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Neuromodulation for pharmacoresistant epilepsy: From bench to bed

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Neuromodulation for pharmacoresistant epilepsy: From bench to bed

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Editorial: Neuromodulation for pharmacoresistant epilepsy: from bench to bed

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Editorial on the Research Topic
Neuromodulation for pharmacoresistant epilepsy: from bench to bed

Epilepsy is a persistent neurological disorder that affects more than 70 million people worldwide. It is characterized by a long-lasting predisposition to recurrently generate epileptic seizures, as well as accompanying psychiatric and cognitive comorbidities (1). Currently, about one-third of all people with epilepsy was drug-resistant epilepsy. Resection of epileptogenic tissue to suppress the epileptic crisis remains the last resort in some drug-resistant patients. However, a large number of patients are not candidates for surgical resective therapy, facing unmet medical needs. Therefore, it is imperative to develop alternative therapies leading to seizure remission. Neuromodulation is one such alternative treatment. There are several neuromodulation methods, including invasive therapies that require an implantable device and electrodes—such as deep brain stimulation (DBS), responsive neurostimulation (RNS), and vagus nerve stimulation (VNS)—and non-invasive approaches, such as transcranial magnetic stimulation (TMS) and ultrasonic therapy (2). Patients' selection, optimal anatomical targets, best stimulation parameters, prediction of neuromodulation therapy outcome, and understanding the underlying mechanisms are currently challenging.

Regarding these, we are pleased to present the collection of papers in this Research Topic, *Neuromodulation for pharmacoresistant epilepsy: from bench to bed*. This Research Topic includes 10 articles covering from clinical to basic research. It consists of six original articles, two study protocols, one original research review, and one brief research report.

DBS of the anterior nucleus of the thalamus (ANT-DBS) is currently approved for the treatment of refractory focal epilepsy. Based on a single central clinical result, the original clinical research article by Yan et al. demonstrated that ANT-DBS was effective for patients with either temporal lobe epilepsy or extratemporal lobe epilepsy. In addition, DBS of subthalamic nucleus could potentially serve as an effective therapy for patients with motor seizures, particularly when the epileptogenic zone overlaps with the sensorimotor cortex. Centromedian nucleus (CMN) and pulvinar nucleus could be regarded as modulating targets for patients with Lennox-Gastaut syndrome-like epilepsy or occipital lobe epilepsy, respectively. Another single center research article by Dague et al. presented the possible undesired psychiatric side effects and the short/long-term effects on patients'

neuropsychological assessment. To clarify the possible reason of these side effects might help to improve the clinical operation and postoperative programing for ANT-DBS.

The RNS system delivers electrical stimulation on detection of ictal intracranial EEG for medically refractory focal-onset epilepsy. The original clinical research article by Fields et al. was conducted in a multicenter retrospective study of patients treated in the thalamus RNS from seven epilepsy centers in the United States. The article suggested that RNS treatment in either the ANT or CMN of thalamus was safe and effective in reducing seizure frequency and improving quality of life in patients with different seizure types. The single center research article by Owens et al. suggested that preoperative stereoelectroencephalography (sEEG) was helpful to increase the positive response rates of RNS in patients.

VNS is regarded as a minimally invasive, peripheral method for modulating epileptic networks. The original clinical research article by Guo et al. demonstrated the efficacy and safety of VNS in the treatment of pharmacoresistant epilepsy secondary to encephalomalacia. Moreover, the article suggested the potential predictors of VNS effectiveness, including seizure onset age (>18 years old), unilateral interictal epileptic discharges, and unilateral encephalomalacia on MRI. The original clinical research article by Iimura et al. determined that generalized seizure was most responsive to VNS and investigated the preventive effect of VNS on status epilepticus (SE) recurrence. The study protocol article by Verner et al. described a prospective, open-label, multicenter phase I clinical trial designed to evaluate the potential safety and efficacy of high frequency bursts of stimulation known as "Microburst VNS" (μVNS) in patients with refractory focal and generalized epilepsies. This protocol also utilized an investigational, fMRI-guided titration approach that allows for personalized dosing of μVNS based on the thalamic blood-oxygen-level-dependent signal.

Repetitive TMS (rTMS), as a focal, non-invasive method, shows potential for applications in epilepsy. The original clinical research article by Yang et al. described the favorable outcomes after low-frequency rTMS (≤1 Hz) in patients with self-limited epilepsy with centrotemporal spikes (SeLECTS) with electrical status epilepticus in sleep (ESES). By analyzing the aperiodic offset and slope of EEG data, they determined the impact of rTMS on the excitation–inhibition imbalance in the patients' brains. The findings suggested that rTMS might lead to a reduction in firing rates in neuronal populations, particularly at the site of stimulation.

