the age range of 10-70 years. The results fully indicated that sodium valproate combined with TPM has significant curative effect on refractory epilepsy compared with sodium valproate alone, which can reduce epilepsy attack frequency. Here, we conducted the meta-analysis to provide the comprehensive and explicit evidence-based evaluation of relative efficacy of the two therapeutic strategies. To our knowledge, this

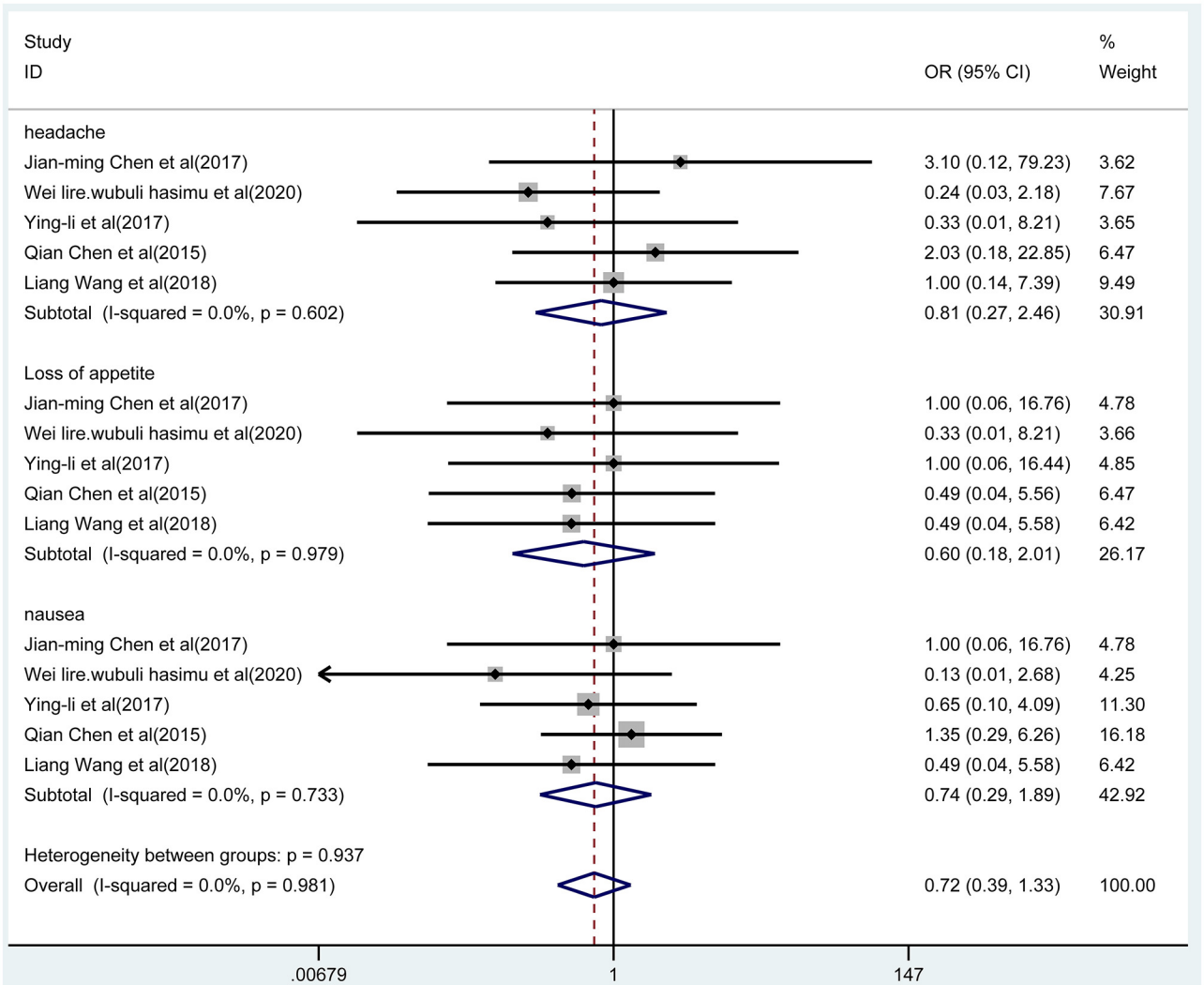

FIGURE 8 | The forest plot of adverse events, the combined group vs. monotherapy group.

meta-analysis was the first evaluation in regard to clinical effect of sodium valproate combined with TPM vs. sodium valproate alone for refractory epilepsy.

There were similar design features among included studies, and the low heterogeneity between trials enhances the estimates' accuracy (41). The results fully indicated that total effective rate of the combined group was significantly higher than that of the monotherapy group. Notably, the frequency of absence seizures, atonic seizures, and tonic–clonic seizures decreased significantly in the combined group. In addition, compared with monotherapy, the adverse events of patients during the combination therapy were not increased. Overall, all evaluation results of this meta-analysis fully indicated that the efficacy of sodium valproate combined with TPM was better than that of sodium valproate alone.

Sodium valproate, as a typical broad-spectrum AED, has become the first choice for treating epileptic absence seizures and generalized tonic–clonic seizures in clinical practice (8). It has the pharmacological effect involving a variety of mechanisms, including blockade of voltage-gated sodium channels, reduced effect of excitatory amino acids, and also potentiation of γ-aminobutyric acid (GABA) ergic transmission (42). TPM, a structurally novel broad-spectrum AED, also has the same mechanism of action as sodium valproate, including the state-dependent inhibition of sodium channels, the potentiation of GABA-induced chloride influx, and the blockade of glutamate-related excitatory neurotransmission (43). In this meta-analysis, we found that the efficacy of sodium valproate in combination with TPM was obviously superior to sodium valproate alone, which was identical with the literature reported (44). We speculate that abnormal neuronal excitability associated with seizures suppressed through the two drugs' common mechanism of block the persistent Na^+ current can account for decline of seizure frequency. Moreover, one study reported that

TPM-induced reduction in tonic–clonic seizures corresponded well with the decrease of glutamate levels in SER (45). More interestingly, in addition to the same mechanism of action, TPM was found to be neuroprotective in rodent models of focal cerebral ischemia (46, 47) and experimental status epilepticus (48), which may compensate for this shortcoming of sodium valproate. Given this, we assumed that valproate and TPM might synergistically play an inhibition effect on the glutamate-related excitatory neurotransmission, which contributes to seizures decrease. However, the combination of lamotrigine (LTG) and valproate has been suggested to be particularly efficacious for epilepsy due to the synergistic effect in the previous studies (49, 50). LTG, a novel broad-spectrum antiepileptic agent, has the mechanism of action such as inhibiting the release of the excitatory amino acid glutamate through sodium channel blockade similar to TPM or valproate (51). Previous study has also demonstrated that the combination of LTG and valproate produced a supralinear "synergistic" effect based on the antiglutaminergic effect of LTG (52). Similarly, we speculated that the combination of TPM and valproate might have a similar synergistic interaction that of LTG combined with valproate. Certainly, further studies should definitely explore whether the combination of valproate and TPM is associated with additive or synergistic efficacy, and also their mechanisms of action. Comfortingly, our findings demonstrated that sodium valproate combined with TPM therapy may be a promising treatment strategy for refractory epilepsy clinically.

Our research maintains some validity. First, the included studies in our meta-analysis statistical strictly met the selection criteria. Second, no publication bias was shown, indicating that there was no bias among the pooled results. Even so, deficiencies should be taken into account when interpreting the research results. There may be several limitations to the results of this meta-analysis. First, most of the included RCTs had no descriptions of the details including blind method and allocation concealment, which may lead to deviations in implementation and measurement. Second, the published studies' quantity in our meta-analysis was insufficient, and small-sample studies may not have sufficient statistical power for estimating the relevance. Third, the current clinical data were primarily from China, with a lack of population from other countries. Finally, stratified seclusion was not described in all studies, and the corresponding risk was judged as high risk. Thus, we should carry out multicenter, randomized, strictly designed, large-scale, and double-blind research, collecting international clinical research data, so as to better assess the efficacy of sodium valproate combined with TPM vs. sodium valproate alone for refractory epilepsy. In future researches, we require higher-quality evaluations to validate our findings.

In summary, results of our meta-analysis indicated that the efficacy of sodium valproate combined with TPM was better than that of sodium valproate alone for epilepsy. This meta-analysis provides feasibility data for a larger-scale study on AED therapy of refractory epilepsy and may contribute to better therapy strategies for epilepsy clinically.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

Z-YJ conceived conceptualization, performed data analysis, and supervised the project. Z-YJ and Y-QH contributed to methodology. Y-QH provided the resources and contributed to project administration. Y-QH and W-ZH performed data curation. W-ZH wrote original draft and involved in writing, reviewing, and editing. All authors contributed to the article and approved the submitted version.

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Direct Cortical Stimulation to Probe the Ictogenicity of the Epileptogenic Nodes in Temporal Lobe Epilepsy

Auriana Irannejad[1,2], *Ganne Chaitanya*[1,2], *Emilia Toth*[1,2], *Diana Pizarro*[1,2] and *Sandipan Pati*[1,2*†]

[1] Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, United States, [2] Epilepsy and Cognitive Neurophysiology Laboratory, University of Alabama at Birmingham, Birmingham, AL, United States

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Giuseppe Didato,
Epilepsy Unit, Carlo Besta Neurological Institute (IRCCS), Italy

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Thandar Aung,
University of Pittsburgh, United States

***Correspondence:**
Sandipan Pati
patilabuab@gmail.com

†Present address:
Sandipan Pati,
Epilepsy and Cognitive Neurophysiology Laboratory, Department of Neurology, Texas Comprehensive Epilepsy Center, McGovern Medical School, Houston, TX, United States

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Accurate mapping of the seizure onset zone (SOZ) is critical to the success of epilepsy surgery outcomes. Epileptogenicity index (EI) is a statistical method that delineates hyperexcitable brain regions involved in the generation and early propagation of seizures. However, EI can overestimate the SOZ for particular electrographic seizure onset patterns. Therefore, using direct cortical stimulation (DCS) as a probing tool to identify seizure generators, we systematically evaluated the causality of the high EI nodes (>0.3) in replicating the patient's habitual seizures. Specifically, we assessed the diagnostic yield of high EI nodes, i.e., the proportion of high EI nodes that evoked habitual seizures. A retrospective single-center study that included post-stereo encephalography (SEEG) confirmed TLE patients ($n = 37$) that had all high EI nodes stimulated, intending to induce a seizure. We evaluated the nodal responses (true and false responder rate) to stimulation and correlated with electrographic seizure onset patterns (hypersynchronous-HYP and low amplitude fast activity patterns-LAFA) and clinically defined SOZ. The ictogenicity (i.e., the propensity to induce the patient's habitual seizure) of a high EI node was only 44.5%. The LAFA onset pattern had a significantly higher response rate to DCS (i.e., higher evoked seizures). The concordance of an evoked habitual seizure with a clinically defined SOZ with good outcomes was over 50% ($p = 0.0025$). These results support targeted mapping of SOZ in LAFA onset patterns by performing DCS in high EI nodes to distinguish seizure generators (true responders) from hyperexcitable nodes that may be involved in early propagation.

Keywords: direct cortical stimulation, seizure onset zone, ictogenicity, temporal lobe epilepsy, epileptogenicity

INTRODUCTION

Intracranial EEG investigation aims to localize seizure generators and, in resection cases, to define the anatomical extent of surgical resection that will maximize the chance of seizure freedom. The epileptogenic zone (EZ) is conceptualized as the area of the cortex that is indispensable for the generation of epileptic seizures, the removal of which would contribute to seizure freedom (1) Increasingly, the EZ is considered a network of functionally interconnected structures that can involve anatomically non-contiguous regions (2, 3). In temporal lobe epilepsy (TLE), the epileptogenic network (EN) can extend beyond the mesial temporal structures to include nearby extra-temporal regions such as the orbitofrontal cortex.

Failure to identify and resect these extra-temporal structures (known as TLE-plus) is associated with seizure recurrence following anterior temporal lobectomy (4–6). Thus, there is a clinical need to develop imaging or electrophysiological parameters (or biomarkers) to delineate the full extent of the EN preoperatively to optimize the surgical outcome.

Stereoelectroencephalography (SEEG) allows high-resolution mapping of candidate biomarkers of epileptogenicity and offers insights into pathophysiological processes within the EN (5). Both lower and higher-frequency neural activities (infra slow- and high-frequency oscillations) and the epileptogenicity index (EI) are some of the parameters used to map the EN (7–11). Specifically, the EI statistically summarizes the spectro-temporal parameters of SEEG signals at seizure genesis and is related to the propensity of a brain area to generate low voltage fast discharges (12). Thus, the EI can be used to quantify the epileptogenicity of brain structures in the early organization of seizure genesis with an index ranging from 0 (no epileptogenicity) to 1 (maximal epileptogenicity).

However, there are a few challenges in the clinical interpretation of the EI. First, the EI does not distinguish nodes involved in the initiation vs. early propagation of seizures (5). Second, the estimation of EI is susceptible to the imperfect spatial sampling that is inherent to any invasive EEG, including SEEG. For example, the low voltage fast discharges at seizure onset can present quasi-simultaneously over a vast territory that may overestimate the EN, or the seemingly first electrographic changes may represent propagated ictal activity, thereby false localizing the EN. Direct cortical stimulation (DCS) to evoke and replicate a patient's habitual aura offers an alternative strategy to probe the putative epileptogenic nodes and delineate the EN that is indispensable for seizure generation (13, 14).

Prior studies have validated the EI with clinically identified seizure onset zone (3), interictal high-frequency oscillation maps (15), and post-resection seizure outcome (5), but none to date have correlated the EI with DCS. In the present study, using DCS as a probing tool to identify seizure generators, we systematically evaluated the causality of the high epileptogenicity index nodes (>0.3) in replicating the patient's habitual seizures. Specifically, using DCS in a cohort of highly selected patients, we evaluated the diagnostic yield of high EI nodes, i.e., the proportion of high EI nodes that evoked habitual seizures. We hypothesized that high EI nodes overlapped with the clinically defined seizure onset zone would yield the highest in evoking habitual seizures.

METHODS

Patient Selection and Study Design

We performed a single-center, retrospective study at a level-IV epilepsy center using protocols approved by the University of Alabama Birmingham Institutional Review Board. Since the inception of SEEG investigation at our center, eighty-six adults (>19-years old) with drug-resistant focal epilepsy have undergone the procedure successfully between January 2014 and January 2020. Forty-five of them had confirmed mesial TLE or TLE-plus epilepsies (the "plus" indicates additional seizure foci in neighboring regions, such as the insula, the suprasylvian operculum, the orbito-frontal cortex, and the temporo-parietooccipital junction) were included in this study (4, 16) (**Figure 1A**). The localization of the seizure onset zone (SOZ) was confirmed based on consensus among the multidisciplinary epilepsy group after reviewing the anatomical and electroclinical findings. DCS was performed as a part of the clinical protocol by the epileptologist investigating the patient. The inclusion criteria for the retrospective study were: (a) confirmed TLE or TLE plus epilepsies, (b) DCS performed on a significant proportion of sampled electrodes in clinically identified onset zones and propagated regions, including all of the high EI nodes. Patients were excluded if DCS was not performed on all of the high EI nodes.

Stereoencephalography Surgery and Data Acquisition

SEEG electrodes were implanted into predetermined regions of interest for seizure localization using a robotic platform (ROSA® robot, Medtech, Montpelier). SEEG was recorded with cylindrical intracranial electrodes (0.8 mm outer diameter) with 5–20 contacts per electrode. Each contact was 2 mm in length with 1.5 mm intercontact distance (PMT® Corporation, Chanhassen, MN). The localization of the electrodes was confirmed using AAL2 atlas and iElectrodes toolbox (17, 18). Clinically defined seizure onset channels, along with contacts localized to gray matter, were parsed to reconstruct bipolar derivatives for subsequent estimation of EI. Contacts in white matter were not used for the analysis of EI. Intracranial video-EEG was sampled at 2048 Hz (Natus Medical Incorporated, Pleasanton, CA). An extracranial electrode common to all was placed posteriorly in the occiput near the hairline as the reference signal.

Estimation of Epileptogenicity Index

The EI was used to quantify the epileptogenicity of brain structures. The EI delineates regions (or nodes) of the recorded brain activity involved in the generation of a rapid discharge (12) (**Figures 1B–D**). The energy spectral density ratio (ER) was estimated as a measure of an abrupt increase in fast oscillations in the SEEG signal [formula: $ER = (E_{12-127Hz})/(E_{4-12Hz})$]. The cumulative sum algorithm by Page and Hinkley helped improve the time point of detection of fast oscillations. EI was therefore calculated as the averaged ER overtime immediately following detection of a rapid discharge in the first channel divided by the delay of involvement across other channels. The EI values were computed for all the channels identified in the gray matter. The first 20 s of the seizure were analyzed with −10 s to +10 s segment selected around the seizure onset as determined by epileptologists. For a channel to be considered within the epileptogenic network—and subsequently involved seizure onset channels—they had to demonstrate an average EI value above

Abbreviations: EI, epileptogenicity index; DCS, direct cortical stimulation; SOZ, seizure onset zone; EZ, epileptogenic zone; EN, epileptogenic network; TLE, Temporal lobe epilepsy; SEEG, stereo EEG; HYP, hypersynchronous patterns; LAFA, low amplitude fast activity; LITT, laser interstitial thermal therapy.

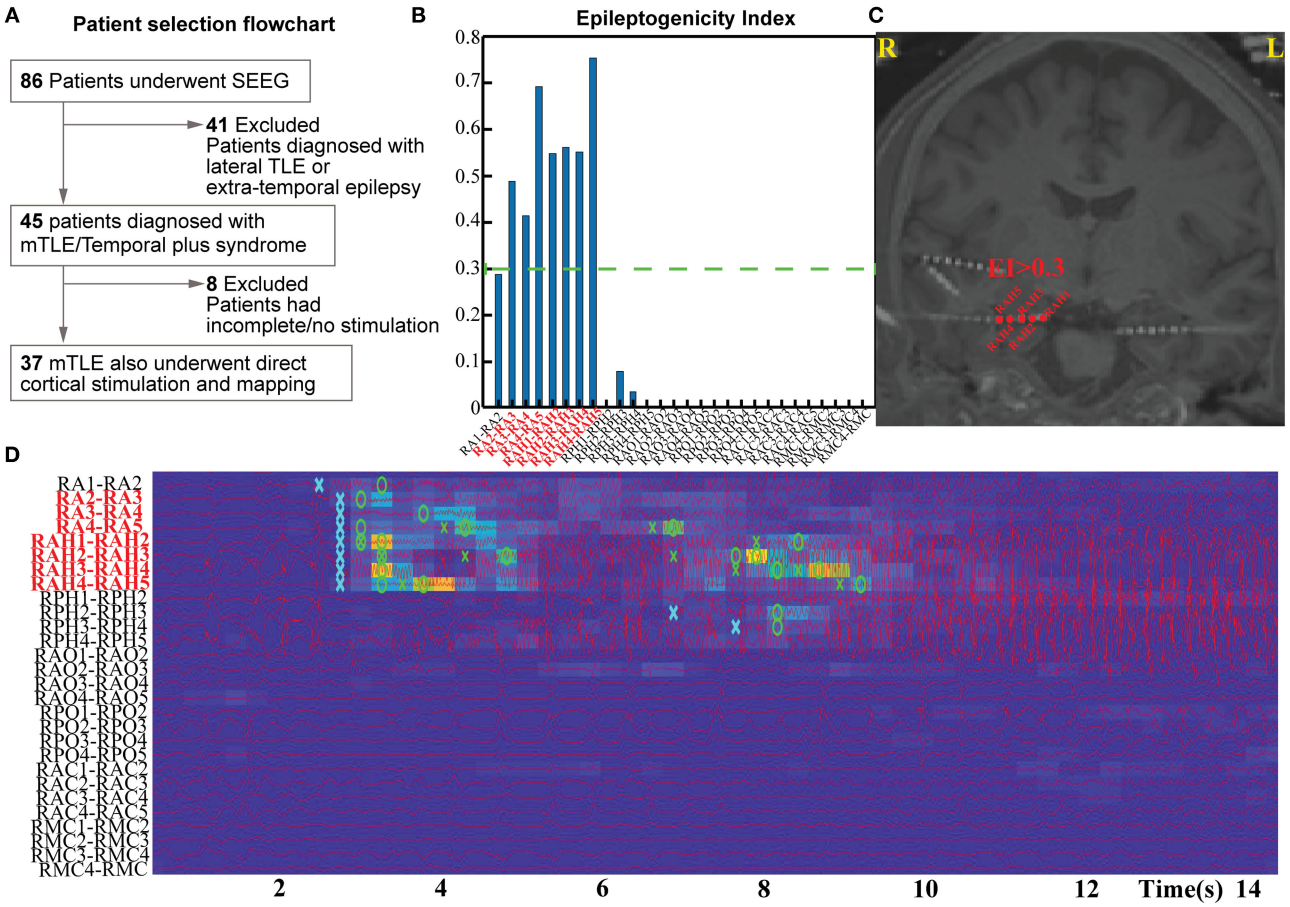

FIGURE 1 | Patient selection flow chart **(A)** and estimation pipeline for Epileptogenicity Index (EI) for their seizures **(B–D)**.

0.3 (calculated from all available seizures per patient). Multiple seizures (2–8) were analyzed per subject to estimate the EI.

Electrographic Patterns at Seizure Onset

Electrographic seizure onset patterns have been associated with various epileptogenic lesions, distribution of high-frequency oscillations, and surgical outcomes (19–21). Although a repertoire of electrographic onset patterns has been reported, we restricted the seizure onset patterns to three predominant types due to the limited sample size. These patterns were: hypersynchronous patterns (HYP), low amplitude fast activity (LAFA), or mixed if they had both LAFA and HYP features intermixed at the seizure onset.

Direct Cortical Stimulation

DCS was performed (Nicolet® stimulator) by the epileptologist responsible for the surgical evaluation of the patient while admitted to the epilepsy monitoring unit (EMU). At the time of DCS, the clinician was unaware of the EI-identified nodes. The stimulation was performed toward the end of the EMU admission after spontaneous seizures were recorded and anti-seizure drugs were resumed. At our institute, stimulation is performed between bipolar channels at stimulation frequencies of either 50 or 1 Hz. Pulses were biphasic with pulse-widths ranging between 200 and −400 μ s. The stimulation trial begins with a brief survey of increasing current amplitudes (range 1–8 mA) tested in one or two brain regions (always remote to the seizure onset sites) to evaluate the threshold for after-discharges. Once the threshold is determined, the current strength for the subsequent trials is kept relatively unchanged. The most common current strength ranged between 3 and 5 mA (median 4 mA) that was delivered for 3–4 s for 50 Hz trials and 10 s for 1 Hz trials. Each stimulation session lasted between 45 min and 2 h, and in some patients, multiple sessions were performed over several days. The patient was awake during the stimulation, and the family was allowed to stay at the bedside. Parenteral lorazepam was available at the bedside to treat evoked seizures that were secondarily generalized. Video EEG of the stimulation sessions was archived for future reporting.