Therapeutic focused ultrasound (FUS) is a noninvasive brain stimulation treatment that targets a specific part of the brain by using energy in the form of acoustic waves beyond the range of human hearing.

The review by Cornelssen et al. discussed preclinical and clinical FUS studies to treat seizures and presented investigated potential applications of FUS for targeted drug delivery to the seizure foci. Additionally, they summarized its effective parameters and analyzed the future directions and constraints of FUS in the treatment of epilepsy.

Cognitive dysfunction is prevalent in epilepsy which may have a significant impact on social functioning and quality of life. The study protocol article by Puteikis et al. described a randomized waitlist-controlled trial of cognitive rehabilitation in epilepsy (CoRE) with the aim of improving both quality of life and cognitive functioning in a mixed sample of people with epilepsy (PWE). Through the endeavor, neuropsychological evaluation experience would be further translated into non-invasive add-on rehabilitation treatments that addressed PWE's bothersome cognitive difficulties.

Author contributions

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Vagus nerve stimulation for pharmacoresistant epilepsy secondary to encephalomalacia: A single-center retrospective study

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Objective: Vagus nerve stimulation (VNS) is an adjunctive treatment for pharmacoresistant epilepsy. Encephalomalacia is one of the most common MRI findings in the preoperative evaluation of patients with pharmacoresistant epilepsy. This is the first study that aimed to determine the effectiveness of VNS for pharmacoresistant epilepsy secondary to encephalomalacia and evaluate the potential predictors of VNS effectiveness.

Methods: We retrospectively analyzed the seizure outcomes of VNS with at least 1 year of follow-up in all patients with pharmacoresistant epilepsy secondary to encephalomalacia. Based on the effectiveness of VNS (≥50% or <50% reduction in seizure frequency), patients were divided into two subgroups: responders and non-responders. Preoperative data were analyzed to screen for potential predictors of VNS effectiveness.

Results: A total of 93 patients with epilepsy secondary to encephalomalacia who underwent VNS therapy were recruited. Responders were found in 64.5% of patients, and 16.1% of patients achieved seizure freedom at the last follow-up. In addition, the responder rate increased over time, with 36.6, 50.5, 64.5, and 65.4% at the 3-, 6-, 12-, and 24-month follow-ups, respectively. After multivariate analysis, seizure onset in adults (>18 years old) (OR: 0.236, 95%CI: 0.059–0.949) was found to be a positive predictor, and the bilateral interictal epileptic discharges (IEDs) (OR: 3.397, 95%CI: 1.148–10.054) and the bilateral encephalomalacia on MRI (OR: 3.193, 95%CI: 1.217–8.381) were found to be negative predictors of VNS effectiveness.

Conclusion: The results demonstrated the effectiveness and safety of VNS therapy in patients with pharmacoresistant epilepsy secondary to encephalomalacia. Patients with seizure onset in adults (>18 years old),

unilateral IEDs, or unilateral encephalomalacia on MRI were found to have better seizure outcomes after VNS therapy.

KEYWORDS

encephalomalacia, pharmacoresistant epilepsy, vagus nerve stimulation, effectiveness, predictor

1. Introduction

Focal encephalomalacia is a common structural brain lesion detected during magnetic resonance imaging (MRI) in patients with pharmacoresistant epilepsy (1, 2). The etiology of encephalomalacia includes brain trauma, perinatal hypoxia, infection, intracranial hematoma, surgical procedures, as well as some unknown factors (3). Although the encephalomalacia alone may not cause seizures, the surrounding scars may interfere with the normal electrophysiological activity of neurons and cause hyperplastic glial dysfunction, which in turn leads to abnormal discharge associated with seizures (4, 5). Patients with pharmacoresistant epilepsy secondary to encephalomalacia are usually resistant to anti-seizure medications, and surgical intervention is another widely accepted treatment option (3, 6). However, in conditions of widely distributed encephalomalacia involved in eloquent brain regions or bilateral hemispheres, patients are not good candidates for resection (5, 7). Thus, for those unsuitable for surgical therapy or with unsatisfactory surgical outcomes, it is urgent to explore novel therapeutic strategies.

Since its first reported use in humans in 1988 and more than 100,000 subsequent implantations, vagus nerve stimulation (VNS) has become a reliable method of treating patients with pharmacoresistant epilepsy who are not good candidates for epilepsy surgery or in whom surgery resulted in no benefit (8). According to the results of randomized controlled trials (9), meta-analyses (10), and retrospective studies (11, 12), ∼50–60% of patients achieve a seizure reduction of ≥50% after VNS surgery, with a rate of complete seizure freedom ranging from 6 to 8%. Predictors of VNS effectiveness are a focus of related research at present. Several potential predictors updated recently include brain connectomic profiling (13), heart rate variability (14), and genetic variations of adenosine kinase (15). The effectiveness and safety of VNS are also demonstrated in some specific types of epilepsy, such as tuberous sclerosis complex (16), Lennox–Gastaut syndrome (17), post-encephalitic epilepsy (18), and post-traumatic epilepsy (19). Based on the advantages of VNS therapy, it may shed some light on the therapy of pharmacoresistant epilepsy secondary to encephalomalacia.

Various causes can lead to encephalomalacia in the brain, such as stroke (20, 21), head trauma (19, 22, 23), and encephalitis (18, 24), in which the effectiveness of VNS for epilepsy has been reported, separately. This present study aimed to demonstrate the effectiveness of VNS in 93 patients with pharmacoresistant epilepsy secondary to encephalomalacia under different conditions, as well as to evaluate potential predictors for VNS effectiveness.

2. Materials and methods

2.1. Patients

We retrospectively studied VNS effectiveness in patients with pharmacoresistant epilepsy who received VNS implantation from Sanbo Brain Hospital, Capital Medical University, between September 2008 and April 2021. All enrolled patients had evidence of encephalomalacia on brain MRI. Encephalomalacia in this study was defined as a loss of parenchymal thickness accompanied by laminar necrosis in the brain (5, 25, 26). Representative MR images of encephalomalacia are shown in Figure 2. The inclusion criteria for enrolled patients were as follows: (1) patients with pharmacoresistant epilepsy who received VNS therapy; (2) patients with evidence of encephalomalacia on brain MRI; and (3) patients whose MRI findings of encephalomalacia were associated with epilepsy after detailed preoperative evaluation. Thus, those with pharmacoresistant epilepsy secondary to encephalomalacia who received VNS therapy were included in this study (Figure 1). All recruited patients were followed up by at least 1 year. Detailed demographic and clinical information were collected from the medical records.

This study complied with the World Medical Association Declaration of Helsinki published on the website of the Journal of American Medical Association and was approved by the Ethics Committee of Sanbo Brain Hospital, Capital Medical University (SBNK-2017-15-01). Written informed consent was obtained from all patients or their guardians.

2.2. Preoperative evaluation

Patients in our comprehensive epilepsy center were all evaluated by MRI and video electroencephalography (VEEG) before the operation. Some patients further received

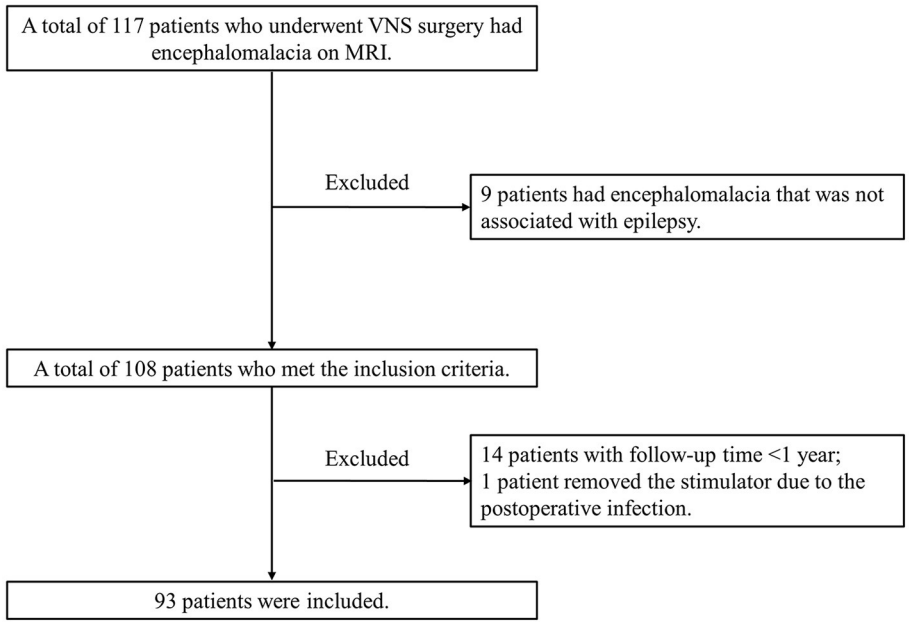

FIGURE 1
Flowchart for recruiting patients who satisfy the inclusion and exclusion criteria.