Definition and Interpretation of Electroclinical Responses to DCS

The nodal responses to DCS can be summed by characterizing electrographic and clinical changes (**Figure 2**). The following are the definitions used in this study:

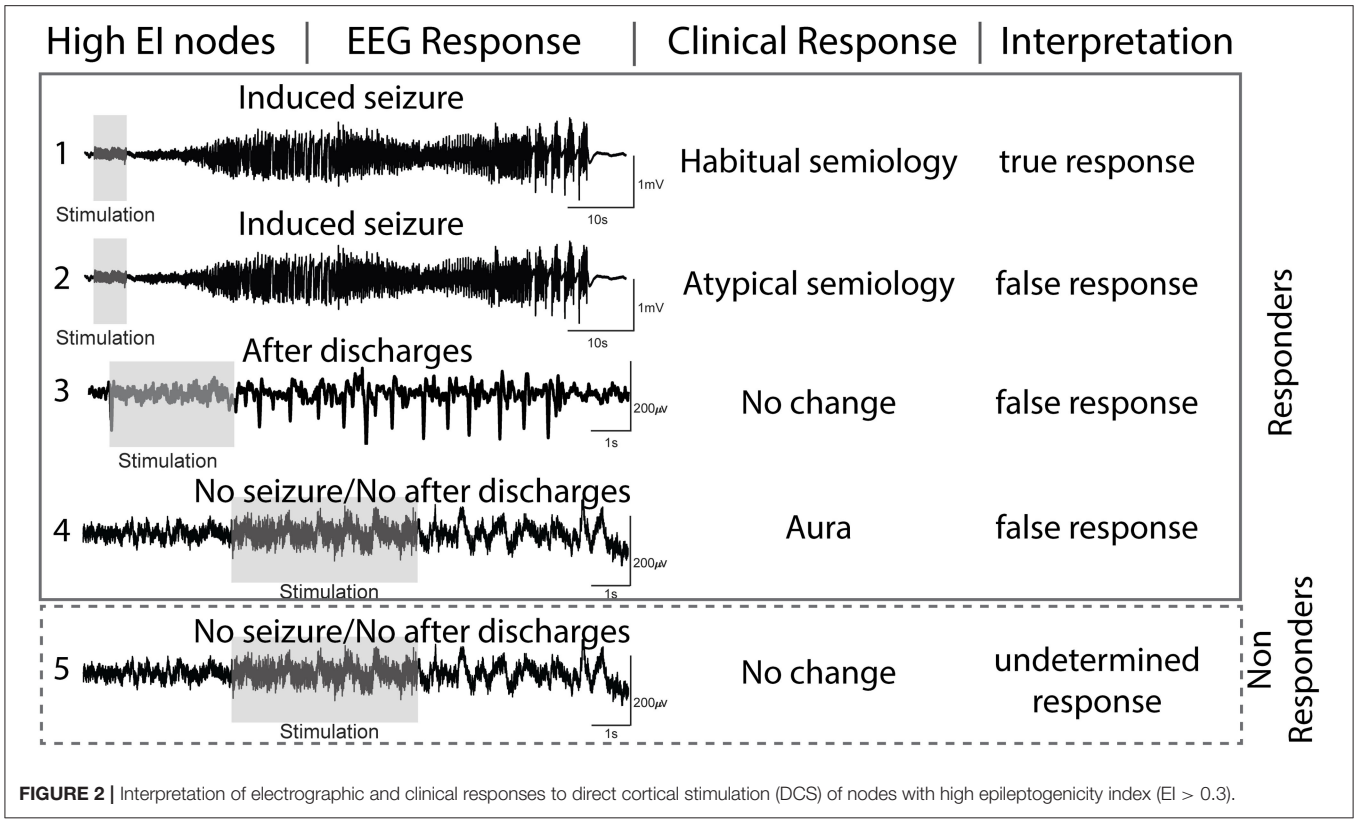

FIGURE 2 | Interpretation of electrographic and clinical responses to direct cortical stimulation (DCS) of nodes with high epileptogenicity index (EI > 0.3).

(a) After-discharges (AD)- After discharges were defined as rhythmic discharges (spikes, poly-spikes, sharp waves, or spike-wave complexes), which were clearly distinct from the pre-stimulation electrographic activity and occurred immediately following DCS (22). Any clinical symptoms did not accompany the discharges.
(b) Seizures (typical and atypical)- DCS-induced seizures were defined as trains of AD's that evolved morphologically, spatially, and/or in frequency and were accompanied by clinical manifestations. If the patient or family members recognized the behavioral changes as similar to spontaneous seizures, then we defined them as a habitual seizure. All other evoked seizures, including electrographic seizures, were considered atypical. Semiology was classified as: focal aware seizures (FAS), focal impaired awareness seizures (FIAS), and focal to bilateral tonic-clonic seizures (FBTCS) (23).
(c) Clinical response only- The term was reserved for patient-reported symptoms (e.g., motor activity or unusual feeling) evoked with DCS that lacked any electrographic changes (AD or seizure).
(d) No response (NR)- With DCS, there was no AD or seizure, and the patient did not report any clinical symptoms.

Based on the above-mentioned definitions, we interpreted the evoked electroclinical responses of the high EI nodes to DCS as-

(a) true response (TR) when the high EI nodes evoked a habitual seizure.
(b) false-response (FR) when high EI nodes failed to evoke a habitual seizure but either (1) evoked AD's, (2) evoked an atypical seizure, or (3) evoked a clinical response only. Since seizures are an all-or-none phenomenon, the presence of AD'sa confirmed that the node was stimulated adequately but failed to evoke a seizure. The presence of a clinical response without electrographic changes also ruled out a seizure and was interpreted as a false response.
(c) undetermined response (UR): high EI nodes that failed to evoke any response (electrographic or clinical) to DCS were considered undetermined as one cannot confirm with certainty if the nodes were stimulated adequately. Lack of response to DCS can be due to suboptimal stimulation.

Seizure Outcome

We used the Engel scale to classify the outcome of interventional therapy (resection, ablation, or neuromodulation) at the last clinic visit. The median range in clinical follow-up post-intervention was eleven months, and the range was between 5 months and 4.2 years. Engel class I indicated free of disabling seizures; Engel class II, rare disabling seizures; Engel class III, worthwhile improvement; and Engel class IV, no worthwhile improvement.

Statistical Measures

Based on the nodal responses to DCS, the diagnostic yield of high EI nodes were estimated as

(a) Responder rate = TR + FR/ TR + FR + UR
(b) Non-responder rate = UR/TR + FR + UR
(c) True responder rate: TR/TR + FR
(d) False responder rate: FR/FR + TR

Chi-square statistical analysis with a significance set at $p < 0.05$ was performed to evaluate if a nodal response (vs. no response) was different for the two EEG onset patterns (LAFA vs. HYP). Fisher exact test was performed to assess the responses (true or false response) of the nodes localized within vs. outside the clinically defined seizure onset zone.

RESULTS

Cohort Demographics

Thirty-seven patients (female = 23) with a median age of 37 years (range 19–63 y) met the inclusion criteria (**Table 1**). The total number of depth electrodes implanted was 460 (median 12, range 7–20). Eighteen subjects had a bilateral implant. The seizure onset regions were mesial TLE (amygdala, hippocampus) and TLE-plus ($N = 13$), where the seizure foci extended beyond the amygdala-hippocampus to the insula, superior temporal gyrus, or orbitofrontal regions. Eleven patients (30%) had an epileptogenic lesion (e.g., hippocampal sclerosis, focal cortical dysplasia) identifiable in the preoperative brain MRI. One-hundred and sixty seizures (median 5 per subject) were analyzed to identify the high EI nodes. Twelve patients underwent subsequent anterior temporal lobectomy, five had an extended temporal lobectomy, and seven had Responsive Neurostimulation (RNS) Therapy.

High EI Nodes That Responded to DCS

Overall, in 37 patients, there were 112 high EI nodes (range 1–5 nodes per subject). Of the 112 stimulated nodes, 92 (82%) responded to DCS (**Figure 3A**). The remaining 20 (18%) were non-responders, i.e., they did not result in electrographic or clinical response to DCS. The LAFA pattern had a significantly higher responder rate than the HYP ($p < 0.00001$). Among the non-responders, the predominant electrographic onset patterns were mixed ($n = 12$, 60%) followed by HYP ($n = 5$) patterns (**Figure 3B**).

High EI Nodes With a True Response to DCS

Forty-one nodes (37%) responded positively to DCS, i.e., evoked an electroclinical habitual seizure. The *true responder rate* of a high EI node was 44.5%. Among the true responders, 52% had LAFA, 41% had mixed, while 7% had a hypersynchronous pattern of seizure onset. Overall, there were 30 evoked FSA and 13 FIAS seizures. The concordance of an evoked habitual seizure with a clinically identified SOZ that had Engel I or II outcome was over 50% ($p = 0.0025$) (**Figure 3C**), and the regions were mostly hippocampus and amygdala ($N = 12$), although there were few insular and anterior cingulate regions (**Table 1**). These patients had a follow-up over 2–4 years after resection.

TABLE 1 | Clinico-demographic characteristics of the patients.

Patients	***N* = 37**
Age (years)	38.13 ± 11.44
Gender (male: female)	14:23
Duration of epilepsy (years)	14.69 ± 11.68
MRI pathology laterality	
Normal	13
Bilateral	10
Right	10
Left	4
MRI pathology type (epileptogenic lesion)	11 (30%)
Electrode implant laterality	
Left	11
Right	8
Bilateral	18
Number of electrodes per patient [median (range)]	12 (7–20)
SEEG seizure onset pattern	
Hypersynchronous (HYP)	12
Low amplitude fast activity (LAFA)	12
Mixed	13
Number of seizures analyzed to measure EI [total (median, range)]	160 (5, 2–8)
Stimulation protocol types (number of trials across all patients)	
50Hz,5–6mA	8
50Hz,4–8mA	1
50Hz,4–6mA	12
50Hz,4–5mA	3
1Hz,5—mA	7
50Hz,4–7mA	2
50Hz,5–7mA	7
50Hz,6–7mA	2
50Hz,3–5mA	1
SEEG seizure onset zone localization	
TLE (hippocampus amygdala complex)	24
TLE+ (ictal changes beyond mesial temporal structures)	13
Post SEEG therapy	
Anterior temporal lobectomy	12
Extended anterior temporal lobectomy	3
Other resections (temporal pole resection, cingulate, OF)	3
RNS	10
Awaiting treatment or patient declined intervention Rx	7
Stimulated high EI nodes across all patients (total, range/patient)	112, 1–5 contacts/patient
Responsive contacts	92 (82%)
Non responsive contacts	20 (18%)
Engel outcome for patients with resection (*N* of patients)	
Engel I	9
Engel II	8
Engel III	1
Engel outcome for patients with RNS (*N* of patients)	
Engel I	0
Engel II	3
Engel III	7

TLE, temporal lobe epilepsy; EI, epileptogenicity index; RNS, responsive neurostimulation; OF, orbitofrontal.

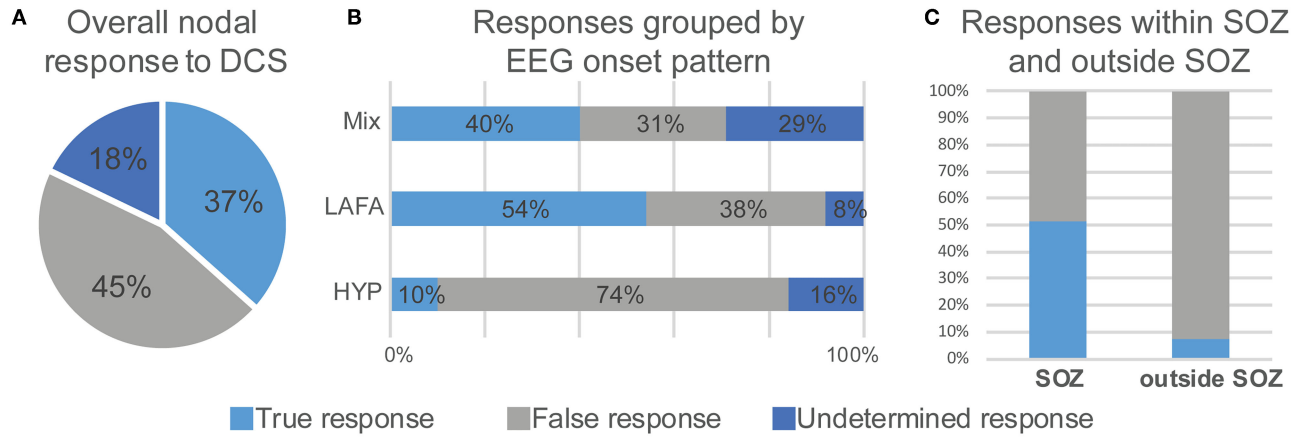

FIGURE 3 | Electroclinical responses to direct cortical stimulation (DCS) of nodes with high epileptogenicity index (EI > 0.3). Overall nodal responses **(A)** and distribution of responses as a function of seizure onset pattern **(B)** and colocalization with seizure onset zone **(C)**. LAFA = low amplitude fast activity. HYP, hypersynchronous onset; SOZ, seizure onset zone.

High EI Nodes With a False Response to DCS

Fifty-one nodes (45%) had a false response, with the presence of either AD's ($n = 49$), an atypical seizure ($n = 1$), or clinical symptoms without electrographic changes ($n = 1$). The *false responder rate* of a high EI node was 55.4. Hypersynchronous patterns (45%) yielded the maximum number of false responses, followed by LAFA (29.4%). After-discharges were the most common false responses (**Figures 4**, **5**). The HYP pattern had ADs predominantly in the amygdala and hippocampus contralateral to clinical SOZ. For LAFA, the nodes were localized to the insula, posterior temporal, basal temporal, and lateral prefrontal regions.

DISCUSSION

DCS is a valuable tool in assessing the epileptogenic cortex and is essential in planning epilepsy surgery (24). DCS is used for functional mapping of the eloquent cortex and to delineate surgical resection margins by identifying hyperexcitable structures within the seizure generating network (25). Stimulation-induced seizures have been co-localized with spontaneous seizures, interictal pathological high-frequency oscillations and positively correlated with post-resection seizure-free outcomes (25–28). In the present study, we used DCS to investigate the ictogenicity of the putative epileptogenic nodes that had high EI values (>0.3). We demonstrated that the ictogenicity (i.e., inducing the patient's habitual seizure) of a high EI node is only 44.5%, while 55.4% failed to induce a seizure but had runs of after-discharges.

Electrographic Onset Pattern Influenced Response to DCS

The LAFA onset pattern had a significantly higher responder rate to DCS (i.e., had a higher propensity to induce a seizure), while the HYP pattern yielded maximum false responses (i.e., had runs of AD's instead of seizures). The results are in agreement with a previous modeling study and underscore the differences in the mechanism of seizure genesis between the two patterns (29–31). The LAFA onset is initiated by the coalescence of multiple scattered regions of localized high-frequency activity over time (32). The EI overestimated the number of nodes for the LAFA pattern, and these nodes were localized outside the clinically identified SOZ, often in the temporal or frontal neocortex. Importantly, these nodes failed to evoke a seizure but had after-discharges. The HYP onset is characterized by an increase in the excitability of the surrounding tissue, which by itself does not generate seizures, but can support seizure activity. The lower ictogenicity and the higher false response rate of HYP in our study concur with the hypothesized mechanism.

Probing High EI Nodes With DCS: A Translational Approach to Map Seizure Onset Network

The goal of intracranial EEG investigation is to delineate the brain regions that are involved in seizure generation, and this can be more challenging in MRI-normal non-lesional cases, typically necessitating a greater number of depth electrodes (median 12 in our cohort). DCS mapping of evoked seizures is an accepted approach to confirm the SOZ and co-localization have been positively correlated with good surgical outcomes. However, stimulating over 100–150 contacts is not feasible in routine clinical practice and is likely to be unpleasant for the patient. Rather, a targeted approach using DCS to probe high EI nodes can be more time-efficient and can distinguish hyperexcitable nodes involved in seizure generation (true responder) from nodes supporting early propagation (false responder). Such an approach in the future may also guide therapeutic decision-making by localizing more precise targets for laser therapy for a focal onset or facilitating placement of responsive neuromodulation stimulation electrodes.

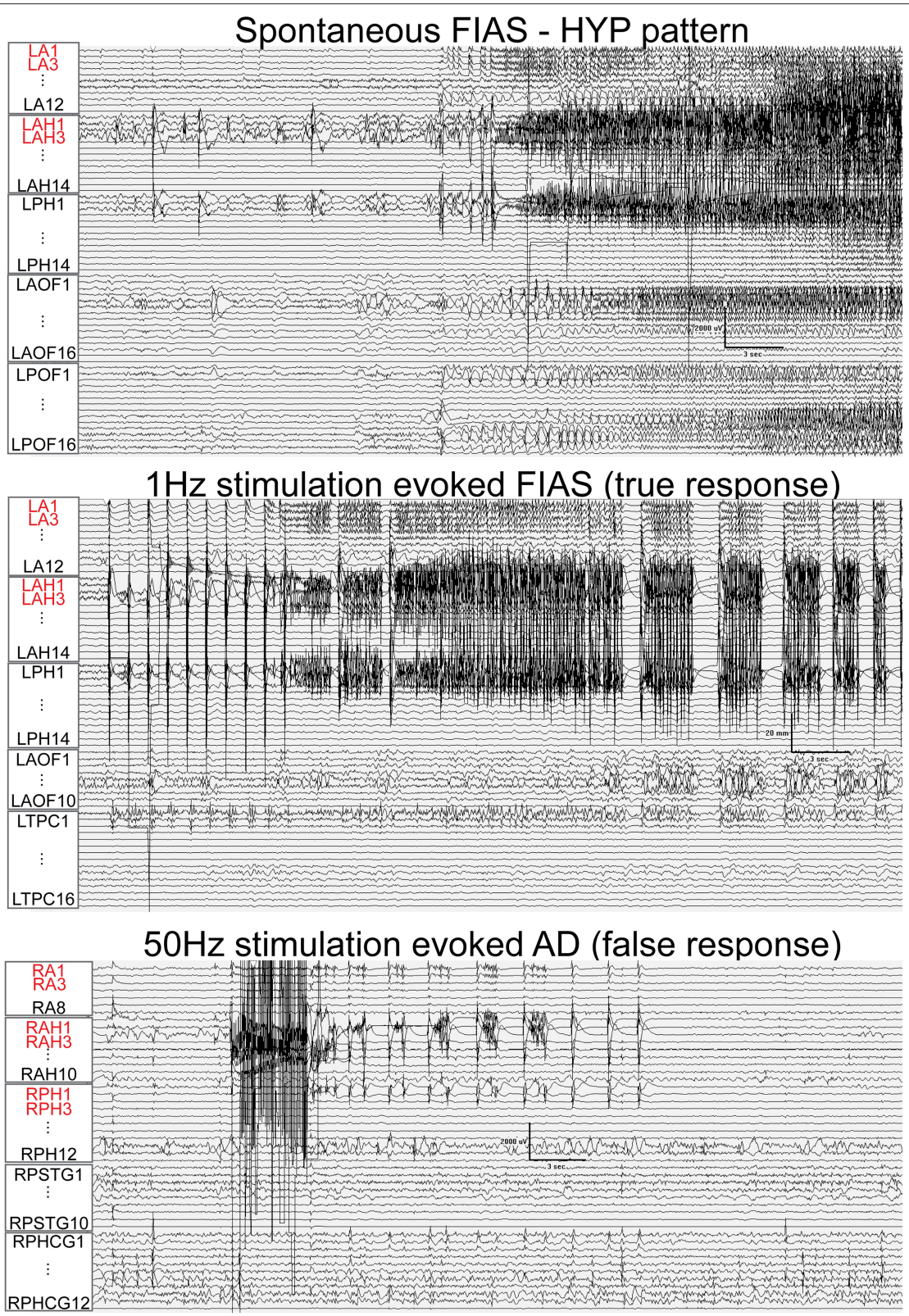

FIGURE 4 | Train of 1 Hz and 50 Hz stimulation of hippocampus evoked seizure (true response) and after-discharges (AD, false responses) in different patients that had hypersynchronous (HYP) electrographic onset pattern of spontaneous seizure. Nodes with a high epileptogenicity index (>0.3) are highlighted in red. HYP, hypersynchronous pattern; FIAS, focal impaired awareness seizure.

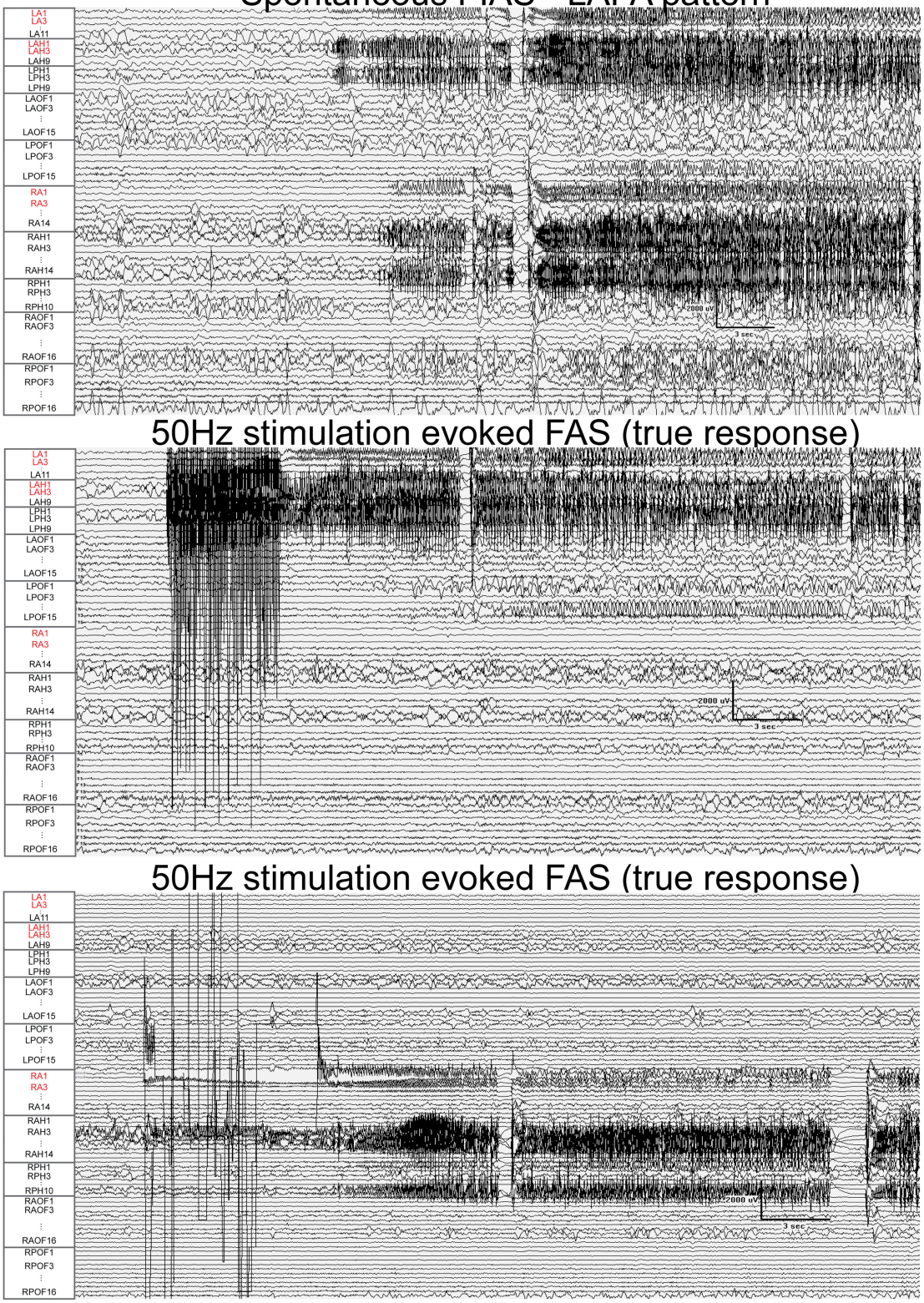

FIGURE 5 | Fifty Hertz stimulation of left hippocampus and right amygdala evoked seizures (true responses) in a patient with bi-temporal epilepsy. Nodes with a high epileptogenicity index (>0.3) are highlighted in red. The spontaneous seizure had LAFA (low amplitude fast activity) pattern that emanated from the left hippocampus with a rapid propagation to the left amygdala, right amygdala, and hippocampus. FAS, focal seizure with retained awareness. FIAS, focal impaired awareness seizure.

Study Limitations

The study had three major limitations. 1) The responses to DCS were only restricted to high EI nodes. Although DCS was performed in nodes with lower EI (<0.3), due to the heterogeneity in the sparse data, we could not perform meaningful statistics. An ideal study to assess EI's diagnostic yield (sensitivity, specificity) should include stimulation of a significant proportion of nodes (both low and high EI) in a large cohort prospectively. Planning such a study should also involve ethical approval as a patient-level of tolerance and safety should be considered. The second limitation is the inability to correlate true responsive nodes with the surgical outcome, as anterior temporal lobectomy (performed in 38% of our cohort) included structures beyond just the high EI nodes (like hippocampus and amygdala). A focal therapy such as LITT could provide a more accurate correlation of nodal response to outcome in the future (33). 2) The presence of anti-seizure drugs could have influenced the cortical excitability and response to DCS. However, restarting medications before DCS is commonly practiced to prevent evoked tonic-clonic seizures.

CONCLUSION

In the present study, we used DCS to investigate the ictogenicity of putative epileptogenic nodes with high EI values (>0.3). We observed that ictogenicity (i.e., the propensity to induce habitual seizures) of a high EI node is only 44.5%, while 55.4% failed to induce a seizure but had runs of ADs. The LAFA onset pattern had a significantly higher responder rate to DCS (i.e., induced a seizure), while the HYP pattern yielded maximum false responses (i.e., runs of AD's without seizures). The information may be used to support targeted mapping of SOZ in LAFA onset patterns by performing DCS in high EI nodes to distinguish seizure generators (true responders) from hyperexcitable nodes that may be involved in early propagation.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: requests to access the datasets must first be approved by the University of Alabama at Birmingham (UAB) Institutional Review Board (IRB). Requests to access these datasets should be directed to Sandipan Pati, patilabuab@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UAB IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AI curated the data, performed analysis, and helped in drafting the manuscript. GC, ET, and DP helped in data analysis and revised the manuscript. SP obtained approval and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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More Than Spikes: On the Added Value of Non-linear Intracranial EEG Analysis for Surgery Planning in Temporal Lobe Epilepsy

*Michael Müller[1], Martijn Dekkers[2], Roland Wiest[1], Kaspar Schindler[2] and Christian Rummel[1]**

[1] Support Center for Advanced Neuroimaging (SCAN), University Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern, Switzerland, [2] Department of Neurology, Inselspital, Bern University Hospital, University Bern, Bern, Switzerland

Epilepsy surgery can be a very effective therapy in medication refractory patients. During patient evaluation intracranial EEG is analyzed by clinical experts to identify the brain tissue generating epileptiform events. Quantitative EEG analysis increasingly complements this approach in research settings, but not yet in clinical routine. We investigate the correspondence between epileptiform events and a specific quantitative EEG marker. We analyzed 99 preictal epochs of multichannel intracranial EEG of 40 patients with mixed etiologies. Time and channel of occurrence of epileptiform events (spikes, slow waves, sharp waves, fast oscillations) were annotated by a human expert and non-linear excess interrelations were calculated as a quantitative EEG marker. We assessed whether the visually identified preictal events predicted channels that belonged to the seizure onset zone, that were later resected or that showed strong non-linear interrelations. We also investigated whether the seizure onset zone or the resection were predicted by channels with strong non-linear interrelations. In patients with temporal lobe epilepsy (32 of 40), epileptic spikes and the seizure onset zone predicted the resected brain tissue much better in patients with favorable seizure control after surgery than in unfavorable outcomes. Beyond that, our analysis did not reveal any significant associations with epileptiform EEG events. Specifically, none of the epileptiform event types did predict non-linear interrelations. In contrast, channels with strong non-linear excess EEG interrelations predicted the resected channels better in patients with temporal lobe epilepsy and favorable outcome. Also in the small number of patients with seizure onset in the frontal and parietal lobes, no association between epileptiform events and channels with strong non-linear excess EEG interrelations was detectable. In contrast to patients with temporal seizure onset, EEG channels with strong non-linear excess interrelations did neither predict the seizure onset zone nor the resection of these patients or allow separation between patients with favorable and unfavorable seizure control. Our study indicates that non-linear excess EEG interrelations are not strictly associated with epileptiform events, which are one key concept of current clinical EEG assessment. Rather, they may provide information relevant for surgery planning in temporal lobe epilepsy. Our study suggests to incorporate quantitative EEG

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***Correspondence:**
Christian Rummel
crummel@web.de

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analysis in the workup of clinical cases. We make the EEG epochs and expert annotations publicly available in anonymized form to foster similar analyses for other quantitative EEG methods.

Keywords: epilepsy, epileptiform events, quantitative EEG, epilepsy surgery, non-linear interrelations

1. INTRODUCTION

Surgical removal of seizure-generating brain tissue is an established and often beneficial treatment option for patients with drug-resistant epilepsy. Identification of the tissue necessary and sufficient to cease seizure activity [the "epileptogenic zone," EZ, (1, 2)] is essential but challenging, especially if there is no obvious anatomical correlate (as e.g., a brain lesion or tumor).

The decision on which area to resect and how this will putatively influence epileptic activity is individually determined for each patient, taking various diagnostic information sources into consideration (including scalp EEG, structural and functional MRI, psychological assessments and intracranial EEG if necessary). Although these assessments usually follow established concepts like the importance of the "seizure onset zone" (SOZ), which is used as a proxy for the EZ, the procedure suffers from a considerable amount of subjectivity. The limitations of the current approaches regarding reliable prediction of the patients' benefit from epilepsy surgery are apparent, since only about half of all patients undergoing surgery become permanently seizure free, a rate that has practically not improved over decades (3–10). This issue is strongly associated with the heterogeneity of the disorder. It is now generally accepted that epilepsy needs to be considered a network-based disease, characterized by the interaction of multiple brain regions (11–15). Due to the lack of methodologies allowing to record brain activity with simultaneously high spatial and temporal resolution and full coverage, seizure dynamics are still not understood in full detail.

Intracranial EEG (iEEG) is currently the gold standard in this regard, providing excellent temporal and spatial resolution with the drawback of limited spatial coverage. However, purely visual analysis is limited due to the abundance of potential interrelations between dozens of iEEG channels (16), exacerbated by the ever-growing amount of data due to increasing spatial resolution (17) and recording time (18, 19). Quantitative EEG (qEEG) methods, capable of capturing a variety of signal properties (including very complex, visually undetectable ones) and processing large amounts of data have been presented over the last decades. They hold great promise to discern and provide additional information and ultimately increase the success rate of epilepsy surgery. High frequency oscillations (80–500 Hz) have long been considered a promising marker of the EZ (20–22). Along with the network conception of epilepsy, multivariate methods, quantifying signal dependencies, gained increasing attention [see (23, 24) for reviews]. In congruence with the strong evidence for high non-linearity of epileptic activity (25–29), segregated non-linear signal dependencies have been demonstrated to contain relevant information (27, 30).

Despite a large variety of qEEG measures have shown to capture some disease-related properties, none is applied in clinical routine to date. Besides undefined standardization of methods and interpretation and a lack of implementation in certified software, one reason might be the suspicion that qEEG markers could only be sensitive to signal features that are similarly detectable by visual expert analysis, like e.g., frequent interictal spikes (31). Thus, besides an extensive evaluation of qEEG measures, a better understanding to what extent these are related to traditional markers of epilepsy and what they might reflect beyond, will be very helpful in the effort to gain clinical acceptance.

Strictly speaking, the epileptogenicity of brain tissue (i.e., its belonging to the EZ, a theoretical concept) is not accessible by iEEG or any other current mapping technique. This implies that when aiming to identify markers that are closely associated with the brain tissue's epileptogenicity, one is confronted with the problem of a missing ground truth. The SOZ can be visually determined by experts from the transition from preictal to ictal EEG *before* surgery (i.e., agnostic of post-surgical seizure control) but is known to be only an approximation of the EZ (1). In addition, the extent of its observation depends on electrode placement. On the other hand, the resected brain tissue (RBT) is available only in patients who undergo surgery, often larger than minimally required and (by definition) fully contains the EZ only in patients who became seizure free. From this we hypothesized that the ability of any marker of epileptogenicity to determine the RBT should be larger in patients who became seizure free after surgery than in patients with unfavorable outcome. In contrast, the agreement between the SOZ and any marker of epileptogenicity might depend on post-surgical seizure control only indirectly.

In our previous study (32), we have demonstrated for patients with mesiotemporal implantation of depth electrodes that surrogate corrected non-linear interrelations between iEEG signals were associated with the individual pathology. In addition, the spatial overlap of salient non-linear interrelations with the RBT was associated with post-surgical seizure control. Here, we investigated the relationship between the occurrence of salient non-linear interrelations and traditional markers of epileptogenicity (33), namely spikes, slow waves, sharp waves, and fast oscillations, as identified by a human expert. In addition, we determined the relationship with the SOZ and where applicable with the RBT. We manually annotated and analyzed 99 preictal epochs of multi-channel iEEG from 40 patients including several types of epilepsy syndromes and etiologies as well as electrode implantation schemes beyond mesio-temporal depth electrodes. To reduce data heterogeneity, we limited our main analyses to patients with seizure onset in the temporal lobe, which were the vast majority in our

dataset (32/40). Explorative examination of patients with a non-temporal seizure onset (six frontal, two parietal) are provided in the **Supplementary Materials**. To assess the association of epileptogenic brain tissue with EEG markers (be they visual or quantitative), we contrasted accuracy quantifiers on the channel level between patients with favorable and unfavorable post-surgical outcomes.

To foster similar analyses, we make the full EEG recordings and expert annotations used in this paper publicly available in anonymized form via GitHub together with a custom EEG reader (github.com/SCAN-NRAD/scanEEGviewer).

2. METHODS

2.1. Patients and Data

We included data of 40 patients with drug-resistant epilepsies, who were considered for epilepsy surgery at the Inselspital Bern (58% female, median age 35 years, IQR 19 years, range 9 − 66 years). More detailed patient information is provided in **Table 1**. To characterize success of the intervention, we used the first available outcome assessment at least three months after surgery according to the Engel scale. The first assessment is most representative of the direct effects of the surgery, not influenced by subsequent effects like neuronal plasticity and changes in patient compliance, which might change the long-term outcome but are hardly predictable. In total, 19 patients became completely seizure free (Engel class I), 4 patients became almost seizure free (Engel class II), 4 patients had worthwhile improvement (Engel class III), and 7 patients had no improvement (Engel class IV). In the group analyses presented in the main text we only included patients with seizure onset in the temporal lobe to preserve data homogeneity. The results for the remaining patients are compiled in the **Supplementary Materials**. At the same time, to increase sample size, we dichotomized outcomes into "favorable" (Engel classes I & II) and "unfavorable" (Engel classes III & IV). Using coregistration of a post-implantation CT and a postsurgical MRI, the patient-specific RBT and thereby the iEEG channels recording from this tissue were determined [see (34) for a detailed description of this procedure].

This study was approved by the Ethics Committee of the Kanton of Bern (approval number 2017-00697). All decisions regarding the actual treatment of the patients (especially implantation and resection) were made solely on clinical grounds prior to this retrospective study and all patients gave written and informed consent that EEG and imaging data may be used for research purposes.

2.2. EEG Data, Epoch Selection, and Manual Annotation

EEG data was recorded using a NicoletOneTM recording system with a C64 amplifier (VIASYS Healthcore Inc., Madison, Wisconsin, USA) and intracranial depth, strip, and grid electrodes (AD-TECH, Wisconsin, USA). The sampling rate was 512 or 1,024 Hz, depending on whether more or less than 64 channels were used. Signals were referenced to an extracranial electrode (localized between 10–20 positions Fz and Cz) during recording and later re-referenced against the median of all artifact free channels. In addition, signals were band-pass filtered between 0.5 and 150 Hz using a fourth-order Butterworth filter.

Since the extensive manual annotation of iEEG data, typically comprising between 50 and 60 channels, is very time-consuming, it was impossible to analyze the entire long-term EEG recordings. In addition, the calculation of the qEEG measure used in this study (see below) is computationally expensive and prohibits long-term analysis beyond the range of minutes. In consequence, a compromise between epoch duration included per patient and the number of patients was inevitable. To minimize bias toward patients with many seizures we restricted the number of iEEG epochs per patient to at most three. All epochs had a duration between 110 and 200 s and ended at seizure onset. Permanently artifact corrupted channels (according to visual analysis by experts) were excluded from detailed visual or quantitative analysis ($< 5\%$ of channels).

Several studies have shown that epilepsy dynamics underlie oscillations on various timescales, from circadian to multidien rhytms (35–39). Correspondingly, network measures calculated from iEEG data exhibit large circadian variations (40). To confine the arbitrariness of temporal data selection, we chose in each patient segments directly preceding the earliest artifact-free seizures recorded after implantation of the intracranial electrodes. This period serves as a relevant baseline for visual EEG analysis in clinical routine, and in contrast to ictal data, avoids artifacts that might be caused by seizure manifestation.

A clinical expert (M.D.) visually inspected all included iEEG epochs and manually annotated the extent of all epileptiform events (33) regarding time of occurrence and affected channels, corresponding to at least one of the following types: (1) spikes, (2) slow waves, (3) sharp waves, (4) fast oscillations. Channels were scored in a custom EEG-reader in referential mode. We scored pre-ictal transients as typical for epilepsy based on its sharp configuration and compared to the background activity in the same channel, looking either for high amplitudes or a disruption of ongoing rhythms. We distinguished spikes (duration < 70 ms) and sharp waves (duration $70 - 200$ ms). Slow wave activity was scored based on either a marked focal slowing of background activity, or the presence of slow waves with a high amplitude compared to the background activity. Fast oscillations were identified as episodes of focal activity with a frequency above 30 Hz. In addition, the channels comprising the seizure-specific SOZ were identified based on the presence of low-amplitude fast activity at seizure onset.

2.3. Non-linear Signal Dependence and Identification of Core Channels

The qEEG measure used in this study was introduced by Rummel et al. (34, 41) and has been applied in (32, 42, 43). A similar measure was also used in (16, 27, 30). In brief, non-linear interrelation matrices were determined by calculating mutual information of signal pairs over segments of 8 s duration, which were shifted over the entire epoch by 1-s steps. Mutual information quantifies the amount of information one signal provides about the other. Since it is sensitive to both linear

TABLE 1 | Patients included in this study.

Patient	Engel class	epoch dur. [s]	Seizure onset	Histology/MRI	Type of resection	# of channels	# of ch. in RBT
p1	I	180/176/182	T (B)	Non-lesional	TPE + SAHE (R)	102	13
*p2	I	182/177	T (R)	Hippocampal sclerosis	T2/3E	32	5
*p3	I	199/179	T (R)	Hippocampal sclerosis	T2/3E	38	8
*p4	I	179/170	T (R)	Hippocampal sclerosis	SAHE	31	13
*p5.1	I	167/169	F (L)	Ectopic Neurons	LE SMA	76	7
p5.2	I	177/176	F (L)	Ectopic Neurons	LE SMA	86	14
*p6	I	170/180	T (R)	Hippocampal sclerosis	SAHE	32	7
p7	I	180/177/181	T (L)	Hippocampal sclerosis	LE	37/35/34	8/8/7
p8	I	185/183	T (L)	Hippocampal sclerosis	T2/3	64	13
p9	I	197/188	T (L)	Non-lesional	TLE	56	5
p10	I	176/184/180	T (R)	Hippocampal sclerosis	SAHE	34	10
*p11	I	140/129/123	T (R)	Hippocampal sclerosis	TPE + SAHE	37/38/38	9
p12	I	178/166	T (L)	Glioma	LE T	74	13
p13	I	147/155	F (R)	Hemorrhage	LE	80	6
p14	I	115/122	T (L)	Bilateral HC sclerosis	SAHE	59	17
p15	I	185/171/179	T (L)	Hippocampal sclerosis	LE T	40	11
*p16	I	164/185	T (R)	Hippocampal sclerosis	LE MT	32	4
p17	I	180/181	F (R)	Non-lesional, mild FCD	LE	66	5
*p18	I	151/166	T (L)	Hippocampal sclerosis	SAHE	31	7
*p19	I	174/177	F (L)	Post-traumatic lesion	LE F	88	7
*p20	II	177/182	T (L)	Hippocampal sclerosis	TLE + SAHE	48	7
p21	II	186/180	T (L)	Other abnormal	TLE + SAHE	32	16
p22	II	183/180	T (R)	Non-lesional	SAHE	99	11
*p23	II	185/182/187	T (L)	Post-ischemic cyst	LE MT	29	2
*p24	III	180/179/158	F (L)	Non-lesional, FCD Ib	LE	69/70/70	6/4/4
p25	III	188/180	F (R)	FCD II	LE F+T	92	8
*p26	III	154/186	T (L)	Non-lesional	T2/3E	32	9
*p27	III	158/186/182	T (R)	Discrete alterations	SAHE	76	16
p28.1	IV	180/179	T (L)	Other abnormal	LE	59	2
p29.1	IV	182/180/183	T (L)	Non-lesional, Meningitis	TLE	61	10
p29.2	IV	168/168/165	T (L)	Non-lesional, Meningitis	TLE	48	8
p30	IV	179/179	T (R)	Non-lesional, Gliosis	T2/3E	100	13
p31	IV	113/112	T (L)	MT asymmetry	T2/3E	49	8
p32	IV	181/178/180	P (L)	MT asymmetry	LE	92/94/94	4
p33	IV	113/120	T (L)	FCD IIb	LE MT	24	6
*p34	IV	182/184	T (B)	MT sclerosis	SAHE (R)	32	14
*p28.2		179/178	T (L)	Other abnormal		64	
*p35		180/180/177	T (B)	Thickened MT structures		32	
p36		180/189	T (L)	TO Pachygyria right		59	
p37		129/177	P (L)	FCD		68	
*p38		197/180/195	T (R)	Non-lesional		24	
*p39		178/181	T (B)	Other abnormal		32	
p40		179/180	T (R)	MT asymmetry		32	

*Indicated are the post-surgical seizure control according to the Engel classification scheme, durations of the included epochs, the location of seizure onset, etiological factors, the type of resection, the total number of artifact free channels, and the number of channels recording from RBT. Nineteen of these patients were already included in our preceding study (32) and are indicated by an asterisk *. One patient (p5) had two implantation schemes before resection, one patient (p29) had two distinct implantation schemes both followed by resection, and one patient (p28) had a second implantation after the surgical removal of brain tissue but no second resection.*

L, left; R, right; B, bilateral; T, temporal; F, frontal; P, parietal; FCD, focal cortial dysplasia; SMA, supplementary motor area; LE, lesionectomy; TLE, temporal lobectomy; TPE, temporal pole-ectomy; T2/3E, temporal 2/3 resection; SAHE, selective amygdala-hippocampectomy.

an non-linear dependences alike, we used multivariate iterative amplitude adjusted Fourier transform (IAAFT) surrogate time series with conserved Pearson correlation matrix (44) to account for linear interrelation effects. Non-zero elements of the resulting interaction matrices had significantly stronger mutual information than the surrogate time series with conserved Pearson correlation. Hence, the matrices describe the non-linear *excess* interrelations, i.e., the interrelation that is not measurable by linear measures. To condense information, we averaged the resulting matrices over time. Since patient-wise contrasting of separate averages over segments with and without epileptiform events (45) were not consistently possible due to too dense or too sparse event occurrence in some patients, we averaged the interrelation matrices over the entire preictal epochs. From the resulting mean interrelation matrix, we calculated the normalized "node strength" (i.e., the mean interrelation of a channel with the remainder). This single value per channel is confined to the range [0, 1] and indicates how strongly it is connected with all others. Based on the channels' connection strength, we automatically separated the most strongly connected channels by sorting all channels by their node strengths and identifying the largest difference between two adjacent values on the linear and the logarithmic scale (32, 46). We call these epoch-specific channel collections the "core" and based on our previous findings (32, 34) hypothesized them to be indicative of pathological epileptic activity.

2.4. Statistical Analyses

To rule out the possibility of systematic differences, we compared the following quantifiers between patients of different outcome groups: total number of channels implanted, total number and relative portion of channels containing events, epoch-wise average number of channels per event, average event duration, total epoch duration. Likewise, we compared the total number and relative portion of resected channels, core channels, and channels constituting the SOZ and RBT. Moreover, we tested for different proportions of event types depending on the patients' post-surgical seizure control.

We used non-parametric testing throughout this study because sample sizes were small and distributions potentially skewed. Since patients who did not undergo surgery are likely a mixture of the favorable and unfavorable outcome groups with respect to surgery independent quantifiers, we excluded them from all outcome-dependent statistical comparisons, which enabled Mann-Whitney *U*-tests (MWU) between only two groups. Nevertheless, we display these data in our figures to document that this patient group did not behave systematically different. To compare event proportions between different groups we used Chi-squared tests.

The main objective of this study was to investigate the association between the channel-wise occurence of epileptiform events identified by expert EEG reading and sets of iEEG channels defined by the SOZ, the RBT, and the core channels of non-linear excess interrelation (see Figure S1 of the **Supplementary Materials** for an illustration), which either require information aggregation, surgical intervention or quantitative analysis. This was done by studying the degree to which one of these channel sets predicted another. Besides, we also examined dependences between these sets. Specifically, we defined a predictive set of iEEG channels, and a target set of channels. We then labeled all channels according to whether they were part of both sets (true positives, TP), only part of the predictive set (false positives, FP), only part of the target set (false negatives, FN), or not part of any set (true negatives, TN). Whenever epileptiform events were used as predictors, we performed this analysis separately for the four event types as well as for all types in aggregation. For every epoch and patient, we then pooled true/false positives/negatives over all events (same type and aggregated). Among the other channel sets, we determined for each epoch the predictive power of the presurgically defined SOZ for the RBT, which becomes available only after surgery. Similarly, as a specific example of qEEG analysis, we have assessed the predictive power of the core of non-linear excess interrelations for both the SOZ and the RBT.

Since events and the aforementioned sets of channels typically only comprised a minority of all iEEG channels, the number of TN by far exceeded those of the other categories in virtually all cases, heavily biasing all dependent accuracy measures. To avoid such bias, we report our results in terms of the TN-independent quantities precision and recall. As an overall accuracy quantifier we used their harmonic mean, the F1-score (see **Supplementary Materials** for details). All these quantifiers range in the interval $[0, 1]$. The precision (also called positive predictive value) specifies how indicative the predictive set is for the target set. Low values indicate that channels in the predictive set are often not part of the target set (many FP). Recall (also called sensitivity) specifies to what degree the target set is determined by the predictive set. Low values indicate that channels of the target set are often missed by the predictive set (many FN).

For all statistics we used an uncorrected significance level $\alpha = 0.01$. Values $p < 0.05$ were interpreted as trends. Since each accuracy quantifier (precision, recall, F1-score) was tested for six different combinations of predictive and target sets, we applied Bonferroni correction when comparing predictions. The significance level was adjusted to $\alpha_{\text{Bonf}} = 0.0017$ and values $p < 0.0083$ were interpreted as trends.

3. RESULTS

In total, our data set contained 99 epochs of intracranial EEG. We found no outcome-dependent differences in the absolute numbers of artifact-free EEG channels, epoch duration, number of channels constituting the SOZ, RBT, or core channels of non-linear excess interrelation between iEEG channels (all $p > 0.09$, MWU). **Figure 1** illustrates the relation between iEEG waveforms, visually detectable epileptiform events (here slow and sharp waves, many of them outside the RBT) and the non-linear excess interrelations at the example of patient p10. The selected segment is representative for the total interrelation pattern and shows high precision as well as low recall regarding prediction of the RBT by channels of the core of non-linear excess interrelations or epileptiform events.

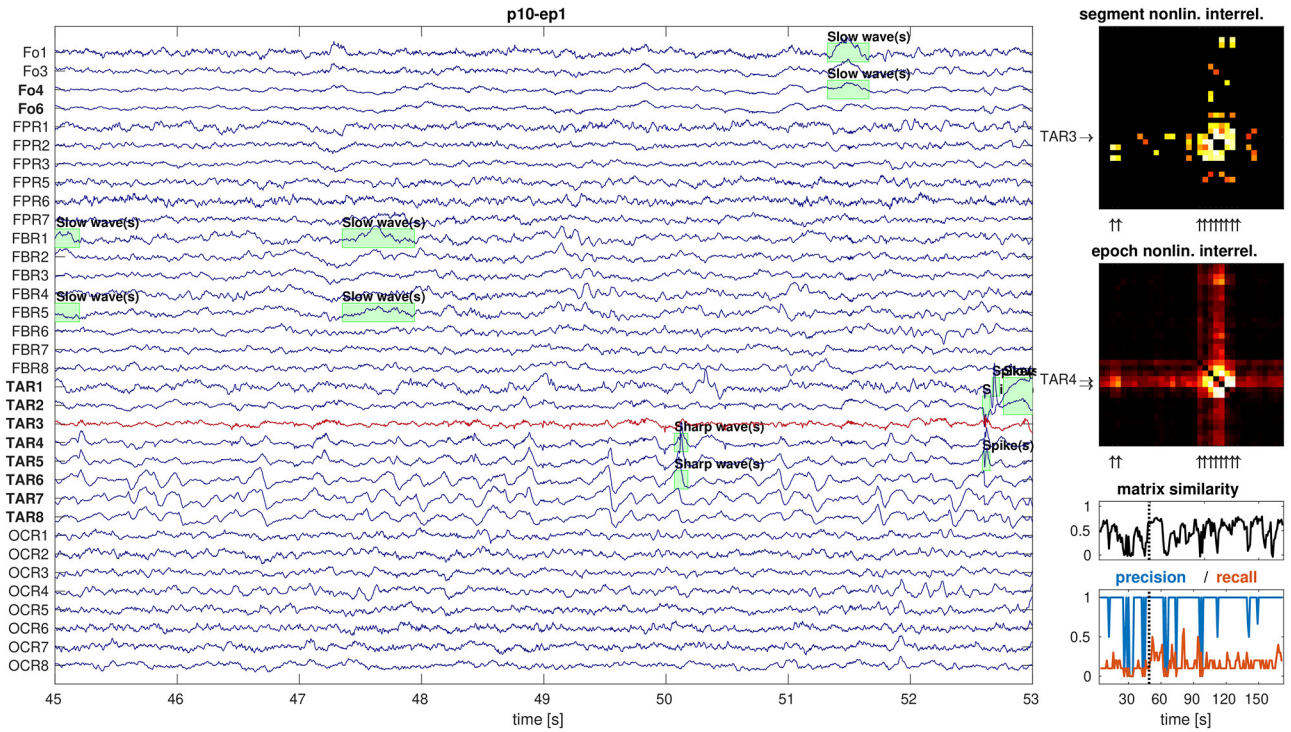

FIGURE 1 | Example display of iEEG signals and corresponding non-linear excess interrelations. Shown are 8 s of preictal iEEG signals (panel 1) with various annotations of epileptiform events (green boxes). The non-linear excess interrelation matrices are shown for the selected 8-s segment (panel 2) and as average over the entire epoch of 180 s duration (panel 3). The core channels of both matrices are indicated by arrows on the respective y-axes and the selected segment's core channel TAR3 is in addition plotted in red in the EEG display. The RBT is indicated by arrows on the x-axes of the matrices and typeset in boldface in the EEG display. The similarity between all segment-wise matrices and their epoch-wise average was measured by the Pearson correlation coefficient between their elements (panel 4). High precision and low recall of the core of the selected segment to predict the RBT are representative for the entire epoch (panel 5).