positron emission tomography-computed tomography (PET-CT), magnetoencephalography (MEG), and neuropsychological assessments. At a multidisciplinary team (MDT) conference, all results of the preoperative evaluation were analyzed in detail by experienced neurologists, neurosurgeons, neuroradiologists, and electrophysiologists, to determine treatment strategies for each patient (16). Based on our previous strategies (16), VNS was recommended in the following conditions: (1) patients whose epileptogenic focus could not be accurately localized; (2) patients with epileptogenic focus overlapping with the eloquent areas, which could be determined by SEEG and the Wada test; (3) patients who did not accept surgical resection; and (4) patients with early surgical failure. VNS implantations were conducted by two neurosurgeons according to standard procedures (27). Based on available guidelines (28), the stimulation parameters were adjusted routinely after device implantation.

2.3. Programming strategy of VNS

The parameter setting of VNS was conducted based on our previous programming strategy (16). In the 93 patients recruited in our study, two models of vagus nerve stimulators were implanted: Model 103 (Demipulse, LivaNova, England) implanted in 61.3% (57/93) of patients, and Model G111 (Beijing PINS Medical Co., Ltd, China) implanted in 38.7% (36/93) of patients. After 7 days of the stimulator implantation, the stimulation was initiated. For the initial parameter settings, the out current was set as 0.5 mA, the signal on time was set as 30 s, and the signal off time was set as 5 min. The signal frequency (30 Hz) and the pulse width (250 μs) were kept consistent, and the magnet current was set as 0.25 mA higher than the output current. The out current was elevated to 1.25–1.5 mA in 1 month at the outpatient clinic. From then on, the parameters would be modified to 0.25 mA every 3–6 months based on improvements in seizure control and tolerance of patients.

2.4. Clinical data collection

The collected medical history of patients included sex, age of VNS implantation, age of epilepsy onset, epilepsy duration, predominant type and frequency of seizures, number of preoperative anti-seizure medications (ASMs), preoperative neurological deficit, history of status epilepticus (SE), the spatial distribution of EEG, and encephalomalacia on brain MRI. Detailed information on antecedent events of encephalomalacia was analyzed in patients with specific etiology of encephalomalacia, including the type of etiology, age of etiology, and the interval between etiology and the first seizure.

According to the medical documents, the seizure type of each patient was defined as the most frequent seizure type, which was classified as "focal onset" and "generalized onset" based on the 2017 ILAE classification of epilepsy (29). The duration of follow-up was divided into "≤2," "2–6," and "≥6" years.

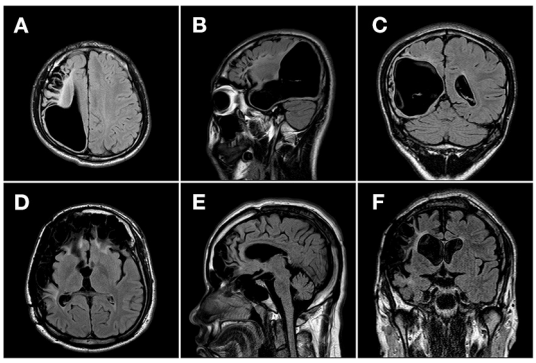

FIGURE 2
Representative MR images of patients with pharmacoresistant epilepsy secondary to encephalomalacia. Representative MR images (T2-weighted fluid-attenuated inversion recovery image) of two patients with pharmacoresistant epilepsy secondary to encephalomalacia in the axial **(A, D)**, sagittal **(B, E)**, and coronal **(C, F)** planes. **(A–C)** A 17-year-old boy with unilateral encephalomalacia on MRI due to intracranial hematoma. The encephalomalacia was observed in the right frontal, parietal, and temporal lobes. The patient got a reduction of 80% in seizure frequency after 1 year following the VNS therapy. **(D–F)** A 24-year-old man with bilateral encephalomalacia on MRI due to head trauma. The encephalomalacia was observed in the right temporal and parietal lobes, as well as in bilateral frontal lobes. The patient got no reduction in seizure frequency during a 3-year follow-up after the VNS therapy.

2.5. MRI

Brain 1.5-T MRI scans were conducted in all included patients, including T1-weighted, T2-weighted, and T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences. Encephalomalacia was defined as a loss of parenchymal thickness accompanied by laminar necrosis in the brain (5, 25, 26). The MR images of all patients were reviewed and classified as follows: (1) unilateral: the encephalomalacia showed by MRI involved only one hemisphere; and (2) bilateral: the encephalomalacia showed by MRI involved both hemispheres. Based on our previous study, the image archiving and communication system of Hinacom Software and Technology was used to define the regions of the responsible lesion (3). The lesions were inspected by a group of experienced neuroradiologists, neurologists, and neurosurgeons.

2.6. Scalp EEG findings

All patients were monitored with 64-channel long-term video EEG for at least 24 h using a standard 10–20 electrode placement system. The interictal epileptic discharges (IEDs) were divided into two types: (1) unilateral: the IEDs involved only one hemisphere; or (2) bilateral: the IEDs involved both hemispheres and were either diffused or generalized. Similarly, for patients whose seizures were recorded, the ictal onset rhythms were also classified as unilateral or bilateral. Of note, concordance of the interictal and ictal EEG findings was defined as localization of the interictal and ictal epileptic discharges in the same brain region or hemisphere.

2.7. Magnetoencephalography

A total of 36 (38.7%) patients underwent MEG. Concordance of the IEDs and MEG findings was defined as the localization of the IEDs and MEG spike sources to the same brain region.

2.8. Seizure outcome and follow-up

All enrolled patients were followed for at least 1 year after VNS therapy. The seizure outcomes were collected by questionnaire when patients were readmitted for adjustment of stimulation parameters or online remote follow-up. Based on our previous study (18), patients with a reduction of over 50% in baseline seizure frequency of the predominant seizure type were defined as responders. Seizure freedom in this study referred to the complete freedom of all types of seizures at the last follow-up. The seizure outcomes were collected at 3, 6, 12, and 24 months and the last follow-up after VNS surgery. Results at the last follow-up were used to define the overall effectiveness and potential predictors of VNS.

2.9. Statistical analysis

The SPSS Software version 23.0 was used for all analyses. All calculated *P*-values in the present study were two-tailed, and a p-value of <0.05 was considered statistically significant. Categorical variables were shown as frequencies. Pearson's chi-square or Fisher's exact test was used for univariate analysis. To determine the threshold of continuous variables that may predict seizure outcomes, continuous variables were stratified using a receiver operating curve analysis, and the cutoff values were determined according to Youden's index. Variables showing a p-value <0.05 in the univariate analysis were then entered into a multivariate logistic regression model in a backward manner.

3. Results

3.1. Demographic characteristics

The overall process of patient enrollment is shown in Figure 1. Of the 108 patients with pharmacoresistant epilepsy secondary to encephalomalacia who met the inclusion criteria, 14 patients with a follow-up of <1 year and 1 patient removed

the stimulator due to post-operative infection. This study was based on the remaining 93 patients (77 men and 16 women) managed during 2008–2021. The most frequently reported adverse events included voice hoarse, coughing, and throat pain, while all the side effects above were tolerable and transient.

Among all included patients, the median (interquartile range, IQR) age of VNS implantation, age at seizure onset, and duration of seizures were 20.0 (IQR 13.4–29.5) years, 9.0 (IQR 5.0–17.0) years, and 6.0 (IQR 2.6–14.6) years, respectively. Notably, 11 (11.8%) patients had a history of SE, and aura occurred in 22 (23.7%) patients at the beginning of seizures. There were 29 (31.2%) patients accompanied by preoperative neurological deficits: 23 (24.6%) reported hemiparesis, 1 (1.1%) reported aphasia, 2 (2.2%) reported both hemiparesis and aphasia, 2 (2.2%) reported ataxia, and 1 (1.1%) was defined as a persistent vegetative state. Based on the medical records, antecedent events of encephalomalacia were found in 78 (83.9%) patients: 34 (36.6%) had head trauma, 17 (18.3%) had perinatal hypoxia, 17 (18.3%) had meningoencephalitis, 3 (3.2%) had undergone previous surgical procedures, and 7 (7.5%) had an intracranial hematoma. The median age of the antecedent events was 5.0 (IQR: 0.0–17.0) years, and the median interval between the antecedent events and the first seizure was 2.0 (IQR: 0.1–6.0) years. Other patient characteristics are shown in Table 1. Besides, we also evaluated the comparison of demographic characteristics between patients who got seizure freedom at the last follow-up and the others. Detailed information is shown in Supplementary Table 1.

3.2. MRI results

Brain MRI results were reviewed in all patients. Encephalomalacia was observed in only one hemisphere in 44 (47.3%) patients, and in the other 49 (52.7%) patients, encephalomalacia was found in both hemispheres. Representative MR images are shown in Figure 2. Among the 93 patients in this study, encephalomalacia in 10 (10.8%) patients involved the frontal lobe, 6 (6.5%) patients involved the temporal lobe, 4 (4.3%) patients involved the parietal lobe, 4 (4.3%) patients involved the occipital lobe, and 69 (74.1%) patients involved $\geq$2 lobes (multilobar).