In total, 15,070 preictal epileptiform events have been included: 5,693 spikes (37.8%), 5,226 slow waves (34.7%), 3,369 sharp waves (22.4%), and 782 fast oscillations (5.2%). We found no outcome-dependent difference in average event duration, total number of channels containing events, average number of channels per event, and number of events per minute and channel (all $p > 0.5$, MWU). Likewise, we found no outcome-dependent difference in the relative portion of channels being part of the SOZ, the RBT, or the core of our qEEG analysis (all $p > 0.2$, MWU). However, there was a trend toward a higher portion of channels containing visually detectable epileptiform events in the favorable outcome group ($p = 0.016$, MWU).

The number of epileptiform events identified before seizure onset largely varied between different patients and epochs (see **Figure 2**). Whereas spikes, slow waves, and sharp waves occurred in all patients, fast oscillations were present only in some. The relative partition of event types clearly differed between patients and was roughly patient-specific. In addition, a highly significant outcome-dependent difference in the relative frequencies of event-types was found (spikes, slow waves, sharp waves, fast oscillations), indicating reduced proportion of sharp waves in patients with favorable outcome ($p = 0$, Chi-Square).

After removal of patients with a non-temporal seizure onset from the main analysis (see **Table 1**), 44 epochs from patients with favorable outcome, 21 from patients with unfavorable outcome, and 14 from patients without surgery were used in our group-wise comparisons.

3.1. Do Preictal Epileptiform Events Predict SOZ, RBT or Core Channels?

Figure 3 shows the precision for prediction of the SOZ, the RBT and core channels of the qEEG marker by visually detectable epileptiform events of patients with temporal lobe epilepsy regardless their type. Accuracy quantifiers are summarized in **Table 2**. Similar results for the small patient group with extra-temporal seizure onset are compiled in section 5 of the **Supplementary Materials**. General prediction power of epileptiform events for any of the channel sets was low (F1-scores below 0.37 in more than 75% of epochs). No difference was found between patients with favorable and unfavorable post-surgical seizure control for any channel set or measure (all $p > 0.01$, MWU).

Precision was higher for the prediction of the RBT than of the SOZ ($p = 0.0002$, MWU), whereas for recall the opposite was found ($p = 0.0022$, MWU). For prediction of the RBT the precision was higher than the recall ($p < 10^{-8}$, MWU),

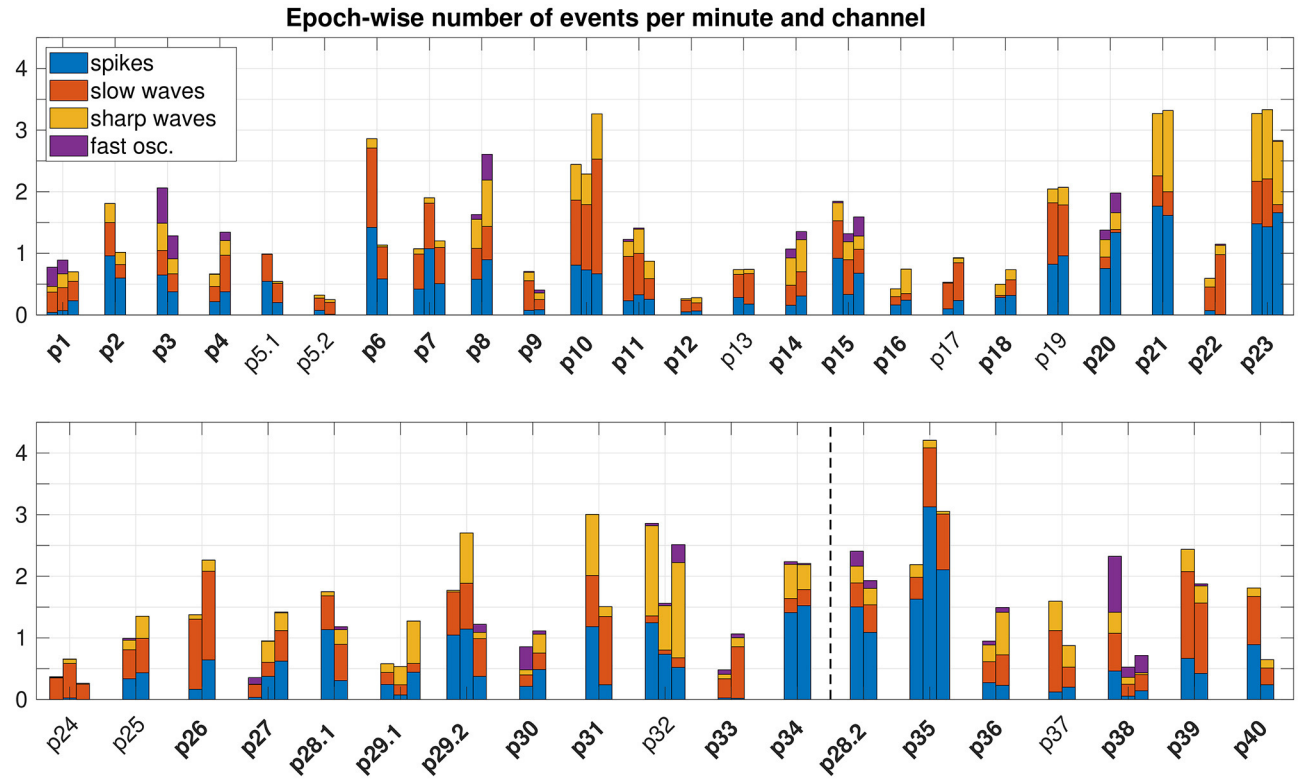

FIGURE 2 | Epoch-wise frequency of preictal epileptiform events. To compare the number of events across different epoch lengths and different implantation schemes (i.e. different number of iEEG channels), we normalized to the epoch duration and total number of channels that comprised events. We did not normalize to the total number of channels implanted, because the portion of channels recording from tissue able to produce epileptiform events varied between patients. Epochs are grouped patient-wise. Patients with a favorable post-surgical outcome appear in the upper panel. The dashed vertical line in the lower panel separates patients with an unfavorable outcome (left) resp. without surgery (right). IDs of patients with temporal lobe epilepsy are plotted in bold face.

indicating that we found more FN than FP. For prediction of core channels a significant difference in the opposite direction was observed ($p < 10^{-3}$, MWU) and no difference was found for prediction of the SOZ.

Results for separate analysis of all four types of epileptiform events in patients with temporal seizure onset are presented in **Figure 4**. The precision for the prediction of the RBT by epileptic spikes was higher in the favorable than in the unfavorable outcome group. Apart from this exception, the observations made for event sub-types separately were not different from the pooled analysis. Specifically, none of the event subtypes was associated with the core channels of non-linear excess interrelations.

3.2. Can SOZ or RBT Be Predicted by Quantitative EEG Analysis?

For patients with temporal seizure onset, the precision for prediction of the RBT by the SOZ was high in the favorable outcome group (see **Figure 5A** and **Table 2**), and the group difference was significant ($p = 0.0004$, MWU). For recall and F1-score trends for higher values in the favorable group were observed (see Figure S6 of the **Supplementary Materials** for a compilation of box plots). Precision was higher than recall in the favorable outcome group ($p < 10^{-7}$, MWU), again indicating that prediction of the RBT by the SOZ yielded many more FN than FP.

Figures 5B,C show precision for the prediction of the SOZ and the RBT by the core channels of the qEEG marker. In both cases the median of all accuracy measures (precision, recall and F1-score, see Figures S7, S8 of the **Supplementary Materials** for box plots) was zero in the unfavorable group but finite if outcome was favorable. In more than 80% of cases with favorable outcome the precision for prediction of the RBT was one, whereas in the unfavorable group it was smaller than 0.7 in 75% of cases. The group difference was significant ($p < 10^{-5}$, MWU). In addition, significantly higher recall and F1-score were found in the favorable group (both $p < 10^{-4}$, MWU).

For prediction of the SOZ there were outcome-dependent trends for higher precision and recall in the favorable group ($p = 0.0023$ resp. $p = 0.0021$, MWU) and a significant difference in the F1-score ($p = 0.0014$, MWU). In the favorable outcome group precision for prediction of the RBT was higher than recall ($p < 10^{-9}$, MWU), again indicating that many more FN than FP were generated. No such difference was found for prediction of the SOZ. The median precision for prediction of the SOZ by

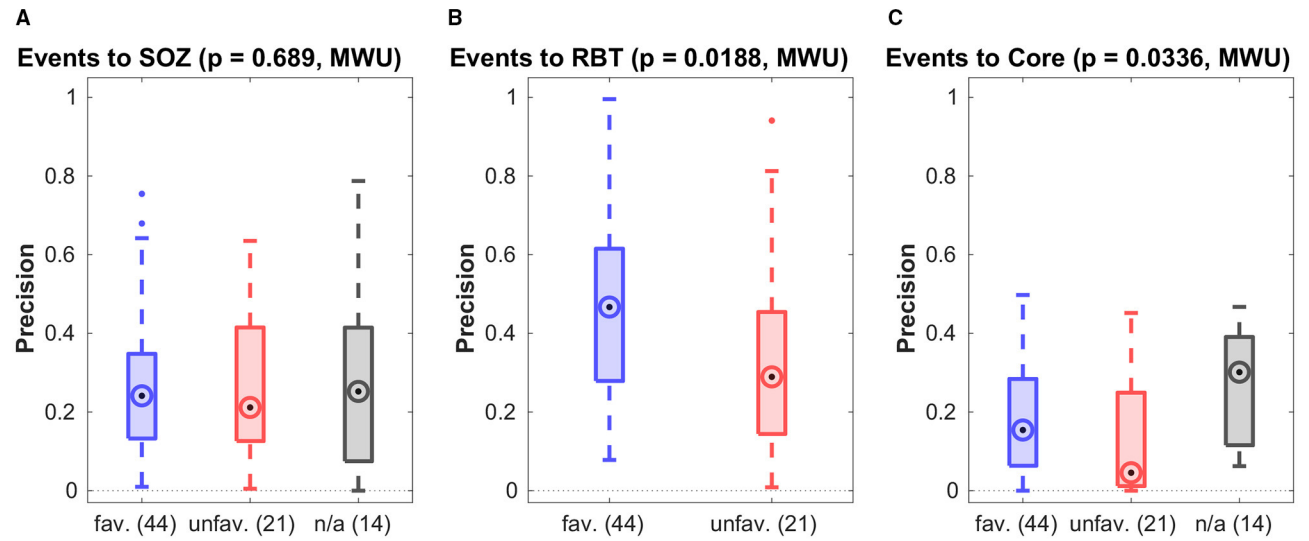

FIGURE 3 | Precision of preictal epileptiform events to predict various channel sets. Results are grouped by post-surgical outcome (favorable/unfavorable) resp. those without surgery (n/a). In all panels the circled dot indicates the median of the distribution, the first ($q1$) and third quartile ($q3$) are indicated by the bottom and top edges of the box and the whiskers comprise all data points in the range $q1 - 1.5 * (q3 - q1)$ to $q3 + 1.5 * (q3 - q1)$. Values beyond this range are displayed as dots. The p-values for differences between the favorable and unfavorable outcome groups is indicated at the top. Similar figures for recall and F1-score can be found in the **Supplementary Materials**.

TABLE 2 | Distribution of epoch-wise accuracy quantifiers for predictions.

		Favorable median [q1, q3]	Unfavorable median [q1, q3]	No surgery median [q1, q3]	*p*-value fav. vs. unfav.
Events to SOZ	Precision	0.24 [0.13, 0.35]	0.21 [0.13, 0.41]	0.25 [0.075, 0.41]	0.689
	Recall	0.25 [0.13, 0.46]	0.19 [0.12, 0.38]	0.25 [0.1, 0.38]	0.296
	F1-score	0.24 [0.13, 0.38]	0.19 [0.12, 0.38]	0.22 [0.087, 0.41]	0.523
Events to RBT	Precision	0.47 [0.28, 0.62]	0.29 [0.14, 0.45]	n/a	0.019
	Recall	0.17 [0.098, 0.28]	0.13 [0.038, 0.18]	n/a	0.018
	F1-score	0.23 [0.15, 0.37]	0.19 [0.06, 0.27]	n/a	0.022
Events to Core	Precision	0.15 [0.064, 0.28]	0.046 [0.012, 0.25]	0.3 [0.12, 0.39]	0.034
	Recall	0.35 [0.22, 0.51]	0.13 [0.026, 0.48]	0.34 [0.25, 0.38]	0.013
	F1-score	0.24 [0.088, 0.35]	0.068 [0.016, 0.28]	0.27 [0.13, 0.35]	0.014
SOZ to RBT	Precision	1 [0.62, 1]	0.2 [0, 0.85]	n/a	$< 10^{-3}$
	Recall	0.29 [0.22, 0.45]	0.062 [0, 0.31]	n/a	0.008
	F1-score	0.44 [0.36, 0.53]	0.095 [0, 0.43]	n/a	0.004
Core to SOZ	Precision	1 [0, 1]	0 [0, 0.05]	0.5 [0, 1]	0.002
	Recall	0.25 [0, 0.5]	0 [0, 0.062]	0.29 [0, 0.8]	0.002
	F1-score	0.4 [0, 0.67]	0 [0, 0.071]	0.34 [0, 0.5]	0.001
Core to RBT	Precision	1 [1, 1]	0 [0, 0.7]	n/a	$< 10^{-5}$
	Recall	0.18 [0.077, 0.25]	0 [0, 0.11]	n/a	$< 10^{-4}$
	F1-score	0.3 [0.14, 0.4]	0 [0, 0.15]	n/a	$< 10^{-4}$

core channels was also 1 in the favorable group, but the IQR was broader.

Our preliminary results in section 5 of the **Supplementary Materials** indicate generally lower associations among epileptiform events, the qEEG marker, the SOZ and the RBT in patients with extra-temporal seizure onset.

3.3. Focus on Patients With Favorable Outcome After Surgery

Reasons for unfavorable seizure control after surgery can be manifold. Since we only know with certainty that the EZ was included in the RBT if seizure freedom was reached, we analyzed the favorable outcome group in more detail. Here, the median

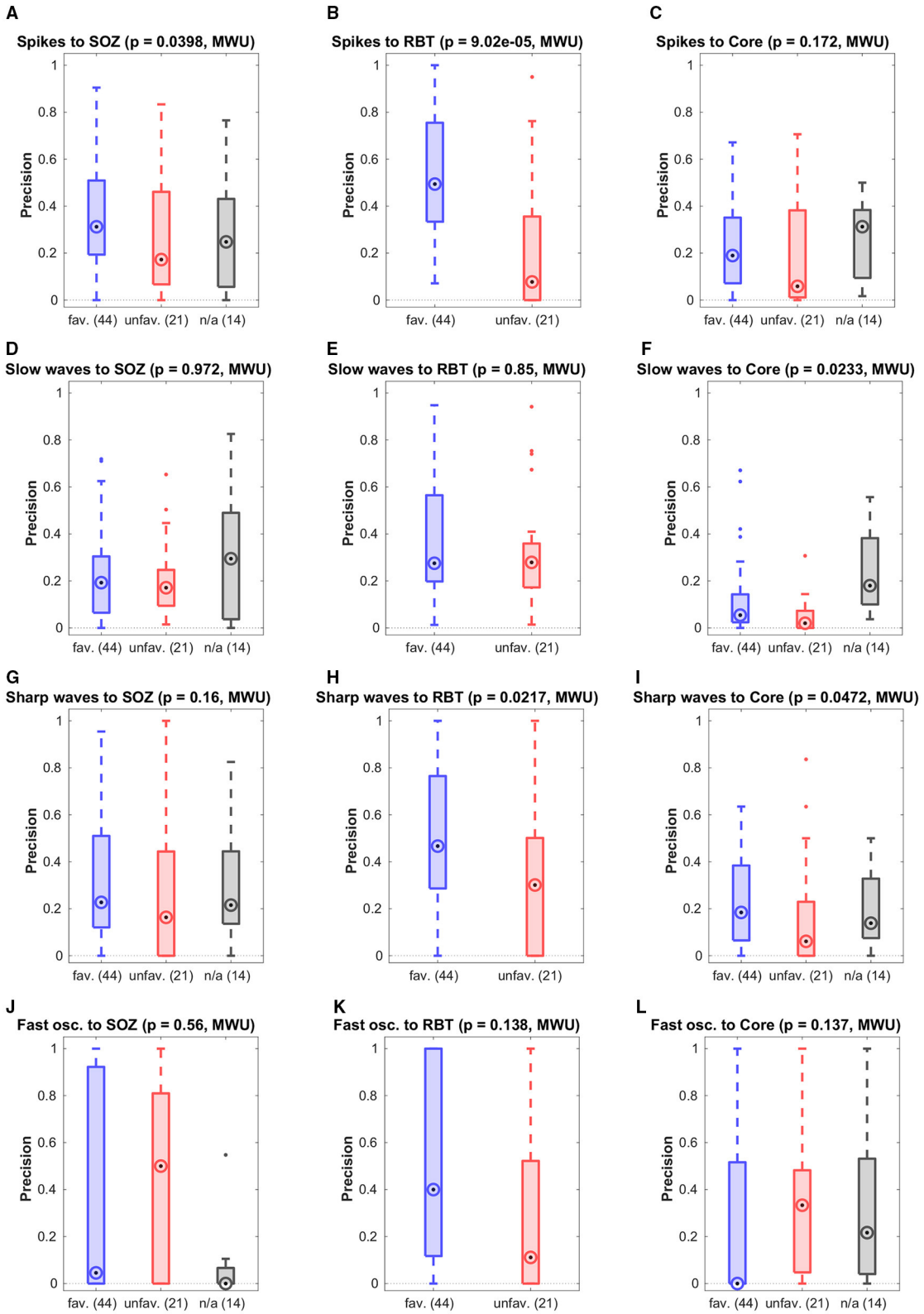

FIGURE 4 | Breakdown of the prediction of channel sets by specific event types. Shown is the precision grouped by the post-surgical outcome.

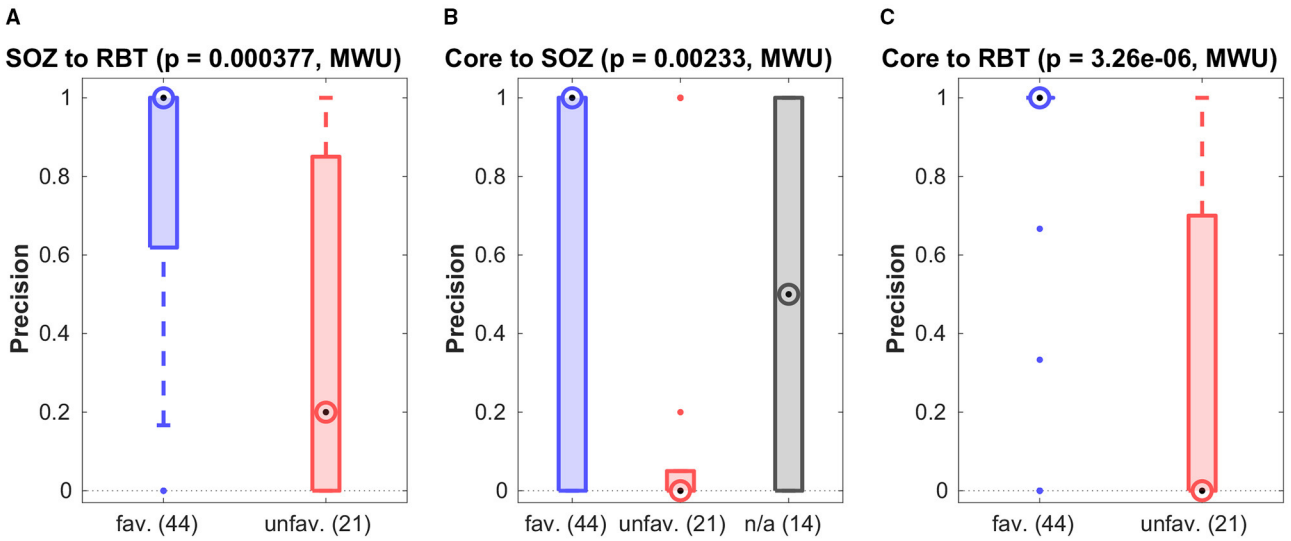

FIGURE 5 | Association among various channel sets. Group-wise precision of the SOZ to predict the RBT resp. of the core to predict either of them.

precision of 1 for core channels of non-linear interrelation to predict the RBT was significantly higher than the value 0.47 of the epileptiform events ($p < 10^{-8}$, MWU, see **Figures 5B,C**). Recall and F1-score were not different, though ($p > 0.45$). For prediction of the SOZ we did not find a performance difference between events and core channels ($p > 0.025$ for all accuracy quantifiers).

3.4. Patients With Bilateral Seizure Onset and Unilateral Resection

Two of the included patients had (unilateral) resections despite bilateral seizure onsets during presurgical evaluation. In these, no epochs preceding seizures with onset contralateral to the resection were included in the previous analyses because they occurred after the first three recorded seizures (which was a selection criterion). However, since we consider these cases as especially elucidating, we analyzed also the seizures with contralateral onset and discuss them separately.

Patient p1 had a right-sided temporal pole-ectomy and selective amygdala-hippocampectomy and became free of disabling seizures after surgery (Engel class I). Epoch-wise averages of the non-linear excess interrelation matrices preceding the first three seizures with left-sided onset are displayed in panels 1 to 3 of **Figure 6**. Epileptiform events were similarly observable in the RBT and the SOZ located in different brain hemispheres. Strong non-linear excess interrelations were present in the right hemisphere and especially in the RBT but not in any of the channels recording from the left hemisphere (electrodes TE1TL, FML, FPL, and FBL). According to our hypothesis that non-linear excess interrelations could be associated with epileptogenic tissue, this suggests favorable post-surgical seizure control after a right-sided resection. This is indeed in agreement with the observed outcome.

Patient p34 was already discussed in detail in our previous study (32), see Figure 8 and associated paragraphs in section 3.4 of that publication. This patient had a right-sided selective amygdala-hippocampectomy without any subsequent worthwhile improvement (Engel class IV). In the epoch preceding the only available seizure with onset in the left hemisphere, virtually all channels recording from this hemisphere (electrodes AL and HL) show strong non-linear excess interrelations (panel 4 in **Figure 6**). Epileptiform events were equally dominant in the hippocampus of both hemispheres. Based on our hypothesis one would expect that these widespread non-linear excess interrelations contradict seizure freedom after surgery. Again, this matches the observed outcome.

4. DISCUSSION

4.1. Summary

The main goal of this work was to investigate the relation between our qEEG marker non-linear excess interrelation (32, 34, 41) and preictal epileptiform events detected by a human expert in visual EEG assessment. Since the large majority of our patients had seizure onset in the temporal lobe (32/40), we restricted our analyses to these cases to increase data homogeneity and investigated patients with extra-temporal seizure onset only exploratively, see section 5 of the **Supplementary Materials**. We did not find a close relation between both; precision for the prediction of core channels of non-linear excess interrelation by preictal events was generally low and so were recall and F1-score (see **Table 2**, **Figure 3C**, right column of **Figure 4** and Figure S5 of the **Supplementary Materials**). No significant separation between the favorable and unfavorable outcome groups was observed.

Our analysis revealed a significant outcome dependence of the association between the qEEG marker and the RBT (see

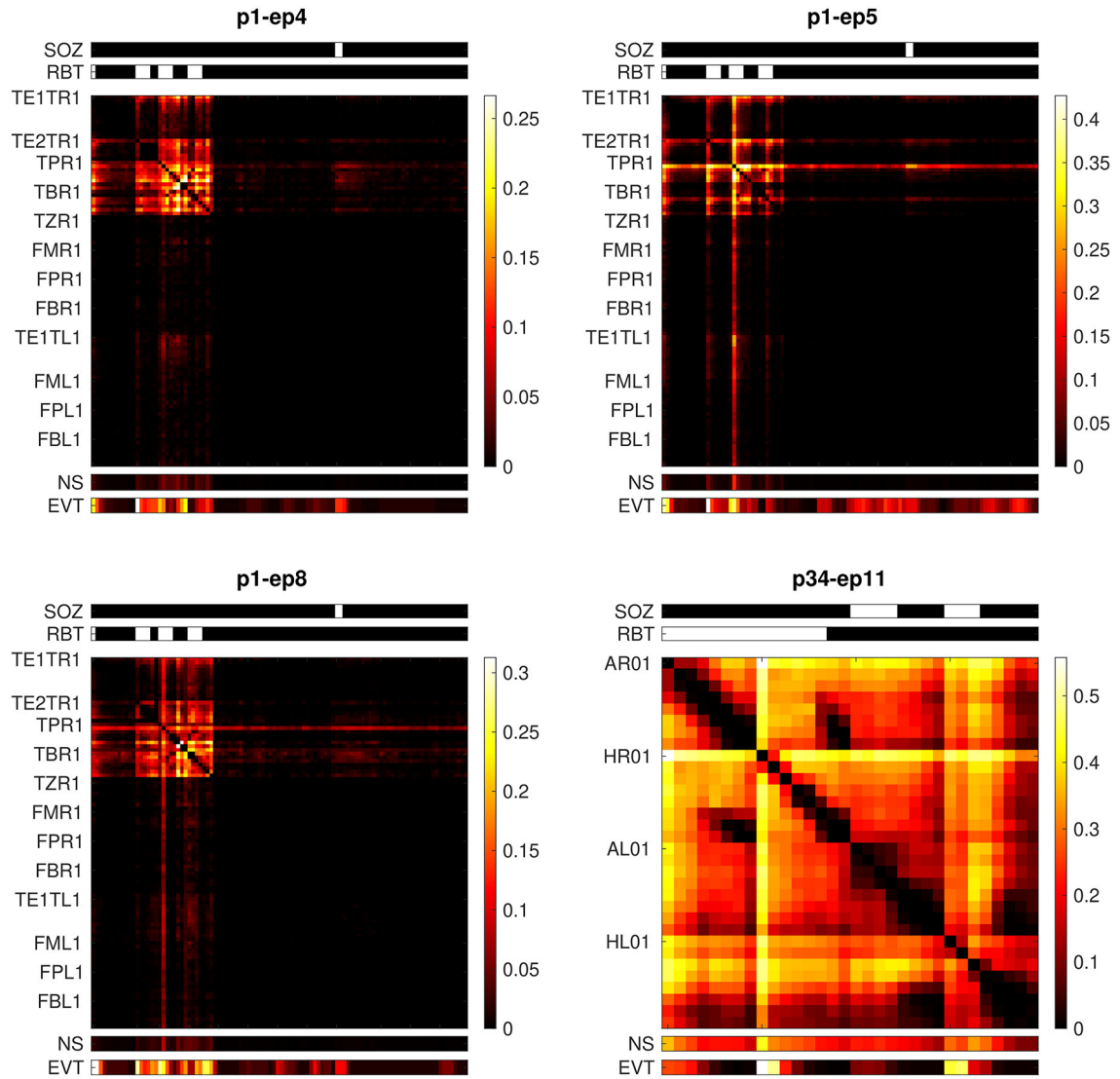

FIGURE 6 | Epoch-wise averaged non-linear excess interrelation matrices of two patients with presurgical bilateral seizure onset. Shown are the epochs preceding the seizures with onset contralateral to the resection. Above the matrices, the SOZ and the RBT are indicated by white bars. Below the matrices, the node strength (NS) and the channel-wise number of events (EVT, normalized to the respective color scale) are displayed.

Figure 5C) as well as an association with the SOZ (see **Figure 5B** and Figure S8B of the **Supplementary Materials**). The main effect was higher precision to predict the RBT in the favorable group ($p < 10^{-5}$), confirming an observation made already in (32) based on patients with standardized mesiotemporal electrode implantations. In the present work we refined this analysis and extended to various electrode implantation schemes with depth, strip and grid electrodes placed in the temporal, frontal and parietal lobes, from which only the by far largest subgroup of patients with temporal lobe epilepsy allowed detailed analysis.

Our findings are in line with recent results of a simulation study by (45). When introducing sporadic synthetic spike-and-wave discharges into scalp EEG of healthy controls with physiologically plausible amplitudes they could not observe a relevant alteration of the network structure or strength as measured by (linear) finite-lag cross-correlation. In contrast, when comparing functional connectivity patterns between patients with infantile spasms and frequent spikes to those of healthy controls, they did find patient-specific differences. We view our own results as consistent with these findings in the sense that iEEG recorded from seizure generating brain tissue is identifyable by its altered non-linear excess interrelation (ability to predict the resection in patients with favorable outcome) but individual epileptiform events do not directly cause this interrelation pattern (no prediction of core channels by epileptiform events).

Regarding prediction of the RBT by any of (i) the epileptiform events, (ii) the SOZ, or (iii) the core channels of non-linear excess interrelation we observed a significantly smaller number of FP than FN in patients of the favorable outcome group. This implies that the predictions mainly fall inside resections that help to render patients seizure free but do not fill them entirely. This is plausible, since the RBT is known to be often larger than minimally required for surgical reasons.

For the association with the SOZ, the outcome-dependent group difference was significant for the F1-score (see Figure S7B of the **Supplementary Materials**) and trends were observed for precision and recall (see **Figure 5B** and Figure S7A of the **Supplementary Materials**).

Taken together, the independence of visual and qEEG markers and the better prediction of the resection in patients with favorable post-surgical seizure control provide evidence that our quantitative iEEG analysis may provide additional information about signals recorded from epileptogenic brain tissue that is not accessible to visual inspection. The more detailed examination of two patients with bilateral seizure onsets additionally support our hypotheses (see **Figure 6**).

The relatively weak association between SOZ and RBT (F1-score $<$ 0.55 in more than 75% of cases, see **Table 2** and Figure S6B of the **Supplementary Materials**) requires explanation, since the resection is usually tailored to remove the SOZ. Precision was high in the majority of cases with favorable outcome (small number of FP), whereas recall was only moderate or even small (considerable number of FN, see **Table 2** and **Figure 5A**). This observation is consistent with the fact that despite the crucial role of the SOZ in surgery planning, the actual resection is typically more extensive for surgical reasons.

Agreement of preictal epileptiform events with the SOZ and the RBT was in general low (see **Figures 3A,B**, **4**). Spikes were the only event sub-type that had differential predictive values in the favorable and unfavorable outcome groups, whereas neither any of the other event sub-types nor all events in conjunction did. Separation between the outcome groups was larger for prediction of the RBT than for prediction of the SOZ. This observation is remarkable, since the SOZ is determined by visual EEG assessment. However, it is crucial to note that the SOZ was defined based on the first *ictal* signal alterations, whereas the epileptiform events studied here were *preictal*. It is known that the mechanisms behind both are not necessarily identical (1, 47–49).

4.2. Limitations

Our study has limitations. First, our indirect argument based on contrasting the favorable (Engel classes I and II) and the unfavorable outcome groups (Engel classes III and IV) may be regarded sub-optimal, because there might be reasons for patients to experience ongoing seizures *other* than incomplete resection of the EZ (e.g., scarring or hypothetical generation of a new EZ). However, this does not affect the data points in the favorable outcome group and our main observations remain valid: The occurrence of preictal epileptiform events does in general not predict the SOZ, the RBT or the core channels of non-linear excess interrelations (see **Figure 3**). At the same time, the ability of core channels to predict the RBT has a median precision of 1 in the favorable outcome group (see **Figure 5C**), a value significantly higher than for epileptiform events.

Second, since seizure onset in our patient group was temporal in the vast majority of cases, our data did not allow to investigate a potential confounding influence of etiology. Instead, we restricted our main group analyses to temporal onset cases. Robust evaluation of patients with extra-temporal seizure onset will require collection of more such cases and remains the scope of future work.

Third, we did not explore the impact of disease duration.

Fourth, EEGs of patients in the favorable outcome group showed a trend toward a higher proportion of channels with visually detectable epileptiform events. A possible explanation is that in "easier patients" the location of the epileptogenic brain tissue was clearer a priori. Thus, also the implantation scheme and the resection were better defined. The relevance of spatial sampling for qEEG results has recently also been highlighted by (50).

Finally, we had expert annotations available only from a single rater since detailed annotating is very time consuming. Publicly available EEG data of epilepsy patients could not be used to enhance our study size for different reasons. These data are either restricted to scalp EEG [(51); isip.piconepress.com/projects/tuh_eeg/], lack at least one essential piece of information about surgery extent, outcome or detailed EEG annotations (ieeg.org, openneuro.org/datasets/ds003029/versions/1.0.2) or require payment of usage fees (epilepsy-database.eu/).

4.3. Conclusion

In conclusion, we herein demonstrated the potential of non-linear excess interrelations between preictal iEEG signals to provide clinically useful additional information for the planning of resective surgery in temporal lobe epilepsy. Importantly, we have shown additionally that this qEEG marker is largely independent from visually detectable preictal epileptiform events and has a higher precision for predicting the RBT than the SOZ in cases with favorable outcome. Hence, our quantitative iEEG analysis is not directly associated with established visually detectable markers of epileptogenic brain tissue, which are regarded as locally restricted phenomena. It rather captures potentially far-reaching non-linear dependencies between brain regions that seem to reflect pathological activity. This further underlines the benefit and importance to incorporate the network concept of epilepsy into presurgical patient evaluation. To foster similar research also for other qEEG makers, we made the iEEG recordings and human annotations used in this paper publicly available. Furthermore, we encourage the scientific community to provide independent expert annotations of these recordings using our custom EEG reader to enable comparison also with inter-rater agreement.

DATA AVAILABILITY STATEMENT

The EEG reader and the raw data supporting the conclusions of this article are available via GitHub: https://github.com/SCAN-NRAD/scanEEGviewer.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Canton of Bern. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CR: study design. MD: data annotation. MM and CR: data analysis and writing of manuscript. KS and CR: data curation. MM: writing of software. MM, MD, KS, RW, and CR: final review of manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.741450/full#supplementary-material

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CASE REPORT
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Case Report: Multisystem Autoimmune and Overlapping GAD65-Antibody-Associated Neurological Disorders With Beneficial Effect of Epilepsy Surgery and Rituximab Treatment

Petia Dimova[1]* *and Krassimir Minkin*[2]

[1] Epileptology Unit at Epilepsy Surgery Center, Department of Neurosurgery, St. Ivan Rilski University Hospital, Sofia, Bulgaria,
[2] Functional and Epilepsy Surgery Center, Department of Neurosurgery, St. Ivan Rilski University Hospital, Sofia, Bulgaria

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Giuseppe Didato, Epilepsy Unit, Carlo Besta Neurological Institute (IRCCS), Italy

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Reinaldo Uribe-San-Martín, Pontificia Universidad Católica de Chile, Chile

***Correspondence:**
Petia Dimova
psdimova@gmail.com

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Glutamic acid decarboxylase (GAD) antibodies are associated with disabling conditions such as stiff person syndrome, temporal lobe epilepsy (TLE), limbic encephalitis, cerebellar ataxia (CA), and ocular movement disorders, which are usually chronic and difficult to treat. GAD-related TLE has poor response to anti-seizure medications and immune therapies, and epilepsy surgery is rarely successful. We report on a 47-year-old female with history of migraine, autoimmune thyroid disease, ankylosing spondylitis, and drug-resistant TLE. A video electroencephalography recorded frequent seizures with temporo-insular semiology, correlating to left temporal epileptiform activity and left mesiotemporal hyperintensity on magnetic resonance imaging. GAD autoimmunity was confirmed by very high GAD antibody titers in serum and cerebrospinal fluid. Steroids, immunoglobulins, and cyclophosphamide had no effect, and selective left amygdalectomy was performed based on very restricted hypermetabolism on positron-emission tomography. After transient seizure freedom, significant epilepsy improvement was observed in spite of memory decline. Transient worsening was noted 1 year later during diabetes mellitus manifestation and 5 years later during presentation of progressive CA, which stabilized on rituximab treatment. We believe this case illustrates the diversity and the frequent overlap of GAD-associated disorders, the need of early and aggressive immunotherapy in severe patients, as well as the possible benefit from epilepsy surgery in some GAD-TLE.

Keywords: autoimmune, GAD, cerebellar, diabetes, epilepsy, insular, temporal, surgery

INTRODUCTION

Glutamic acid decarboxylase antibodies (GAD-Abs; against the enzyme isoform GAD65) are usually associated with chronic conditions, increasingly recognized during the last three decades. Besides type-1 diabetes mellitus (DM1), GAD-Abs have been associated with a number of neurological syndromes, such as stiff-person syndrome (SPS), cerebellar ataxia (CA), limbic

encephalitis (LE) and temporal lobe epilepsy (TLE), ocular movement disorder, and myelitis (1–3). Diverse clinical manifestations are thought to be dictated by GAD-Ab specificity, targeting different epitopes in the catalytic domain of the enzyme (1). Nonetheless, because of massive overlap in epitope recognition, presentations with signs and symptoms of several affected systems may be observed (1, 3, 4). Common features of GAD-Ab-associated neurological disorders are frequent comorbidity with other systemic autoimmune diseases, possibility of developing overlap syndromes, and poor to moderate response to immunotherapies. Here, we present a case with refractory TLE, who was historically diagnosed with migraine, autoimmune thyroid disease, and ankylosing spondylitis (AS). A delayed diagnosis of GAD-Ab autoimmunity was established, and DM1 and CA developed 6 and 10 years after the epilepsy onset, respectively. Immunotherapy with steroids, immunoglobulins, and cyclophosphamide had no effect on seizures, while selective amygdalectomy achieved substantial epilepsy improvement. Rituximab treatment led to stabilization of CA and further seizure reduction.

CASE PRESENTATION

A 42-year-old woman presented for presurgical evaluation due to very frequent epileptic seizures. No febrile convulsions or significant medical antecedents in childhood were reported except for rare migraine attacks since puberty. Historically, the patient was operated at the age of 32 for autoimmune Hashitoxicosis (unfortunately, detailed medical documentation is missing) and was on treatment with 100 μg L-thyroxin. At the age of 36, she was diagnosed with HLA-B27-negative AS based on 6-month clinical manifestation of progressive (predominantly low) back and hip pain, 3-plane limitation of lumbar spine mobility, morning stiffness improving with motion, and confirmation by laboratory (elevated C-reactive protein and negative rheumatoid factor) and radiological findings (bilateral sacroiliac joints changes, syndesmophytosis, and enthesitis in neck and lumbar spine on X-ray). Anti-tumor necrosis factor (anti-TNF) therapy with etanercept (ETN) for 2 years led to AS remission and was discontinued due to tuberculosis (TBC) treated with 4-drug regimen for 4 months.

The epilepsy started at the of age 37 with six bilateral tonic-clonic seizures in sleep. A few months later, focal seizures with preserved or impaired awareness started, initially only few per month but later became weekly and in clusters. According to patient description, they did not change over time and occurred in awake state, and were characterized by goosebumps in the back of the neck, left shoulder, and left arm, followed by a cold sensation in the left hemibody, mostly in the upper extremity and shoulder, subsequent unpleasant, strong and sharp smell, "déjà-vu"/"déjà-vécu" experiences, and trembling of both hands, more on the right. Sometimes, because of a feeling of "breathlessness," she tried to breathe more deeply and frequently. Her relatives confirmed that usually she could warn at onset. Afterwards, motion arrest, eye closure, oral automatisms and facial flush were observed. Her right hand became stiff and immobile, while the left hand was squeezing. Postictally she could not speak and respond for minutes. Several anti-seizure drugs (ASDs) had no or minimal efficacy (oxcarbazepine and levetiracetam), and some of them had also marked adverse effects (valproate and carbamazepine). Therefore, the therapy consisted of lamotrigine (LTG) and low-dose clonazepam (CZP). Standard electroencephalograms (EEGs) were reported as showing left temporal epileptic focus, and four brain magnetic resonance imaging (MRI) examinations were interpreted as demonstrating left hippocampal sclerosis (HS). Memory problems appeared 2 years after epilepsy onset and increased 5 months before admission, when seizure frequency reached 30 to 40 per day.

During 3-day video-EEG monitoring, more than 150 seizures were recorded. They lasted 40–60 s and correlated to left temporal ictal change of initial attenuation and subsequent rhythmic epileptiform discharge (**Figure 1A**). In wakefulness, seizures occurred at fairly regular intervals of 3 to 4 per hour (**Figure 1B**). Rapid titration of topiramate and intravenous (IV) phenytoin did not reduce seizure frequency.

Brain MRI demonstrated bilateral mesiotemporal hyperintensity with clear left predominance and enlarged left amygdala (**Figure 2A**). Neuropsychological testing confirmed verbal memory deficit. Based on clinical history, presentation, and results from the examinations performed, we strongly suspected an autoimmune etiology. Serum and cerebrospinal fluid (CSF) autoimmunity testing by ELISA (Oxford University Hospitals Neuroimmunology Laboratory) was negative for anti-Caspr2, anti-NMDAR, anti-AMPAR-1/2, anti-GABA-b, anti-VGCC, anti-VGKC, and anti-LGI1 Ab, but very high anti-GAD-Ab titers of > 50,000 IU/ml (serum) and >10,000 IU/ml were (CSF) detected. Immunotherapy was immediately started with IV methylprednisolone (MPR), and later continued with IV immunoglobulins (IVIG) and cyclophosphamide, with only brief and transient effect despite decreased serum anti-GAD Ab-titers (15,000 IU/ml).

Control brain MRI did not show progression of mesiotemporal abnormalities but fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed very restricted hypermetabolism in the left amygdala correlating to an ictal event during the examination, as reported by the patient (**Figures 2B,C**). Because of lacking efficacy of ASDs and immunotherapy, and after thorough discussions with the patient and relatives on the chances and risks of epilepsy surgery, we performed a very selective left amygdalectomy. Postoperatively, the patient was 3 months seizure-free but later continued to experience shorter focal aware/unaware seizures mostly with behavioral arrest, decreased/absent responsiveness, and milder dyscognitive features but without the initial vegetative/somatosensory and the later motor signs. Seizure frequency stabilized at 3 to 4 per month with no change in ASDs, an outcome corresponding to Engel Class IIIA (5).

One year later, the patient was diagnosed with DM1 that was initially difficult to compensate, and transient increase in seizure frequency of up to 1–2 daily for about 2 months was also noted. Later on, with Insulin Apart 6 UI t.i.d. and Insulin Degludec 16 UI q.d., the condition with regard to both DM1 and TLE (weekly non-disabling

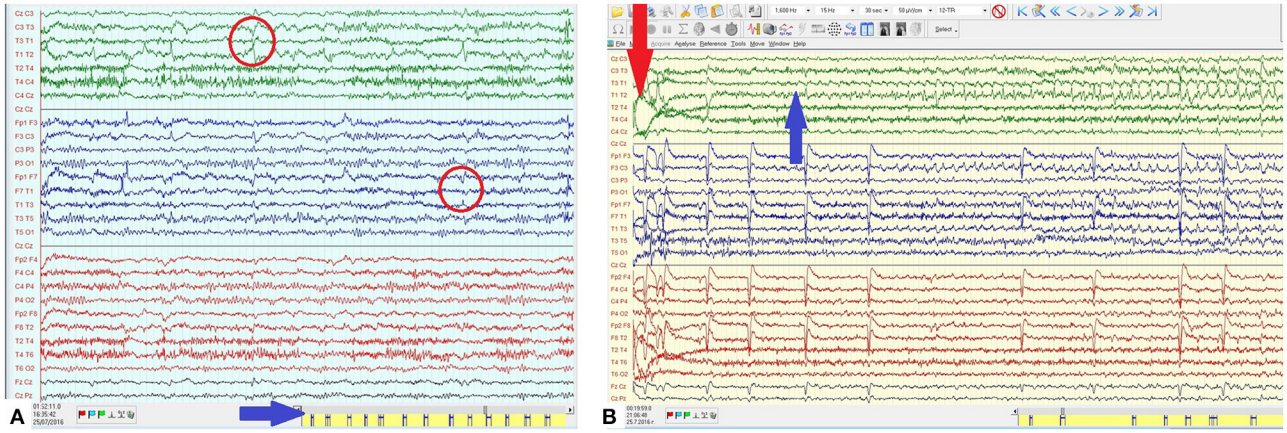

FIGURE 1 | (A) EEG in wakefulness with left temporal sharp- and spike-wave (SW) complexes with maximum and phase reversal on T1-T3 (red arrow). Individual seizures occurring at fairly regular interval and high frequency (blue arrow). **(B)** Ictal EEG epoch from the clinical seizure onset (red arrow) demonstrating the evolution of the left temporal ictal discharge consisting of rhythmic SW with an increasing amplitude and a spread mostly to the central region.

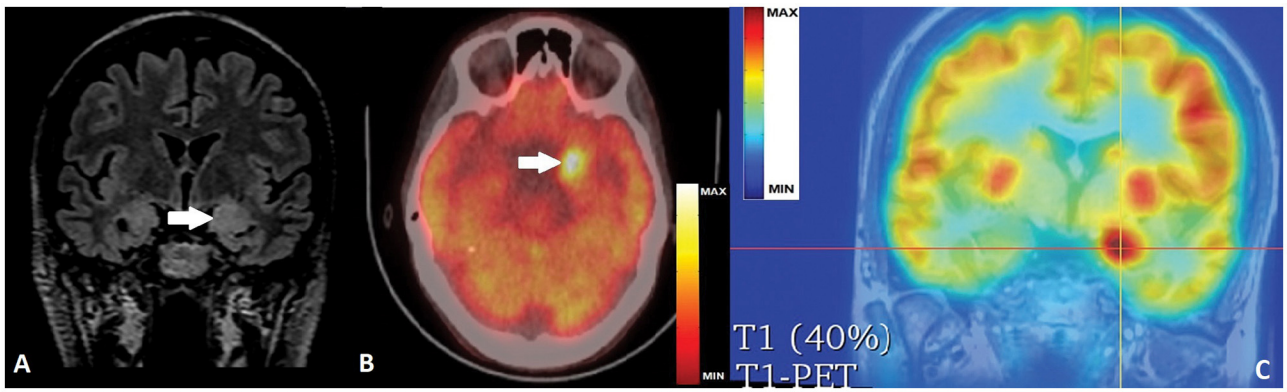

FIGURE 2 | (A) Coronal FLAIR MRI with bi-mesiotemporal hyperintensity, more prominent on the left, with increased volume of left amygdala (white arrow). **(B)** Axial PET-CT scan with hypermetabolic left mesiotemporal spot(white arrow). **(C)** PET-T1 MRI co-registration with clear hyperactivity in the left amygdala (crossed lines' center).

focal seizures) was stable and did not require further treatment adjustments.

Approximately 4 years after the operation, rare episodes of dizziness and falls were reported and interpreted by the patient as probable seizures. They were not recorded on VEEG, but right temporal epileptiform activity was registered, and lacosamide (LCM) was added. The patient continued to report intermittent unsteady gait, diplopia, vertigo, and more frequent falls, related or not to LCM intake. No changes in the neurological exam, MRI, and EEG were found; therefore, these complaints were attributed to LCM and prompted its replacement with brivaracetam without any improvement. Gradually, over the next 5 months, the patient developed a full-blown picture of CA with severe locomotor ataxia, dysdiadochokinesis, dysmetria, nystagmus, and dysarthria. Brain MRI did not reveal obvious signs of cerebellar atrophy but only progress in left HS (**Figure 3**). Paraneoplastic auto-Ab testing was negative for anti-Hu (ANNA-1), anti-Ri (ANNA-2), anti-Yo (PCA-1), anti-PNMA2 (Ma2/Ta), anti-Tr (DNER), anti-amphiphysin, anti-CV-2, anti-Sox-1, anti-ZIC4, anti-recoverin, and anti-titin Ab, but high anti-GAD65 titers of 67 U/ml persisted (positive if $\geq$ 10 U/ml, strong positive $\geq$ 50 U/ml; [10 U/ml $\approx$180 IU/ml]).