3.3. EEG results

Interictal epileptic discharges were observed in all patients during scalp EEG monitoring. There were 33 (35.5%) patients representing unilateral IEDs and 60 (64.5%) patients representing bilateral IEDs. Seizures were recorded in 73 (78.5%) patients, 17 (18.3%) of whom had unilateral epileptic discharges and 56 (60.2%) of whom had bilateral epileptic discharges. Of these 73 patients with recorded seizures, concordance of IEDs and ictal onset rhythms were found in 46 (49.5%) patients.

3.4. MEG results

Magnetoencephalography was conducted in 36 (38.7%) patients. The MEG spike sources were observed in 33 (35.5%) patients, among which 23 (24.7%) results were in concordance with the IEDs.

3.5. Outcomes of VNS

For all included patients, the median time of the last follow-up was 3.0 (IQR 2.0–4.2) years, ranging from 1.0 to 12.0 years. At the last follow-up, 67 (72.0%) patients were found with reduced seizures, with a median reduction in seizure frequency of 66.7% (IQR 0.0%-100.0%). Of note, 60 (64.5%) patients reported a reduction of $\geq$50% in seizure frequency, and 15 (16.1%) patients obtained seizure freedom. Seizure outcomes at the last follow-up were assessed using the McHugh and modified Engel seizure outcome classifications (Table 2).

After VNS therapy, the outcomes of 93 patients with epilepsy secondary to encephalomalacia were shown at the 3-, 6-, and 12-month follow-ups, and the outcomes of 78 patients were shown at the 24-month follow-up (Figure 3). The detailed assessments of VNS outcomes based on the McHugh description at different follow-up time points are shown in Figure 3A. The rates of responder and seizure freedom and the median reduction of seizure frequency were found to gradually increase over time (Figure 3B). At 3, 6, 12, and 24 months of follow-up, the number of responder patients was 34 (36.6%), 47 (50.5%), 60 (64.5%), and 51 (65.4%), respectively; the number of patients with seizure freedom was 4 (4.3%), 7 (7.5%), 8 (8.6%), and 15 (19.2%), respectively; and the median reduction of seizure frequency was 25.0% (IQR 0–77.5%), 50.0% (IQR 0–92.5%), 55.6% (IQR 0–90.9%), and 68.3% (IQR 0–99.9%), respectively.

3.6. Analysis of prognostic factors for VNS effectiveness

In the univariate analysis (Table 1), the following factors were found to be associated with VNS effectiveness: the age at seizure onset, duration of epilepsy, the spatial distribution of IEDs, and the encephalomalacia on MRI. The other factors listed in Table 1 were not associated with VNS effectiveness.

Variables with statistical significance ($P < 0.05$) in the univariate analysis were then put into the multivariate logistic regression model in a backward manner. After multivariate analysis, the seizure onset in adults (>18 years old) (OR: 0.236, 95% CI: 0.059–0.949) was found to be a positive predictor for

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TABLE 1 Patients' demographic and clinical features.

Variables	Total ($n = 93$)	Responder ($n = 60$)	Non-responder ($n = 33$)	*P*-value
Male, *n* (%)	77 (82.8)	52 (86.7)	25 (75.8)	0.148
Age at VNS implantation, year old				0.126
≤12	20 (21.5)	10 (16.7)	10 (30.3)	
>12	73 (78.5)	50 (83.3)	23 (69.7)	
Age at seizure onset, year old				0.021*
≤18	72 (77.4)	42 (70.0)	30 (90.9)	
>18	21 (22.6)	18 (30.0)	3 (9.1)	
Duration of epilepsy, year				0.032*
≤15	71 (76.3)	50 (83.3)	21 (63.6)	
>15	22 (23.7)	10(16.7)	12 (36.4)	
Seizure type, *n* (%)				0.597
Focal onset	82 (88.2)	53 (88.3)	29 (87.9)	
Generalized onset	11 (11.8)	7 (11.7)	4 (12.1)	
Monthly seizure frequency				0.911
≤5	43 (46.2)	28(46.7)	15 (45.5)	
>5	50 (53.8)	32 (53.3)	18 (54.5)	
Aura, *n* (%)				0.921
Yes	22 (23.7)	14 (23.3)	8 (24.2)	
No	71 (76.3)	46 (76.7)	25 (75.8)	
Types of ASMs				0.358
≤2	62 (66.7)	42 (70.0)	20 (60.6)	
>2	31 (33.3)	18 (30.0)	13 (39.4)	
Etiology				0.900
Head trauma	34 (36.6)	22 (36.7)	12 (36.5)	
Perinatal hypoxia	17 (18.3)	10 (16.7)	7 (21.2)	
Meningoencephalitis	17 (18.3)	13 (21.7)	4 (12.1)	
Previous surgical procedure	3 (3.2)	2 (3.3)	1 (3.0)	
Intracranial hematoma	7 (7.5)	4 (6.6)	3 (9.1)	
Unknown	15 (16.1)	9 (15.0)	6 (18.1)	
Age of etiology, year old				0.077
≤20	61 (65.6)	36 (60.0)	25 (75.7)	
>20	17 (18.3)	15 (25.0)	2 (6.1)	
Unknown	15 (16.1)	9 (15.0)	6 (18.2)	
Interval between etiology and the first seizure, year				0.202
≤8	68 (73.1)	42 (70.0)	26 (78.8)	
>8	10 (10.8)	9 (15.0)	1 (3.0)	
Unknown	15 (16.1)	9 (15.0)	6 (18.2)	
Preop neurological deficit, *n* (%)	29 (31.2)	16 (26.7)	13 (39.4)	0.205