Immunotherapy with IV MPR and IVIG had no effect; therefore, rituximab treatment was started. After the first application, marked but transient improvement in CA was noted, and after the second dose, the condition stabilized. Further decrease in seizure frequency to two per month was observed as well, but due to the locomotor and distal limb ataxia at present, the 47-year-old woman is independent and able to fulfill her usual activities at home only. In addition, neuropsychological testing before, 6 months after and most recently, 4.5 years after surgery, demonstrated significant worsening of the memory function from mild short-term verbal memory deficit prior to the selective left amygdalectomy to marked verbal and

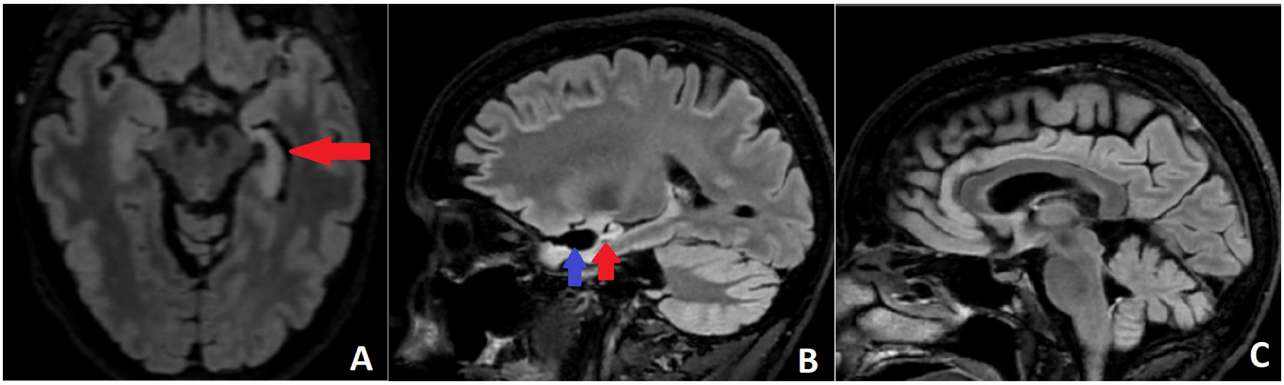

FIGURE 3 | (A) Axial FLAIR MRI with left HS (red arrow). **(B)** Sagittal FLAIR MRI scan demonstrating the postoperative defect (blue arrow) and the left HS (red arrow). **(C)** Sagittal FLAIR MRI without obvious signs of cerebellar and brainstem atrophy.

non-verbal memory decline, favoring continuing underlying bilateral damage, regardless of the stable and even improving epilepsy situation with several EEGs free of left and right temporal epileptiform or slow-wave activity.

The timeline of diseases' onset and course, most important diagnostic workup with relevant results, and therapeutic interventions including doses of the medications are presented in **Figure 4**.

DISCUSSION

After SPS and CA, GAD-TLE is considered the third most common GAD-associated neurological syndrome and one of the most common types of autoimmune epilepsy (3). GAD-Ab association must be suspected in cases with no obvious cause of TLE, and it has been postulated that GAD-Ab need to be found in high serum titers or to be detected in CSF to prove the causal relationship (1, 2, 4, 6, 7). In our case, a very high GAD-Ab titer was found both in serum and CSF, where the recognized abnormal level is >1,000 IU/ml by ELISA (2), and similar to previous reports, the serum level was much higher than that in CSF (7, 8). Although the serum GAD-Ab titer significantly decreased already after the first IV MPR trial, the disease course did not correlate to this Ab-reduction, since very frequent disabling seizures persisted and later on, two other GAD-related conditions (DM1 and CA) developed as well. In our case, the lacking clinical response to the immunomodulatory treatment despite the positive "relative" trend of Ab-decrease confirms important previous observations that without early immunotherapy this autoimmune disorder has a chronic and hard to treat course (9, 10). Obviously, in such difficult cases, GAD-Ab titer changes seem not be an effective indicator of the ongoing inflammation, and the clinical picture with treatment response is the only guide for short- and long-term therapeutic decisions (10).

As in the other GAD-associated neurological syndromes, comorbidity with other autoimmune disorders, such as DM1, could be present in >1/3 of patients with GAD-TLE/LE (11). It was found that usually the epilepsy preceded DM1 in patients with high GAD-Ab titers (12). Our case supports this observation, as TLE developed 6 years before DM1.

An important issue in our case is the possibility of a causal relationship of the autoimmune neurological disorders to the preceding anti-TNF treatment for AS. It is well known that the fundamental change in the treatment of diverse chronic inflammatory diseases brought by anti-TNF drugs increasingly raises many concerns about the safety of those agents because of various adverse events during this targeted biological treatment (13, 14). Our patient suffered from TBC, the most frequent opportunistic infection, after 2-year treatment with ETN, thus exhibiting one of the most frequent anti-TNF therapy complications, as TNFα is critical for localizing and preventing reactivation of latent mycobacterial TBC infection (14).

As to the autoimmunity, up to now, it has been reported that all anti-TNF drugs induce the development of anti-drug Ab, and that the neurological complications related to those agents are demyelinating central and peripheral nervous system diseases (13, 14). Several speculative hypotheses have been proposed to explain the mechanism of the possible relationship between anti-TNF and demyelination, but none is considered unique and adequate; moreover, several factors argue against the true association between anti-TNF therapy and demyelinating disease (14). Based on t available literature data and uncertainties on this issue, we do not consider the GAD-Ab-associated neurological disorders in our case to be related to the anti-TNF treatment, but rather we adopt the view that they are part of a multisystem autoimmune syndrome, especially having in mind the initial manifestation of a (poorly documented) autoimmune thyroid disorder, i.e., Graves' disease alone or in combination with Hashimoto's thyroiditis, as already well-documented (15).

Glutamic acid decarboxylase antibody (GAD-Ab)-associated focal epilepsy seems not to be restricted to the TL and hippocampus; the limbic system is most often affected bilaterally, and insular hypometabolism on PET could serve as an important diagnostic clue (10, 16). In our case, the seizure semiology was in favor of early insular involvement, as ictal onset was with autonomic and somatosensory signs, suggesting generation in the insula or temporo-insular circuit (10, 16–18). Autoimmune

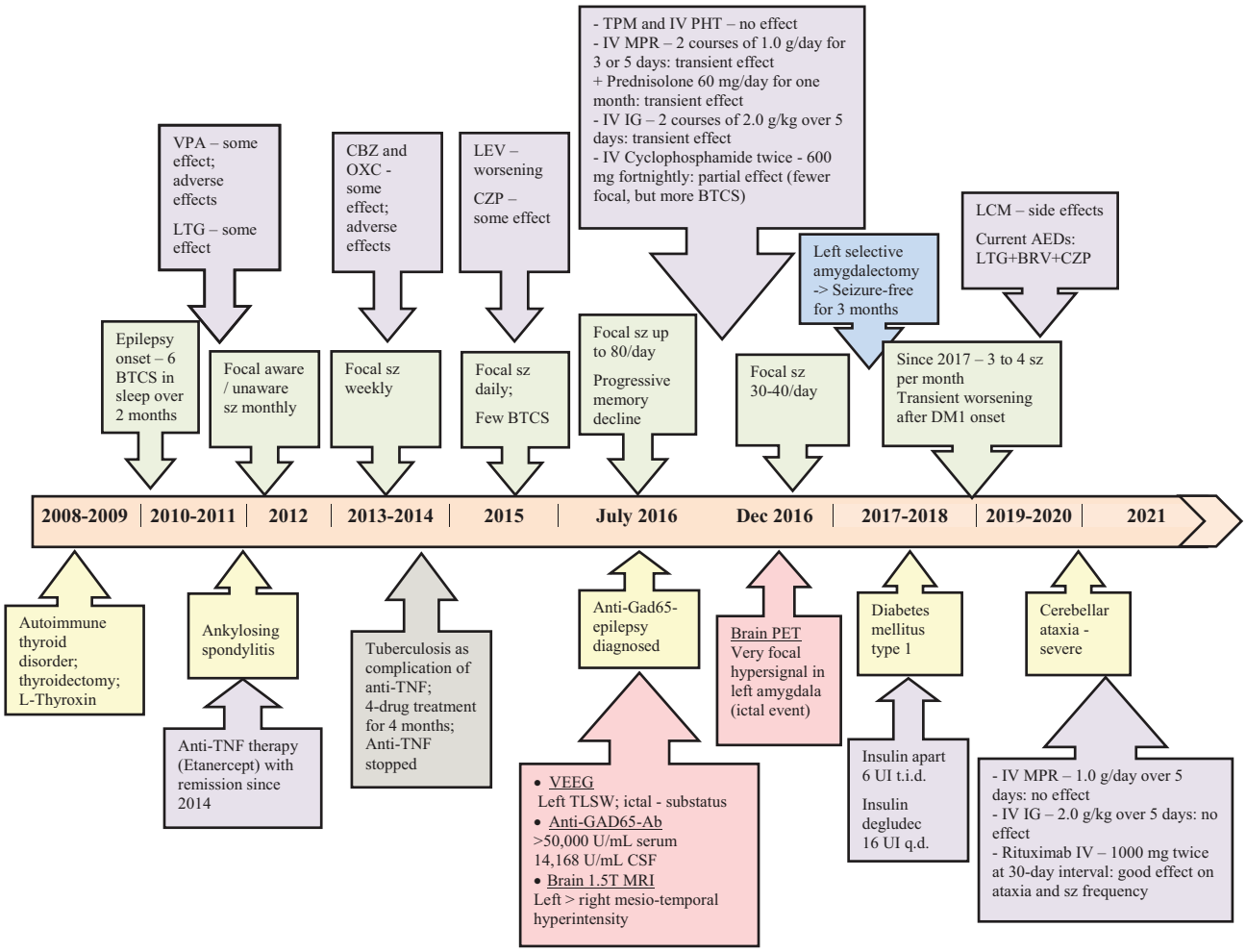

FIGURE 4 | Timeline with diseases' onset and course, the diagnostic work-up, relevant results and therapeutic management.

etiology in seizures with piloerection has been reported in autoimmune TLE (19–23), and to our knowledge there is only one published case of such semiology in GAD-associated temporo-perisylvian epilepsy (23).

Our patient presented for presurgical evaluation 5 years after epilepsy onset with dramatic seizure frequency increase over a few months, concomitantly to progressive memory disturbances, bilaterally hyperintense and swollen mesio-temporal structures, and high GAD-Ab levels. Although one major diagnostic criterion for definite limbic encephalitis is the subacute onset (<3 months) of working memory deficits and seizures (24), we believe that the other findings in our case (bilateral FLAIR-T2 mesio-temporal abnormalities, EEG showing epileptiform and slow-wave activity involving the temporal lobes, and high GAD Ab-titers both in serum and CSF) are sufficient to reasonably exclude alternative causes (24), and to speculate that the condition of our patient could be regarded as an exacerbation of "chronic" LE rather than just worsening of chronic TLE.

In the above cornerstone position article (24), it has been underlined that brain FDG-PET is much more often abnormal than time-matched MRI in cases of autoimmune LE (24–26). Moreover, hypermetabolic PET findings were found to be related to the specific antibody-type, i.e., all patients with Ab against intracellular antigens (such as GAD) showed mesio-temporal PET hyperactivity more frequently than patients with Ab against surface antigens (25). Our patient confirmed that during the PET examination she has had a usual seizure. Therefore, we considered the circumscribed hyperintense area corresponding to the left amygdala as presumable hypermetabolic ictal onset zone, most probably on top of a very active inflammation in the mesiotemporal complex, rather than as possible hypometabolism on the right side.

The surgical outcome in GAD-TLE is worse than in other refractory TLE, as it has been demonstrated by several studies that the majority of operated cases had minimal or no improvement, and that only few became seizure-free (9, 12, 27–29). Moreover, even when selective amygdalohippocampectomy controlled or improved the seizures, in combination with immunotherapy, the long-term performance in verbal and figural memory was worse than with immunomodulation only (27). It is

suggested that high seizure recurrence and memory decline over the long run are related to the frequent bilaterality, widespread involvement of the limbic system by GAD-autoimmunity, and structural changes in the third stage of GAD-TLE rather than to the ongoing inflammatory process (2, 16). In our case, despite significant postoperative seizure decrease, HS on MRI and memory problems progressed; therefore, continuing autoimmune activity seems to be of major role, since DM1 and CA manifested as well.

Cerebellar ataxia (CA) is the second most frequent GAD-autoimmune disorder and is often comorbid with DM1 (3, 30–32). Although infrequent, association with epilepsy is possible, including refractory GAD-TLE preceding the CA by up to 15 years (32). Similar to what was already described (32), the full-blown CA in our case was antedated by intermittent episodes of diplopia, vertigo, and ataxia wrongly attributed to new AED. Most likely, the transient episodes represented subtle dysfunctions that in already proven GAD autoimmunity should raise concern about impending CA and prompt evaluation and immunotherapy to increase the chance of improvement (32).

Patients with delayed diagnosis of GAD-associated epilepsy were found to be usually ASD-resistant and not responding to immunotherapy (29). In such difficult cases, "the interplay between AEDs and immunotherapy" (29) is the cornerstone of management, which, in our patient, was further complicated by the subsequent manifestation of DM1 and CA. The treatment approach in every case must be individually oriented, and in this regard, epilepsy surgery cannot be excluded as an option for improvement. We hope that our case could be accepted as an example of complex clinical scenarios, in which tailored and very selective epilepsy surgery might be a useful treatment option to reduce seizure frequency and improve quality of life.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

All clinical data in this case report were provided by the patient or collected by the authors with the consent of the patient. Written informed consent was obtained from the patient for the publication of this report.

AUTHOR CONTRIBUTIONS

PD participated in patient management, clinical data analysis, and writing of the article. KM participated in patient management and revision of the article. All authors contributed to the article and approved the submitted version.

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Time-Series Generative Adversarial Network Approach of Deep Learning Improves Seizure Detection From the Human Thalamic SEEG

Bhargava Ganti[1†‡], Ganne Chaitanya[2,3‡], Ridhanya Sree Balamurugan[4], Nithin Nagaraj[5†], Karthi Balasubramanian[1†§] and Sandipan Pati[2,3*§]*

[1] Department of Electronics and Communication Engineering, Amrita School of Engineering, Amrita Vishwa Vidyapeetham, Coimbatore, India, [2] Texas Institute of Restorative Neurotechnologies, University of Texas Health Science Center, Houston, TX, United States, [3] Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, United States, [4] School of Biotechnology, National Institute of Technology Calicut, Kozhikode, India, [5] Consciousness Studies Programme, National Institute of Advanced Studies, Bengaluru, India

Seizure detection algorithms are often optimized to detect seizures from the epileptogenic cortex. However, in non-localizable epilepsies, the thalamus is frequently targeted for neuromodulation. Developing a reliable seizure detection algorithm from thalamic SEEG may facilitate the translation of closed-loop neuromodulation. Deep learning algorithms promise reliable seizure detectors, but the major impediment is the lack of larger samples of curated ictal thalamic SEEG needed for training classifiers. We aimed to investigate if synthetic data generated by temporal Generative Adversarial Networks (TGAN) can inflate the sample size to improve the performance of a deep learning classifier of ictal and interictal states from limited samples of thalamic SEEG. Thalamic SEEG from 13 patients (84 seizures) was obtained during stereo EEG evaluation for epilepsy surgery. Overall, TGAN generated synthetic data augmented the performance of the bidirectional Long-Short Term Memory (BiLSTM) performance in classifying thalamic ictal and baseline states. Adding synthetic data improved the accuracy of the detection model by 18.5%. Importantly, this approach can be applied to classify electrographic seizure onset patterns or develop patient-specific seizure detectors from implanted neuromodulation devices.

Keywords: temporal lobe epilepsy, thalamus, Bidirectional Long-Short Term Memory (Bi-LSTM), seizure detection algorithm, Generative Adversarial Network (GAN)

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***Correspondence:**
Sandipan Pati
patilabuab@gmail.com
Karthi Balasubramanian
b_karthi@cb.amrita.edu

†ORCID:
Bhargava Ganti
orcid.org/0000-0002-3348-3032
Karthi Balasubramanian
orcid.org/0000-0002-4418-4898
Nithin Nagaraj
orcid.org/0000-0003-0097-4131

‡These authors share first authorship
§These authors share senior authorship

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INTRODUCTION

Despite significant advances in diagnostic and therapeutic technologies, over 30 million people worldwide have drug-resistant epilepsy (DRE) (1). Increased seizure burden plays a central role in morbidity and mortality, thereby emphasizing the need for seizure preventative therapies (2). Surgical resection of the seizure focus may yield seizure freedom and remains the first line of treatment in DRE. However, in many patients, resection or ablation is not an option if the seizure foci are widespread involving multiple regions or are non-localizable (3, 4). Neuromodulation of the epileptogenic circuit remotely *via* a central hub like the thalami is often the treatment of choice in this cohort (5). Accurate and timely detection of seizures is clinically necessary for

the development of feedback "responsive" therapy and monitoring seizure counts for therapy adjustment. In recent years, the medical community has widely adopted machine learning approaches to develop seizure detection algorithms. Various linear and non-linear features are extracted and have been used for seizure detection and prediction (6–12). However, these seizure detection algorithms have been optimized from electrophysiological signals obtained from the seizure focus. Machine learning algorithms to detect seizures from outside the seizure focus are still in their nascency (13).

There are multiple challenges in developing seizure detectors from regions like the thalamic subnuclei, i.e., (a) the thalami have lower power spectra, and the spectral contents are significantly different from the epileptogenic cortex during interictal and seizure substages (14), (b) the thalami are not routinely implanted during surgical evaluation, and hence electrophysiological recordings during seizures are scarce. Thus, the sample size is small and often inadequate for data-intensive deep learning models, and (c) Chronic local field potentials (LFPs) can be recorded from the thalami in patients with sensing-enabled deep brain stimulators (DBS) and can potentially be the solution to inadequate data. However, establishing the accuracy of detecting seizures in the ambulatory setting is challenging. In the proposed work, we overcome the inadequate sample size by applying a novel deep learning approach for detecting seizures from LFPs recorded directly from the human thalamic subnuclei.

Several deep learning algorithms have been proposed for automatic seizure detection. These include artificial neural networks, convolution, and deep convolution-based seizure detection systems. Amongst them, a widely popular and high-performing method for seizure classification using EEG is the use of temporal models such as recurrent neural network (RNN) and its variants, including Long-Short Term Memory (15)(LSTM) Bidirectional LSTM (BiLSTM), Gated Recurrent Unit (GRU) (16), and Generative Adversarial Networks (GAN). LSTMs are known for their excellence in learning patterns from temporal information while preserving dependencies in very long-time sequences. However, these temporal models (RNN, LSTM, GRU) are first trained in an adequately powered sample to learn the inherent temporal dependencies of the EEG signal that accurately represent the features of a seizure. In the present study, we apply the time-GAN method with the novel goal of detecting temporal lobe seizures from a limited number of the LFPs recorded from the human thalami. We hypothesize that the performance of a deep learning algorithm classifying seizures from the interictal state can be significantly improved by adding synthetic data using the GAN approach.

METHODS

Study Participants and Ethics

Patients diagnosed with drug-refractory temporal lobe epilepsy (TLE) who underwent stereoelectroencephalography (SEEG) for localization of seizure focus were included in the study. The indication for SEEG was clinically necessary and determined in a multidisciplinary patient management conference. Within this cohort, consenting adults who had thalamic implantation for research were included in the present analysis. The multi-step consenting and evaluation process has been described in detail in our previous studies (13, 14, 17). The electrophysiological sampling of the thalamic subnuclei was performed under the supervision of the IRB, and all patients provided written informed consent. To mitigate the risk associated with implanting an additional depth electrode for research sampling of the thalamus, we modified the trajectory of a clinically indicated depth electrode sampling the operculum-insula to track medially for recording from the thalamus. Clinician-identified seizures were documented for all patients, and the SEEG data was clipped and parsed for analysis. Ictal ($N = 84$ from 13 patients) and baseline interictal data (Length: 550 s prior to seizure) were obtained. The demographic details of the study participants are detailed in **Table 1**.

TABLE 1 | Demographic details of the study participants.

Demographics	$N = 13$
Age (years)	42.8 ± 11.9
Gender (M:F)	6:7
Details of recording:	
Number of contacts	2,205 (R: 1,328, L: 877)
Thalamic implant laterality (R:L)	8:3
Thalamic target nucleus (Anterior: Central)	8:3
Disease burden measures:	
Age at Onset (years)	28.8 ± 16.2
Duration of Epilepsy (years)	14.3 ± 16.3
Frequency of focal seizures (/month—median and range)	4 (range: 1–48)
H/o FBTCS (Present: Absent)	6:7
MRI (Abnormal: Normal)	7:6

M, male; F, female; FBTCS, focal to bilateral tonic-clonic seizures; MRI, magnetic resonance imaging.

SEEG Recording

All SEEG implantation procedures were performed using robotic assistance (ROSA device, MedTech, Syracuse, NY) (12–16 contacts per depth electrode, 2 mm contact length, 0.8 mm contact diameter, 1.5 mm intercontact distance, PMT® Corporation, Chanhassen, MN). Once implanted, the patients were monitored over 4–12 days in the epilepsy monitoring unit (EMU). SEED data as recorded using Natus Quantum (Natus Medical Incorporated, Pleasanton, CA, sampling rate 2,048 Hz). Signals were referenced to a common extracranial electrode placed posteriorly in the occiput near the hairline.

Accurate Anatomical Localization of SEEG Depth Electrodes

The details of the accuracy of the implantation strategy have been reported in our previous study (17). Here we highlight the main steps to localize the SEEG electrodes to the various cortical regions and the thalamic subnculei. The post-implant CT-scan was coregistered to preimplant MRI using Advanced Normalization Tools (ANTs) and refined registration of deep

structures was performed using brain shift correction to improve the registration of subcortical structures using Lead-DBS v2 software (18). Both the images were normalized to ICBM 2009b NLIN asymmetric space using the symmetric diffeomorphic image registration. Following this, the localization of the thalamic contacts was performed in Lead-DBS, while the cortical channels were performed in iElecetrodes (19). Thalamic contacts were registered to Morel's thalamus atlas, while cortical contacts were localized using AAL2 atlas (20).

Identification of Interictal Epochs and Seizures in the Seizure Onset Zone and Thalamus

The time of the seizure onsets and offsets was annotated by a board-certified epileptologist (SP). Seizure onset in the cortex was marked as "unequivocal EEG onset" (UEO) at the earliest occurrence of rhythmic or repetitive spikes that was distinct from the background activity. SEEG segments were clipped to include 10 min before this UEO and 10 min after seizure termination. Four different clinical seizure types were included for analysis: focal aware seizures (FAS), focal impaired awareness seizures (FIAS), and focal to bilateral tonic clonic seizures (FBTCS) (21). Epochs of "interictal state" (28 epochs with each epoch lasting 9 min) were visually screened and identified from the non-seizure segment of the SEEG that was at least 1 h preceding seizure. Our previous study showed that the interictal spikes in baseline data need not be actively removed for classifying ictal states from baseline states (13). Secondly, interictal spikes will be present while training real-time data, e.g., line length detection in responsive neuromodulation systems (RNS) (22). Hence for translational purposes, no effort was made to exclude epileptiform spikes in the baseline epochs. **Supplementary Material** shows the details of the ictal and baseline data.

Deep Learning Architectures

The input to the BiLSTM classifier was the interictal baseline and ictal thalamic EEG data. The baseline and the ictal data from the 84 seizures (13 subjects) were initially grouped by the subject identification. Since the length of ictal data was variable, we chose the length of the shortest seizure for any given subject (i.e., 14 s) as the length of the analyzable data. To avoid a discrepancy in the length of data between ictal and baseline segments, we chose a similar 14 s length of SEEG data from the initial segment of the baseline data. The input to the BiLSTM classifier is a 2D array of data. Hence, the 14 s of the data were then clipped into multiple 1 s epochs and rearranged into a two-dimensional array of 14 × 2,048 samples (**Figures 1A–C**).

Principally, the LSTM network only obtains information from the previous input observations but cannot use that information for future input observations. However, the BiLSTM model, composed of two independent LSTM networks, can transmit information bi-directionally and increase the learning ability of the system output (**Figure 2**) (23). Sixty three seizures from 11 subjects (were used to train the classifier differentiating ictal from baseline. Subsequently, 21 seizures collected from 2 patients were used for testing the model. Each BiLSTM classification model consisted of 64 units of LSTMs in the encoding layer and a kernel regularizer of 12 followed by a drop-out layer with a drop-out ratio of 0.25 and a batch normalization layer. This was followed by a dense layer of 64 units with rectified layer unit (ReLU) activation function (24). For the final output, a dense layer with SoftMax activation function of two units was used for the binary classification of baseline interictal and ictal states.

Generation of Synthetic Data With GAN

GANs learn and generate synthetic data by preserving the data distributions. For a generation of sequential data, the temporal dynamics need to be preserved. Yoon et al. (25) proposed the concept of time-series GAN (TGAN) that was able to capture not only the distribution of data at each instant but also the presence of various features across time (**Figures 3A,B**). TGAN differs from other GAN architectures in two ways. (a) By introducing an embedding network, it reduces the dimension of the adversarial learning space, and (b) uses supervised adversarial loss, unlike GAN, where unsupervised methods are used. In our analysis, TGAN was used to generate synthetic data that was 10 times the original data. The data (ictal and baseline) were fed into the TGAN model to produce the augmented data (**Figure 1D**).

Validation of Synthetic Data

The second level BiLSTM analysis classifies ictal and baseline states based on the synthetic TGAN data (**Figure 1E**). Hence it was necessary to validate the similarity of the synthetic data with the original data. The validation was quantified using the Train-Synthetic-Test-Real method (TSTR), where a logistic regression classifier model with a single layer gated recurring units (GRU) with 12 units was used for training both the original and the synthetic data. Each model was trained separately with 75% of the original and the synthetic data, respectively. The testing of both the models is done with the remaining 25% of only the original data set (25). This allowed us to estimate individual seizure level and subject level coefficient of determination (R^2) values and the percentage difference between original and synthetic data (**Table 2**). Finally, a *t*-distributed stochastic neighbor embedding (*t*-SNE) analysis was performed to visualize if the ictal and baseline data could be better segregated using the original or the synthetic data. T-SNEs were generated in MATLAB using the "*exact*" algorithm, with Mahalanobis distance, the perplexity of 50, and PCA dimensions of 3.