(Continued)

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TABLE 1 (Continued)

Variables	Total ($n = 93$)	Responder ($n = 60$)	Non-responder ($n = 33$)	*P*-value
History of SE, *n* (%)	11 (11.8)	8 (13.3)	3 (9.1)	0.741
Spatial distribution of IEDs, *n* (%)				0.010*
Unilateral	33 (35.5)	27 (45.0)	6 (18.2)	
Bilateral	60 (64.5)	33 (55.0)	27 (81.8)	
Ictal onset rhythms of EEG, *n* (%)				0.777
Unilateral	17 (18.3)	10 (16.7)	7 (21.2)	
Bilateral	56 (60.2)	36 (60.0)	20 (60.6)	
Unknown	20 (21.5)	14 (23.3)	6 (18.2)	
Concordance of IEDs and ictal onset rhythms				0.510
Yes	46 (49.5)	27 (45.0)	19 (57.6)	
No	27 (29.0)	19 (31.7)	8 (24.2)	
Unknown	20 (21.5)	14 (23.3)	6 (18.2)	
Encephalomalacia on MRI				0.045*
Unilateral	44 (47.3)	33 (55.0)	11 (33.3)	
Bilateral	49 (52.7)	27 (45.0)	22 (66.7)	
Site of encephalomalacia				0.444
Frontal lobe	10 (10.8)	6 (10.0)	4 (12.1)	
Temporal lobe	6 (6.5)	5 (8.3)	1 (3.0)	
Parietal lobe	4 (4.3)	4 (6.7)	0 (0.0)	
Occipital lobe	4 (4.3)	2 (3.3)	2 (6.1)	
Multilobar	69 (74.1)	43 (71.7)	26 (78.8)	
Performance of MEG, *n* (%)				0.480
Yes	36 (38.7)	21 (35.0)	15 (45.5)	
No	57 (61.3)	39 (65.0)	18 (54.5)	
Concordance of MEG and IEDs				0.573
Yes	23 (24.7)	13 (21.7)	10 (30.3)	
No	10 (10.8)	6 (10.0)	4 (12.1)	
Unknown[a]	60 (64.5)	41 (68.3)	19 (57.6)	
The type of stimulator				0.377
Model 103	57 (61.3)	39 (65.0)	18 (55.5)	
Model G111	36 (38.7)	21 (35.0)	15 (45.5)	
Time of the last follow-up, year				0.673
≤2	28 (30.1)	18 (30.0)	10 (30.3)	
2–6	56 (60.2)	35 (58.3)	21 (63.6)	
≥6	9 (9.7)	7 (11.7)	2 (6.1)	

ASMs, anti-seizure medications; EEG, electroencephalogram; IEDs, interictal epileptiform discharges; MEG, magnetoencephalography; MRI, magnetic resonance imaging; VNS, vagus nerve stimulation; SE, status epilepticus; *$P < 0.05$; [a]MEG was performed in three of these patients, but the spikes sources were not detected.