Performance of BiLSTM on Original vs. Synthetic Data

To estimate the performance of the BiLSTM following metrics were computed: sensitivity (Sn or recall), specificity, accuracy (for training, validation, and testing data), positive predictive value (PPV or precision), F1-score, and area under the curve (AUC). The difference in the performance of the BiLSTM classifiers for original and synthetic data was visualized using ROC (receiver operating characteristic) curve by testing the relationship between sensitivity and 1-specificity.

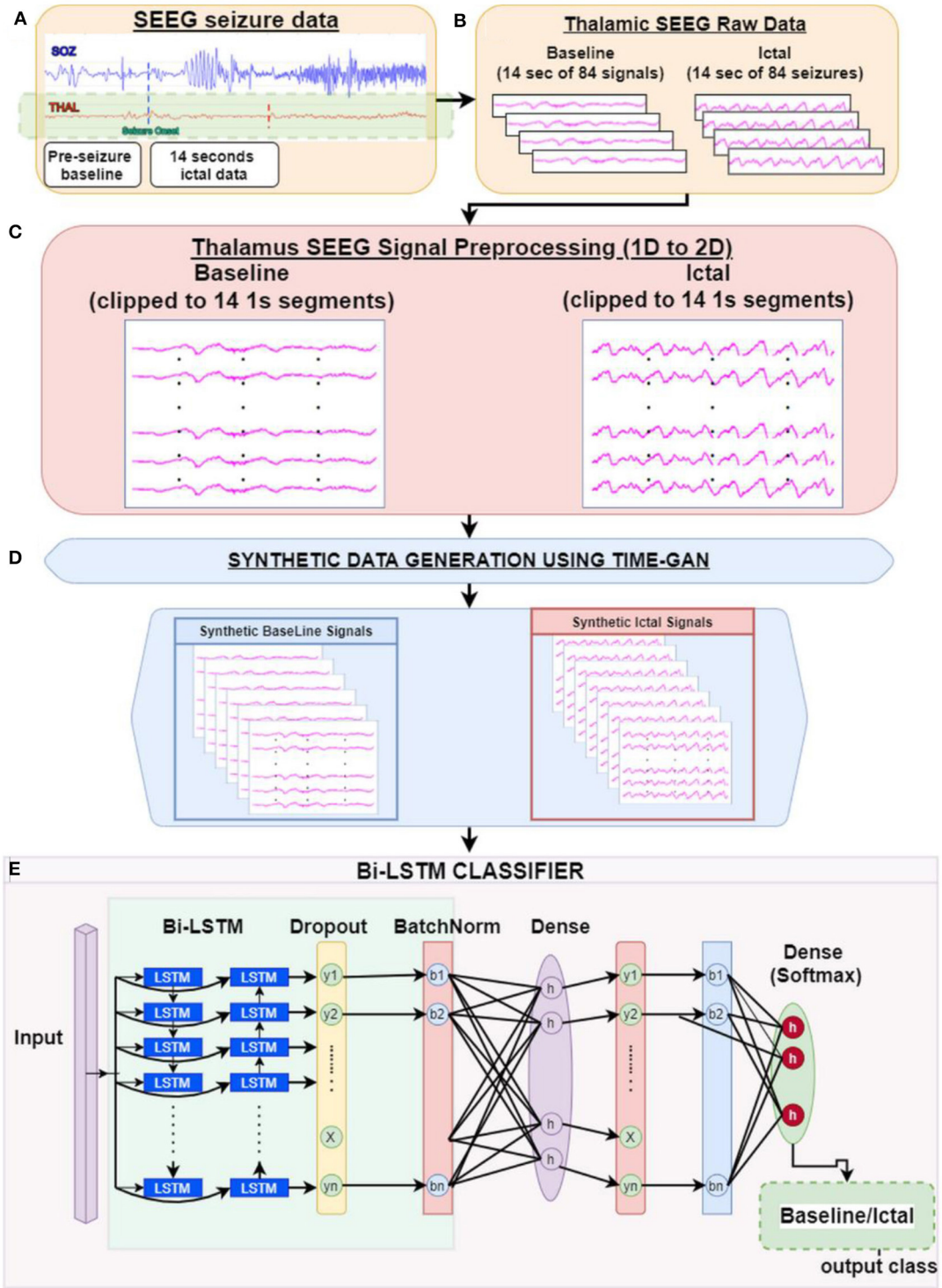

FIGURE 1 | Study pipeline: **(A)** Clinician identified seizure onset timings in the hippocampal-amygdalar complex were determined. We then clipped thalamic EEG segments into epochs of baseline and seizure onset. **(B)** Each epoch consisted of 14 s of raw thalamic EEG segments **(C)**. As an initial step, each 14-s 1D signal epoch was fragmented into 1-s segments to generate a 2D matrix of time × signal (sampling rate: 2,048 samples/s) **(D)**. The data was then submitted to the TGAN system to generate synthetic data at the individual subject level. TGAN is expected to generate synthetic data that mimics original data and augment the sample size required for deep learning. **(E)** Two separate bidirectional long short-term memory (BiLSTM) models were tested independently on original and synthetic data.

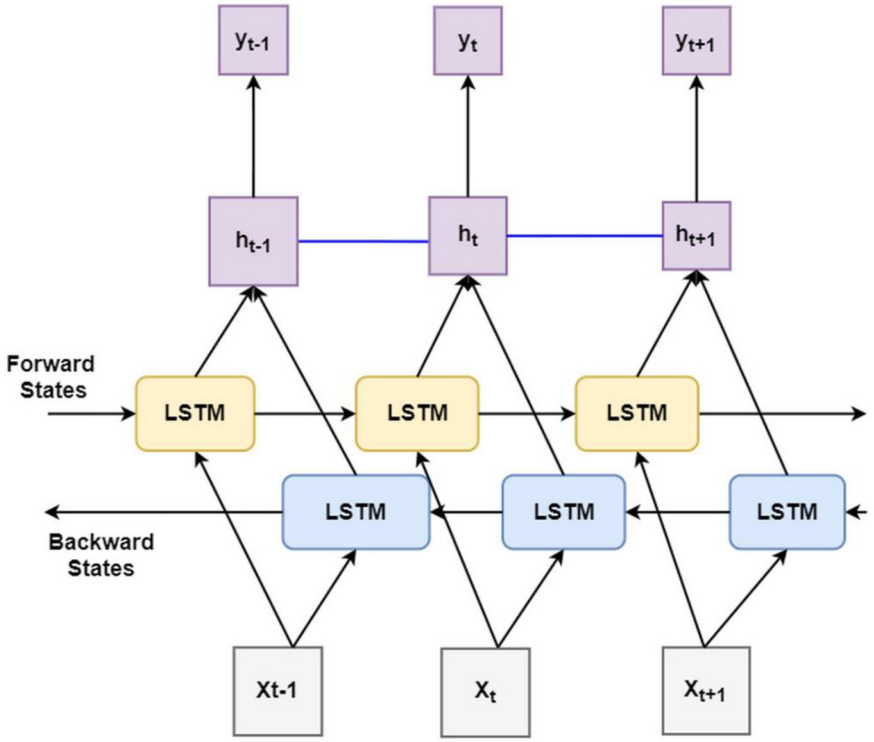

FIGURE 2 | Block diagram of bidirectional long short-term memory learning (BiLSTM): A BiLSTM, is a serial sequence learning model that consists of two LSTMs operating in two directions effectively increase the amount of information available to train and test the network. The first LSTM inputs in data in a forward direction, and the second LSTM in a backwards direction. This improved the context available to the learning algorithm helping it to learn the sequence of the time series data, i.e., what data immediately follows (X_{t+1}) and precedes (X_{t-1}) the events of interest such as the seizure (X).

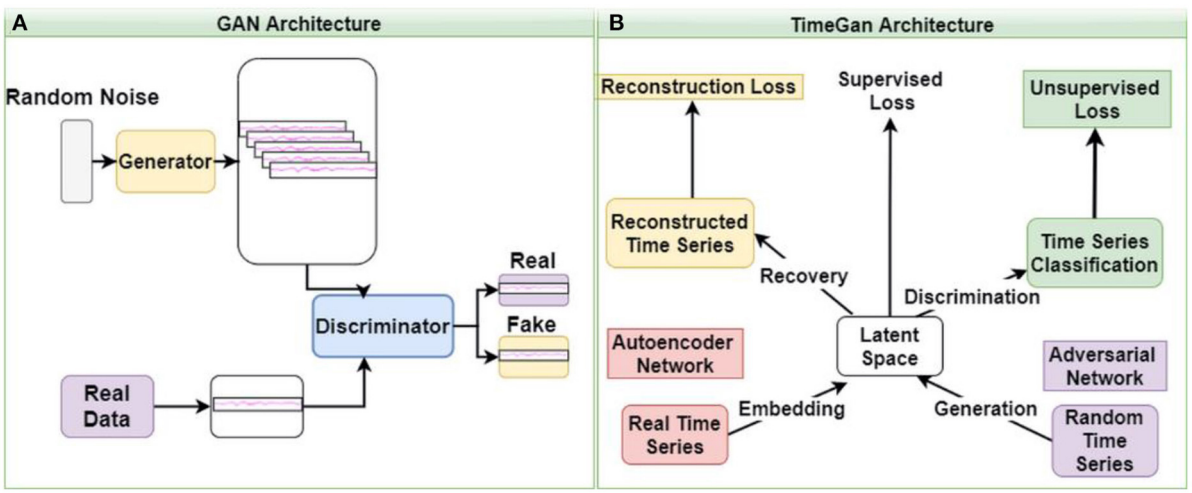

FIGURE 3 | The architecture of GAN **(A)** and time GAN **(B)**. **(A)** Generative Adversarial Networks (GAN) is an unsupervised learning system that involves discovering and learning the patterns in input data to generate a new set of synthetic data that mimics the original dataset. **(B)** Time-series Generative Adversarial Networks (Time-GAN) combines the flexibility of the unsupervised paradigm with the control by incorporating supervised training.

TABLE 2 | Coefficient of determination (R2) and mean absolute error (MAE) values obtained from regression models comparing original and synthetic data for the baseline and ictal data.

S_ID	#Seizures	Baseline					
Validation		R^2			MAE		
		Original	Synthetic	% Difference	Original	Synthetic	% Difference
7	10	0.468	0.469	0	3.219	3.219	0
8	7	0.367	0.370	1	9.220	9.146	1
9	9	0.260	0.268	3	4.876	4.877	0
10	7	0.182	0.180	1	20.189	20.155	0
14	8	0.285	0.275	4	4.349	4.348	0
15	6	0.850	0.880	3	32.485	32.350	0
16	11	0.910	0.920	1	8.976	8.976	0
17	3	0.253	0.250	1	4.348	4.368	0
18	3	0.413	0.420	2	7.171	7.170	0
19	5	0.380	0.380	0	3.104	3.104	0
20	4	0.400	0.420	5	12.628	12.608	0
21	6	0.680	0.640	6	12.979	12.881	1
22	5	0.854	0.866	1	10.977	10.977	0
	Group	0.484 ± 0.251	0.487 ± 0.256	2 ± 1%	10.34 ± 8.25	10.32 ± 8.21	0.1 ± 0.3%
				Ictal			
7	10	0.868	0.869	0	2.958	2.957	0
8	7	0.456	0.470	3	14.710	14.710	0
9	9	0.380	0.370	3	4.828	4.828	0
10	7	0.218	0.210	4	23.593	23.602	0
14	8	0.360	0.365	1	6.533	6.533	0
15	6	0.420	0.426	1	59.375	59.376	0
16	11	0.910	0.910	0	5.825	5.825	0
17	3	0.340	0.335	1	5.215	5.215	0
18	3	0.413	0.420	2	8.114	8.144	0
19	5	0.278	0.269	3	5.617	5.636	0
20	4	0.400	0.400	0	3.729	3.729	0
21	6	0.600	0.600	0	21.081	21.082	0
22	5	0.750	0.760	1	6.807	6.661	2
	Group	0.491 ± 0.221	0.492 ± 0.224	1 ± 1	12.95 ± 15.42	12.94 ± 15.42	0.1 ± 0.5

S_ID, Subject Identification number; #, number of; R^2, coefficient of determination; MAE, mean absolute error; % difference, absolute percentage change in original and synthetic.

Implementation Details

The BiLSTM and TGAN models were tested in Python, and t-SNE analysis was performed in MATLAB. We utilized Keras (26), scikit-learn, an open-source Python API that takes into account the neural organization structures based on top of TensorFlow, to construct all learning models.

RESULTS

Safety and Localization of Thalamic Electrodes

Thirteen subjects were included in the study, with 10 had electrodes localized to the anterior nucleus of the thalamus (ANT) and 3 in the centrolateral thalamic nuclei (**Table 1**, **Figure 4**). CT brain (post-implant and post-explant) did not show any thalamic hemorrhage. Eight subjects were implanted on the right side and three on the left side.

Clinico-Demographic Details of Subjects

Table 1 summarizes the clinic-demographic details of the subjects included in this study. A total of 84 seizures from 13 subjects were analyzed. The seizure onset zone was determined based on the clinical consensus among the epileptologists during the epilepsy surgical conference. The identified seizure focus was: medial temporal (4 subjects), mesial + temporal pole onset (3 subjects), temporal plus (5 subjects), with the plus representing additional seizure foci (orbitofrontal or insula or suprasylvian operculum) (27). The seizure types were: ES (19), FAS (24), FIAS (28), and FBTCS (6).

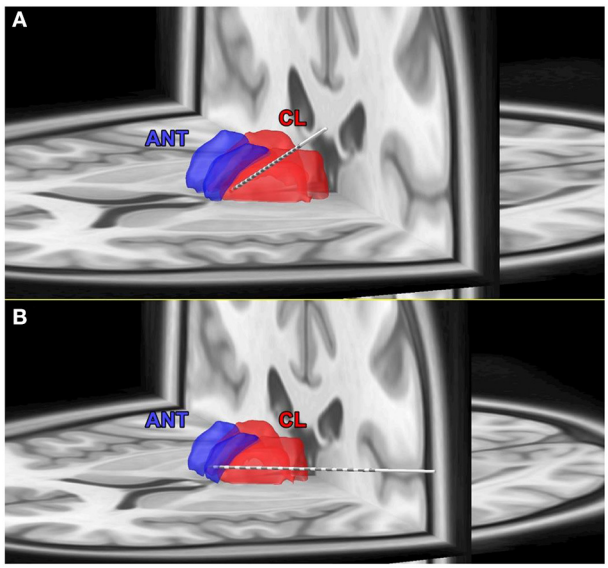

FIGURE 4 | (A) Coregistration of post-implant CT scan on pre-implant MRI and Morel's thalamic atlas to determine the exact localization of thalamic targets. **(A)** An example of the electrode localized to the central thalamic nucleus (CL). **(B)** An example of the electrode localized to the anterior thalamic nucleus (ANT).

TGAN Augmented Synthetic Data Were Comparable to the Original SEEG Data

The TGAN generated synthetic data was similar to the original SEEG data. At baseline, there was no difference between the mean coefficient of determination (R^2) of the original and synthetic data (original: 0.484 ± 0.251, synthetic: 0.487 ± 0.256, $t = -0.6$, $p = 0.27$). Similarly, there was no difference in the mean absolute error (MAE) of original and synthetic data (original: 10.34 ± 8.25, synthetic: 10.32 ± 8.21, $t = 0.008$, $p = 0.49$). Similarly, the TGAN augmented data synthesized during the ictal period did not differ from the original data in R^2 (original: 0.491 ± 0.221, synthetic: 0.492 ± 0.224, $t = -0.0097$, $p = 0.49$) and the MAE (original: 12.95 ± 15.42, synthetic: 12.94 ± 15.42, $t = 0.001$, $p = 0.49$).

TGAN Augmented Synthetic Data Enhanced the Performance of the BiLSTM Classifier

We constructed ROC curves to determine the performance of the BiLSTM on original, and TGAN augmented synthetic data. The classification of the ictal from the baseline data was superior with the synthetic TGAN augmented data compared to the original data (original: AUC: 60% and synthetic: 78.5%, **Figure 5A**). This improvement in the performance of the BiLSTM models could be better visualized using three component t-SNE plots (**Figures 5B–D**). T-SNE of original data failed to parse the ictal and baseline clusters separately (**Figure 5B**), while T-SNE performed on the TGAN augmented synthetic data with the same parameters, demonstrated a clear separation into ictal and the baseline clusters (**Figure 5C**). We initially noted that the ictal clusters were further separated in space into multiple clusters. A t-SNE indexed by the subject ID showed that TGAN amplifies the ictal data specific to each patient that is distinctly different from their comparable baselines (**Figure 5D**). The result suggests that the patient-specific electrographic seizure onset patterns were retained in the TGAN augmented data (**Figure 5D**).

Overall, the performance of the BiLSTM in classifying ictal and baseline states from thalamic SEEG data was enhanced by the use of TGAN generated synthetic data over the original data. The accuracy of the training data improved by 31.75%, the validation data improved by 32.1%, and finally, the testing data improved by 18.5%. The sensitivity and PPV of the BiLSTM classifier on improved by 13 and 10% on the testing data (**Figure 6**).

DISCUSSIONS

Currently the only clinically available neuromodulation system that is based on a close loop system approved by the United States Food and Drug Administration (FDA) is the Responsive neurostimulation. To date this device has been extensively used to target neuromodulation in the cortical regions. This device uses amplitude threshold and line-length as the main seizure detection algorithms. There have been anecdotal reports of implanting the human thalamus with RNS, where the seizures were still detected in the cortex but the stimulation was performed in the ANT. There has been growing literature that thalamus is involved early in focal seizures, particularly in TLE. Some studies have also tried to detect seizures from human thalamus. This detection of seizures from the human thalamus and understanding the pattern of involvement of thalamus on focal seizures is of utmost importance while developing closed-loop DBS systems. To date, it has been shown that ANT DBS (open loop) has had great success in patients with drug resistant epilepsy particularly those patients who are negative for a lesion on the MRI, with a median seizure frequency reduction of 75% at 7 years of therapy.

Newer sensing-enabled DBS systems have been approved by the FDA since 2018 in the practice of epilepsy and since 2002 for Parkinson's disease. These devices offer closed loop sensing and diary functions (record of events) to monitor symptoms and tailor therapeutic stimulation. A recent study has shown that closed loop neurostimulation within the human thalamus has shown a $\geq$50% reduction in seizure frequency with no adverse effects on mood, memory or behavior. With the advent of such sensing-enabled closed loop systems, there is a clinical need to develop seizure detection algorithms from the thalamic SEEG and not just from the cortical seizure onset zone. One of the most critical steps in enabling sensing, is to develop patient-specific detection based on individual subject's thalamic seizure patterns. Often, the data obtained from a single subject is limited and hence the translation of deep learning approaches has been hindered by the lack of larger samples of curated ictal thalamic SEEG needed for training these classifiers. Here, we demonstrate the utility of generating

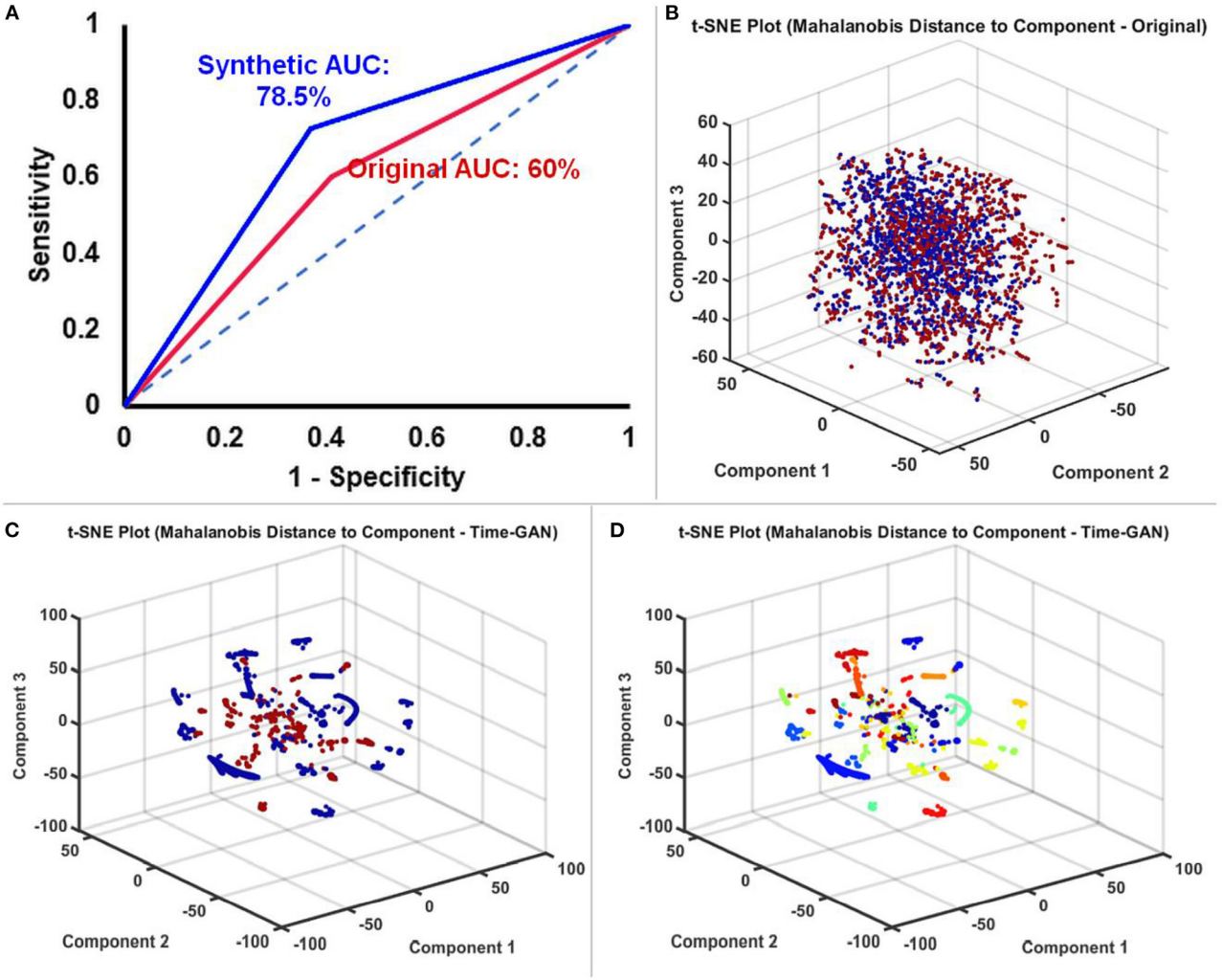

FIGURE 5 | (A) Receiver operator characteristic (ROC) curves comparing the performance of BiLSTM models trained with original and TGAN augmented synthetic data. **(B)** T-SNE plot of the original SEEG data showing the baseline (red) and ictal (blue) data. **(C)** T-SNE plot of the TGAN augmented synthetic data shows a clear distinction between the two groups (baseline in red and ictal in blue). **(D)** A t-SNE indexed by the subject ID showed that TGAN amplifies the ictal data specific to each patient that is distinctly different from their comparable baselines (the different colors are indicative of the data different 13 different subjects). In conjunction with C, we understand that data is not only classified based on ictal and interictal data, but also distinctly clustered based on individual subjects' data.

synthetic data using GAN that can augment the sample size and improve the performance of BiLSTM. Importantly, this approach can be applied to classify electrographic seizure onset patterns or develop patient-specific seizure detectors from implanted neuromodulation devices. In summary, we found that Time-GAN helps generate synthetic time series that resemble the original data, with a very small mean absolute error rate of $0.1 \pm 0.5\%$ between the original and the augmented data. In fact, when this time-GAN augmented data was used in BiLSTM classifier to detect the ictal state, we noticed that the accuracy of the classifier improved by 18.5%, sensitivity by 13% and PPV by 10% when compared to classifying using the original data. Though marginal, such an improvement is promising and further refinement of such models are required to optimize seizure detection in the thalamus.

Performance of Deep Learning Algorithms for Seizure Detection

Table 3 summarizes the performance of deep learning algorithms in detecting seizures from electrophysiological signals recorded from the scalp and intracortical regions (LFPs). To date, deep learning algorithms to detect seizures were applied to EEG obtained from the cortical areas that participate in seizure generation. Our study is distinct and the first of its kind to perform deep learning detection on EEG recordings from a brain region that is remote to the seizure focus.

As expected, the performance of these classifiers was higher with biosignals obtained directly from the cortex than from the scalp which is likely to be closer to the seizure focus. In those studies, the sample size for deep learning consisted of over 100 ictal EEG data. The main motivation of this study is to highlight

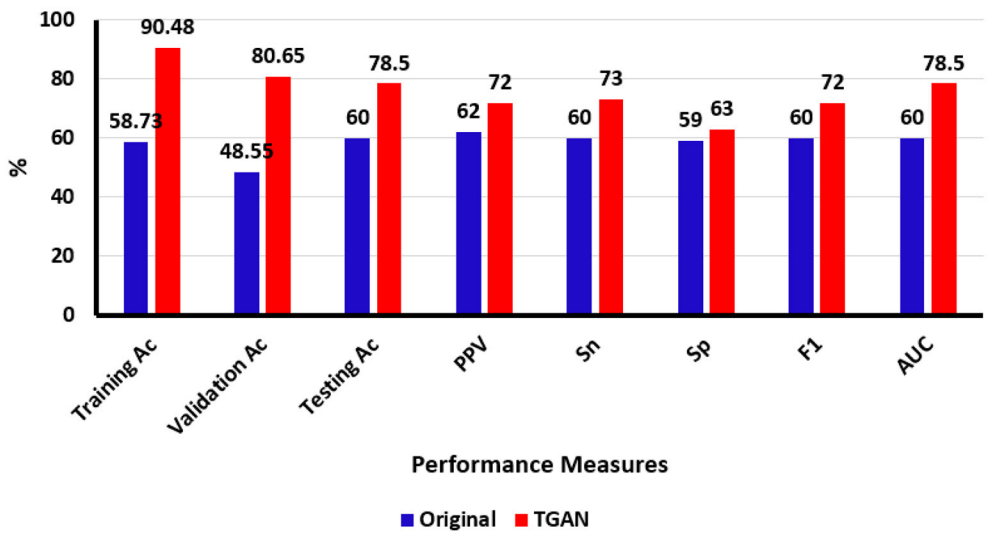

FIGURE 6 | Bi-directional Long Short-Term memory (BiLSTM) classification results using original and time generative adversarial networks (Time-GAN) generated synthetic data. Ac, accuracy; PPV, positive predictive value, Sn, sensitivity; Sp, specificity; F1, F-score; AUC, area under the curve, %, percentage.

TABLE 3 | Summary of prior studies evaluating deep learning for seizure detection.

References	Algorithm	No. of classes	No. of patients: No. of seizures	Accuracy (%)	Data type
Tsiouris et al. (29)	LSTM	2	23:198	99.8	ICEEG
Ullah et al. (30)	CNN	2	5:100	99.8	Scalp and ICEEG
Abdelhameed et al. (31)	Deep LSTM	5	5:100	100	Scalp and ICEEG
Avcu et al. (32)	Deep CNN	2	29:120	93.3	ICEEG
San-segundo et al. (33)	Deep CNN	3	5, 500:3,750, 11,500	95.7	ICEEG
Lu et al. (34)	Deep CNN	3	5, 500:3,750, 11,500	91.8	Scalp
Asif et al. (35)	SeizureNet	2	500:11,500	94.0	Scalp
Yao et al. (28)	BiLSTM	2	23:665	84.55	Scalp
Hu et al. (36)	BiLSTM	2	23:665	93.61	Scalp
Yan et al. (37)	CNN	2	679:177	98	ICEEG

ICEEG, intracranial EEG; LSTM, long short term memory; BiLSTM, bidirectional long short-term memory; CNN, Convolutional Neural Network.

how data augmentation techniques can improve the accuracy of the classifier, albeit a lower overall performance of our classifier in comparison to other studies. Even when data is smaller (84 seizures), we can use data-augmentation methods to enhance the performance of the classifier (accuracy improved by 18% in our current study) and improve the detection performed in subcortical neuromodulatory targets such as the thalamus, which are distant and outside the seizure cortex. Wei et al. (38) were among the pioneering teams in demonstrating improved seizure detection in scalp EEG with GAN models. They used the Wasserstein Generative Adversarial Nets (WGANs) combined with a convolutional neural network (CNN) to demonstrate a 3% improvement in accuracy (81.5–84.4%) and a near 2% improvement in the sensitivity (70.68–72.11%). In our study, the accuracy and sensitivity improved by 18.5 and 13%, respectively. Zhao et al. (39), in their model with a 1D-CNN with data-augmentation on data obtained from intracranial EEG data that was close to seizure focus, achieve an improvement of only 3% (accuracy of 89.28% compared to 86.89 with a support vector machine). They proposed a data augmentation method which leverages feature correlations in the transformed domain rather than in the original domain where time-domain data is converted to the frequency domain by discrete cosine transform (DCT), and new artificial data is generated by combining different frequency bands from different data, and converted back to time-domain data. Overall, these studies and ours, point to the promising future of using data augmentation techniques for better seizure detection to improve therapeutic stimulation.

Augmented Subject-Specific Classification With Temporal GAN

GANs, are deep-learning algorithms where two competing networks, namely the generator and the discriminator, compete against each other until the generator generates artificial data of high quality. According to Goodfellow et al. (40), "the generative models are analogous to a team of counterfeiters trying to produce fake currency without being detected. The discriminative model is analogous to the police trying to detect fake currency. The competition between the generator and discriminator drives improvement until the counterfeiters are indistinguishable from the genuine currency." Thus, GAN has been used to classify interictal spikes and in EEG-based brain-computer interfaces. Our result supports the use of GAN to produce synthetic data to augment the performance by 18% as compared to using only the original data. The ability to classify seizures from limited samples of unprocessed LFP signals may provide a clinical advantage in neuromodulation devices where efficient processing at a lower computational expense is desired.

Study Limitations

There is a proof-of-concept study evaluating the use of synthetic data in augmenting sample size for deep learning. The study needs to be extended to a larger cohort with thalamic recordings of seizures and interictal baseline. One major challenge of the temporal GAN model is that it is computationally intense and consumes time to learn or converge to local minima and hence slows the training process. Another limitation of GAN is that the presence of discontinuous (e.g., ECoGs obtained from clinical neuromodulation devices) data may synthesize incorrect data. In our study, the duration of the data used for time-GAN analysis was 14 s based on the shortest duration of the ictal event from our cohort and in the future the results need to be optimized to individual patients, in whom the seizure durations are likely to vary significantly. This will also have a bearing on minimizing the detection latencies in the future models. Such sophisticated models will help build closed-loop neuromodulation strategies where early seizure detection can be used to pace the brain to abort seizures. Regarding the size of our data-set, we used 63 seizures from 11 patients' data for training and 21 seizures from 2 patients's data for testing the BiLSTM and Time-GAN models. While our study did show a reasonable improvement in the accuracy of the BiLSTM models and can be used as a proof of concept, in the future it is essential to validate this using random sampling of the patients' data and at individual subject level to emphasize and validate its clinical use. Also, cross validation across all patients' data would further strengthen the validity of the model. Since GAN is time consuming and resource demanding, our purpose was not to run it on all subjects but show how even in few subjects an improved accuracy can be obtained. Another limitation is that we did not determine the exact cause of improved accuracy and test the fidelity, diversity, and generalization of the data augmentation method, i.e., TGAN. These measures help determine the point at which the generative model surpasses and fools the discriminative network. Once the TGAN augmented data robustly mimics the real data, the TGAN-output is then used as the input in BiLSTM models improve accuracy. TGANs supersede BiLSTMs at finding a better low dimensional representation and hence may contribute to improved accuracy. In our study, we were interested in showing if the TGAN is able to produce synthetic data effectively from available limited samples and whether that use of the synthetic data shows elevated performance as compared to the using the original data only and a more detailed validation of TGAN was to voluminous for this study.

CONCLUSION

The ability to detect seizures from the thalamus- a structure remote to the seizure focus is clinically necessary for monitoring seizure burden in drug-resistant epilepsies where seizure foci are non-localizable. In this study, we demonstrate the use of synthetic data to augment sample size and improve deep learning performance in detecting seizures from the human thalamic SEEG. The proposed framework should be extended to a larger cohort of patients with thalamic DBS in multifocal epilepsies.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data is controlled by IRB. Requests to access the datasets should be directed to patilabuab@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Alabama Birmingham Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BG and GC analyzed, interpreted, and helped in writing the mansucript. KB supervised data analysis, interpretation, and revised the mansucript. RB and NN provided analytical tools and helped in analysis of the data. SP obtained IRB approval, designed the study, interpreted the data, and wrote and revised the manuscript. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.755094/full#supplementary-material

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Brainstem Associated Somatosensory Evoked Potentials and Response to Vagus Nerve Stimulation: An Investigation of the Vagus Afferent Network

*Hrishikesh Suresh[1,2,3], Karim Mithani[1,3], Karanbir Brar[4], Han Yan[2,3,5], Samuel Strantzas[3], Mike Vandenberk[3], Roy Sharma[6], Ivanna Yau[6], Christina Go[6], Elizabeth Pang[2,6], Elizabeth Kerr[6,7], Ayako Ochi[6], Hiroshi Otsubo[6], Puneet Jain[6], Elizabeth Donner[6], O. Carter Snead[2,6,8] and George M. Ibrahim[1,2,3,8]**

[1] Institute of Biomedical Engineering, University of Toronto, Toronto, ON, Canada, [2] Program in Neuroscience and Mental Health, The Hospital for Sick Children Research Institute, Toronto, ON, Canada, [3] Division of Neurosurgery, Department of Surgery, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [4] Division of General Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada, [5] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [6] Division of Neurology, The Hospital for Sick Children, Toronto, ON, Canada, [7] Department of Psychology, The Hospital for Sick Children, Toronto, ON, Canada, [8] Institute of Medical Science, University of Toronto, Toronto, ON, Canada

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***Correspondence:**
George M. Ibrahim
george.ibrahim@sickkids.ca

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Despite decades of clinical usage, selection of patients with drug resistant epilepsy who are most likely to benefit from vagus nerve stimulation (VNS) remains a challenge. The mechanism of action of VNS is dependent upon afferent brainstem circuitry, which comprises a critical component of the Vagus Afferent Network (VagAN). To evaluate the association between brainstem afferent circuitry and seizure response, we retrospectively collected intraoperative data from sub-cortical recordings of somatosensory evoked potentials (SSEP) in 7 children with focal drug resistant epilepsy who had failed epilepsy surgery and subsequently underwent VNS. Using multivariate linear regression, we demonstrate a robust negative association between SSEP amplitude ($p < 0.01$), and seizure reduction. There was no association between SSEP latency and seizure outcomes. Our findings provide novel insights into the mechanism of VNS and inform our understanding of the importance of brainstem afferent circuitry within the VagAN for seizure responsiveness following VNS.

Keywords: vagus nerve stimulation, somatosensory evoked potentials, epilepsy, outcomes, vagus afferent network

INTRODUCTION

Epilepsy is amongst the most common and debilitating neurological disorders in children, affecting 1–2% of the pediatric population (1). Nearly 30–40% of patients are resistant to antiepileptic medications, and may benefit from surgical management (2). Vagus nerve stimulation (VNS) is a safe and well-tolerated treatment option for drug-resistant epilepsy (DRE) that involves electrical stimulation of the vagus nerve at the level of the neck using an implantable device.

Seizure outcomes after VNS are highly variable and difficult to predict (3, 4), partly due to the fact that its mechanism of action remains incompletely understood (5). Recent advances in connectomics have identified a number of structural and functional biomarkers associated with VNS response (6, 7). For example, diffusion tensor imaging (DTI) and magnetoencephalography (MEG) investigations have revealed that increased structural and functional connectivity within the vagus afferent network (VagAN)—a complex neuronal network that appears to be engaged during stimulation of the vagus nerve—portends VNS response (5, 6, 8). In particular, VNS responders demonstrate greater engagement of VagAN circuitry with stimulation of the median nerve, which shares overlapping afferent neuronal circuitry with the vagus nerve (8).

The neuromodulatory response of VNS is critically dependent upon afferent brainstem circuitry. Most vagus nerve fibers are comprised of afferent projections to the nucleus tractus solitarius (NTS), which has a wide distribution to various areas of the brainstem involved in modulating forebrain activity (9). Several of these direct and indirect projections in this region include the noradrenergic locus coeruleus (LC), the serotonergic dorsal raphe nucleus (DRN), and the parabrachial nucleus (PBN). Despite increasing evidence pointing to intrinsic brain network differences in responders to VNS, relative to non-responders, there have been little data to date that elucidate the role of brainstem pathways in mediating VNS responsiveness (10). Given the critical role of the brainstem pathways within the VagAN (5, 11), we sought to study the robustness of brainstem pathways and their association with VNS response.

In the current study, we explore the association between characteristics of the subcortically recorded component of the somatosensory evoked potential (SSEP) related to brainstem function and their association with VNS response. Previous studies have leveraged the overlapping circuitry between the spinothalamic tract and vagus afferent pathway at the level of the ventral posterolateral and ventral posteromedial nuclei of the thalamus, respectively, to identify differences in cortical activations in response to median nerve stimulation in responders compared to non-responders (8). Here, we index brainstem pathway robustness by the brainstem associated SSEP latency and amplitude following bilateral ulnar nerve stimulation in a cohort of children with drug resistant epilepsy undergoing implantation of a VNS device. We hypothesize that differences in brainstem associated evoked responses are associated with seizure response following VNS. The current work provides insights into the critical role of the brainstem pathways within the VagAN and form the basis for future work aimed at presurgically identifying ideal candidates for VNS.

TABLE 1 | Demographic information of included patients.

Characteristic	Overall ($n = 7$)
Median age, years (range)	12.3 (9.1–18.0)
Sex, *n* (%)	
Male	4 (57.1)
Female	3 (42.9)
Median follow-up, years (range)	1.4 (0.6–7.0)
Median duration of seizures at time of VNS, years (range)	7.1 (2.0–12.0)
Median duration between epilepsy surgery and VNS, years (range)	3 (0.8–7)
Mean number of anti-seizure drugs in treatment regimen (±SD)	2.57 (±0.79)
Seizure etiology, *n* (%)	
Structural	4 (57.1)
Genetic	3 (42.9)
Previous epilepsy surgery, *n* (%)	7 (100.0)
Resection of epileptogenic foci in the Rolandic cortex	2 (28.6)
Lesionectomies	3 (42.9)
Temporal lobectomy	1 (14.3)
Resection of tuber + temporooccipital lobectomy	1 (14.3)
Reason for surgical failure	
Eloquent cortex—limited resection	2 (28.6)
Multifocal disease	2 (28.6)
Biopsy only	1 (14.3)
Unknown	2 (28.6)
Seizure characteristic	
Bilateral tonic-clonic	2 (28.6)
Focal onset	5 (71.4)
Pre-VNS (v)EEG ictal localization	
Focal activity	7 (100.0)
Multifocal activity	0 (0.0)
Generalized activity	0 (0.0)
Pre-VNS (v)EEG interictal localization	
Focal activity	4 (57.1)
Multifocal activity	3 (42.9)
(v)EEG laterality	
Left	5 (71.4)
Right	1 (14.3)
Bilateral	1 (14.3)
Findings	
Subependymal nodule (not tuberous sclerosis)	1 (14.3)
Tonsillar ectopia	1 (14.3)
Non-specific T2/FLAIR high signal lesions	2 (28.6)
Tuberous sclerosis	1 (14.3)
Focal cortical dysplasia	2 (28.6)

METHODS

Patient Selection

We performed a retrospective cohort study of 7 pediatric patients who previously underwent epilepsy surgery prior to VNS, during the implantation of which, intraoperative monitoring with ulnar nerve SSEP was performed. SSEP were recorded under general anesthesia. Demographic information for subjects is included in **Table 1**. This study complies with the principles outlined in the Declaration of Helsinki and was approved by the Research Ethics Board at The Hospital for Sick Children.

Neurophysiologic Investigations

It is routine at our institution for all patients undergoing epilepsy surgery to undergo intraoperative SSEP studies for

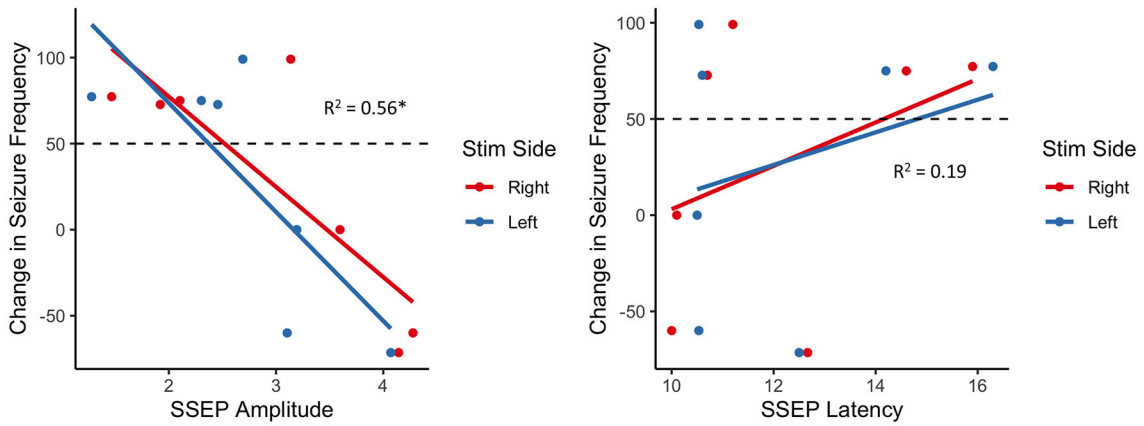

FIGURE 1 | Association between change in seizure frequency and brainstem SSEP amplitude (left) and latency (right); there is a robust negative relationship between SSEP amplitude and change in seizure frequency, with responders (above dashed line) generally exhibiting lower amplitudes than non-responders (below dashed line); $^{*}p < 0.01$.

monitoring purposes (12). Sub-cortical SSEPs from stimulation of the right and left ulnar and nerves were recorded using the Nicolet Endeavor CR platform (Natus Medical, Middleton, WI). Constant current stimulation was provided through pre-gelled surface electrodes (LifeSync Neuro, Lutz, Florida) placed over the ulnar nerve at the wrist. Potentials were elicited using a 300 us square-wave pulse delivered at a rate of 4.7 Hz. Stimulation intensity ranged from 12 to 25 mA for ulnar nerve and was adjusted based on the maximal amplitude response for each individual patient. Sub-cortical potentials were recorded from subdermal needle electrodes placed at the surface of the second cervical vertebra and were referenced to Fpz according to the International 10–20 system (13). Responses were averaged until clear, reproducible waveforms were identified, up to a maximum of 300 trials. Responses were recorded using a 30–500 Hz bandpass filter and waveforms were displayed in a 50-ms window.

Statistical Analysis

Robust Multivariate linear fixed effects models were generated using MM estimation to analyze the association between percentage reduction in seizure frequency and either subcortical SSEP latency or amplitude. Patient age at the time of VNS implantation and side of stimulation were included as covariates in these models. The analysis was done in R (14) version 4.1.1, and the *robustbase* package (15).

RESULTS

Subject Demographics

Seven patients were included in this study with a mean age of 12.3 (9.1–18) years. Four males and 3 females were included. The demographic data are presented in **Table 1** along with the seizure response rates. All patients in this study had previously undergone surgery for epilepsy prior to insertion of VNS, but the surgery had failed. Specifically, 2 patients underwent resection of epileptogenic foci in the Rolandic cortex, 3 patients had lesionectomies (2 for focal cortical dysplasia, 1 for tuberous sclerosis, 1 for filaminopathy), 1 patient had a temporal lobectomy, and 1 patient underwent both a tuberectomy and a temporooccipital lobectomy. All patients had recurrence of seizures that warranted implantation of VNS. Median duration of seizures at the time of VNS was 7.1 (2–12) years. Median duration between original epilepsy surgery and VNS was 3 (0.83–7) years. Mean follow up was 1.4 (0.6–7) years.

Seizure Characteristics and Localization

The majority of patients had exclusively focal seizures (71%), while 28% had bilateral tonic-clonic seizures. On average, patients were on 2.57 $\pm$ 0.79 antiseizure medications.

Five patients were found to have focal ictal patterns on preoperative EEG. Interictal activity was found to be focal in four patients, and multi focal in 2 patients. None of the patients demonstrated generalized ictal activity, however, one patient demonstrated diffuse interictal activity.

Two patients underwent incomplete resections due to the pathology being in eloquent cortex, two other patients were found to have multifocal disease, and one patient only underwent a biopsy. The remaining two patients had seizure recurrence despite having complete resections. However, because they did not have EEGs before VNS, the reason for failure of the previous procedure is unclear.

Imaging Findings

Apart from previous postsurgical findings, one patient had nonspecific T2 changes, one had tonsillar ectopia, and one had a subependymal nodule, two had focal cortical dysplasia and one has tuberous sclerosis.

SSEP Correlation With Surgical Outcome

Considering seizure reduction as a continuous outcome, robust generalized linear regression models were employed to identify associations between SSEP properties and VNS response, while adjusting for the child's age. We found a statistically significant

negative association between SSEP amplitude and percent reduction in seizure frequency ($\beta = -59.3$, adjusted $R^2 = 0.57$, $p = 7.67 \times 10^{-7}$), with no significant effect of age ($p = 0.25$) or side of stimulation ($p = 0.70$) (**Figure 1**). Conversely, there was no significant association between change in seizure frequency and SSEP latency.

DISCUSSION

Vagus nerve stimulation is a promising surgical intervention for certain patients with DRE. Nevertheless, heterogeneous outcomes following surgery underscore the need for preoperative biomarkers to inform patient selection. Intrinsic brain differences within the VagAN between responders and non-responders to VNS are promising biomarkers to predict responsiveness to therapy (16).

One region of the VagAN that has yet to be extensively studied is the brainstem afferent circuitry. Although evoked potentials could be measured from VNS—either transcutaneous or at the time of surgical implantations, technical challenges, such as contamination of signals due to artifacts from neck muscle activation (17) render direct analysis of evoked responses from the vagus nerve impractical. Given the overlapping circuitry between the spinothalamic tract and vagus afferent pathways (8), we sought instead, to assess the utility of SSEPs associated with brainstem function with ulnar nerve stimulation to identify the association between brainstem afferent circuitry and VNS response. We identified a robust negative association between brainstem SSEP amplitudes and changes in seizure frequency with lower amplitudes associated with better response to VNS.

Previous studies have shown that changes in SSEP amplitude, latency, and/or absence or presence of certain SSEP components can be indicative of aberrant CNS connectivity (18, 19). For example, patients with unilateral cerebrovascular lesions have abnormal, high-amplitude SSEPs over the non-affected hemisphere (20). A higher SSEP amplitude in the cerebral cortex or brainstem can also be a marker of increased cortical excitability and reduced seizure threshold. For example, children with various neurological disorders, including several forms of epilepsy, frequently exhibit larger amplitudes of cortical SSEPs (21–23). In particular, patients with progressive myoclonic epilepsy and cortical myoclonus show characteristic "giant" SSEPs, indicating that patients with lower seizure thresholds often have corresponding aberrant SSEP readings (24–27). Patients with systemic illnesses with known CNS involvement, such as primary Sjögren's syndrome, also frequently exhibit increased SSEP amplitudes compared to healthy controls (28).

Our results taken in the context of prior findings present two possibilities. The first is that increased brainstem SSEP amplitudes are indicative of increased cortical disease burden, related to a lower seizure threshold, and a decreased susceptibility to VNS therapy. Alternatively, less robust brainstem circuitry, indexed by increases in subcortical SSEP amplitudes, result in lesser ability of VNS to modulate cortical activity. There was no significant association between SSEP latency and VNS outcome, however we did not correct for limb length intraoperatively. This could be the source of the insignificant result.

CONCLUSION AND LIMITATIONS

VNS is an established treatment for patients with DRE, but there are few biomarkers to inform patient selection. Here, we identify robust negative associations between SSEP amplitude and VNS response. This study is limited by its relatively small sample size, and short period of follow-up. Short term follow up could underestimate the true effect of VNS therapy, and thus affect the strength of the association with brainstem associated SSEPs. The utility of brainstem associated SSEPs for this purpose should be further explored in future studies. Continued neurophysiological investigations on intrinsic nervous system connectivity within the brainstem and its association with VNS treatment response in DRE represent important steps toward both optimizing patient selection and further elucidating the mechanism of action of VNS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hospital for Sick Children Research Ethics Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SS, MV, and RS performed the intraoperative data collection and helped preprocess the data for analysis. AO and HO provided guidance with the analysis of the data. HS and KM analyzed the data. HS, KM, and KB wrote the manuscript with input and feedback from all authors. HY, IY, CG, EP, EK, PJ, ED, and OS provided guidance on the interpretation of the data, and the associated clinical significance. GI was involved along all stages and oversaw the overall direction and planning. All authors contributed to the article and approved the submitted version.

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