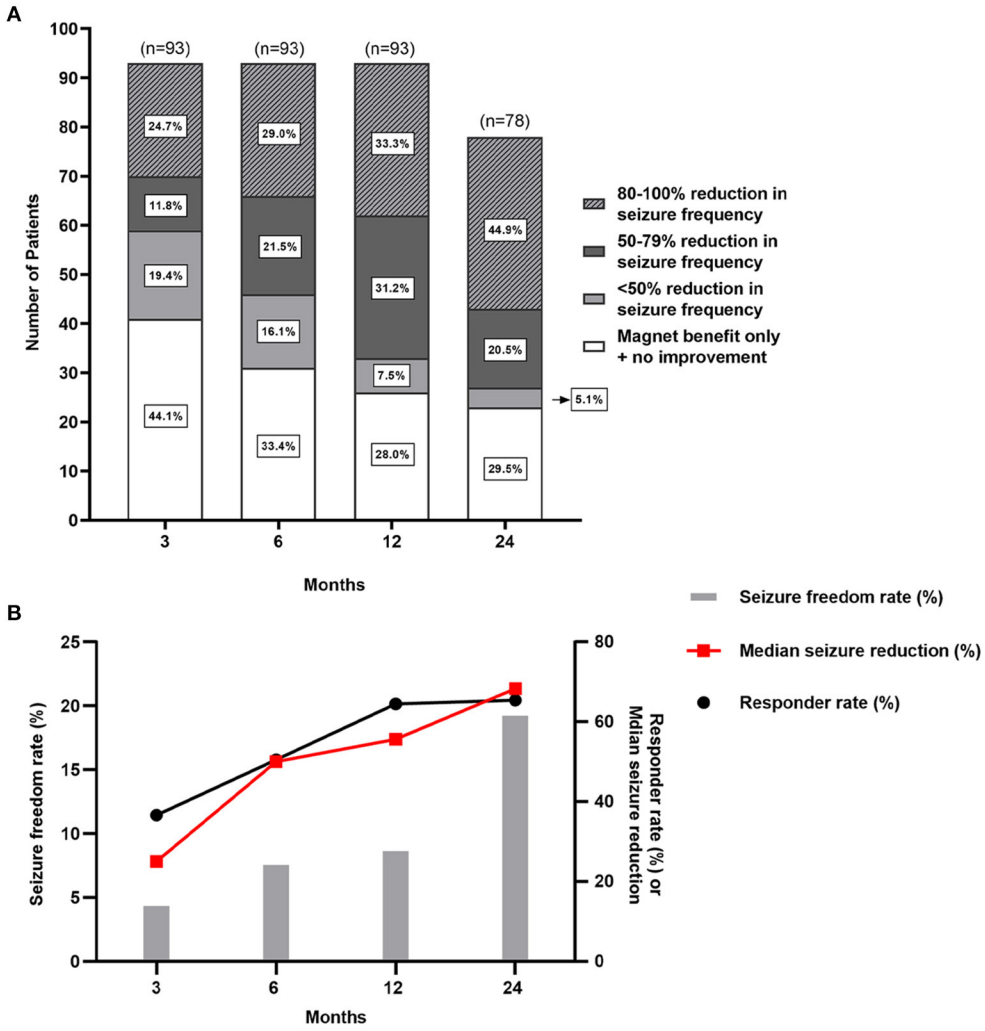

FIGURE 3
Seizure outcomes of patients with pharmacoresistant epilepsy secondary to encephalomalacia after VNS. **(A)** There are seizure outcomes at 3-, 6-, 12-, and 24-month follow-up after VNS therapy with McHugh outcome classification. **(B)** The responder rate, seizure freedom rate, and median reduction of seizure frequency gradually increase over time.

VNS effectiveness; the bilateral IEDs (OR: 3.397, 95% CI: 1.148–10.054) and the bilateral encephalomalacia on MRI (OR: 3.193, 95% CI: 1.217–8.381) were found to be negative predictors for VNS effectiveness (Table 3). The responder rate, seizure freedom rate, and median reduction of seizure frequency according to the results of the independent predictors of VNS effectiveness are illustrated in Figure 4.

In addition, we also evaluated the prognostic factors for seizure freedom among those patients. After the univariate analysis (Supplementary Table 1), the factor of monthly seizure frequency was found with statistical significance and was then put into the univariate logistic regression model. The monthly seizure frequency (>5) (OR: 3.953, 95% CI: 1.155–13.526) was finally found as a negative predictor for seizure freedom.

4. Discussion

Focal encephalomalacia is a common structural brain lesion found in MRI of patients with pharmacoresistant epilepsy. VNS has been used in pharmacoresistant epilepsy for decades. For patients who are unsuitable for resection surgery, VNS may provide better benefits for seizure reduction. However, the long-term seizure outcomes and potential prognostic predictors of VNS in pharmacoresistant epilepsy secondary to encephalomalacia remain unclear. In this study, we first assessed the VNS effectiveness in pharmacoresistant epilepsy secondary to encephalomalacia with a follow-up over 1 year. Out of 93 patients enrolled in this study, 60 (64.5%) patients obtained a reduction of ≥50% in seizure frequency, and seizure

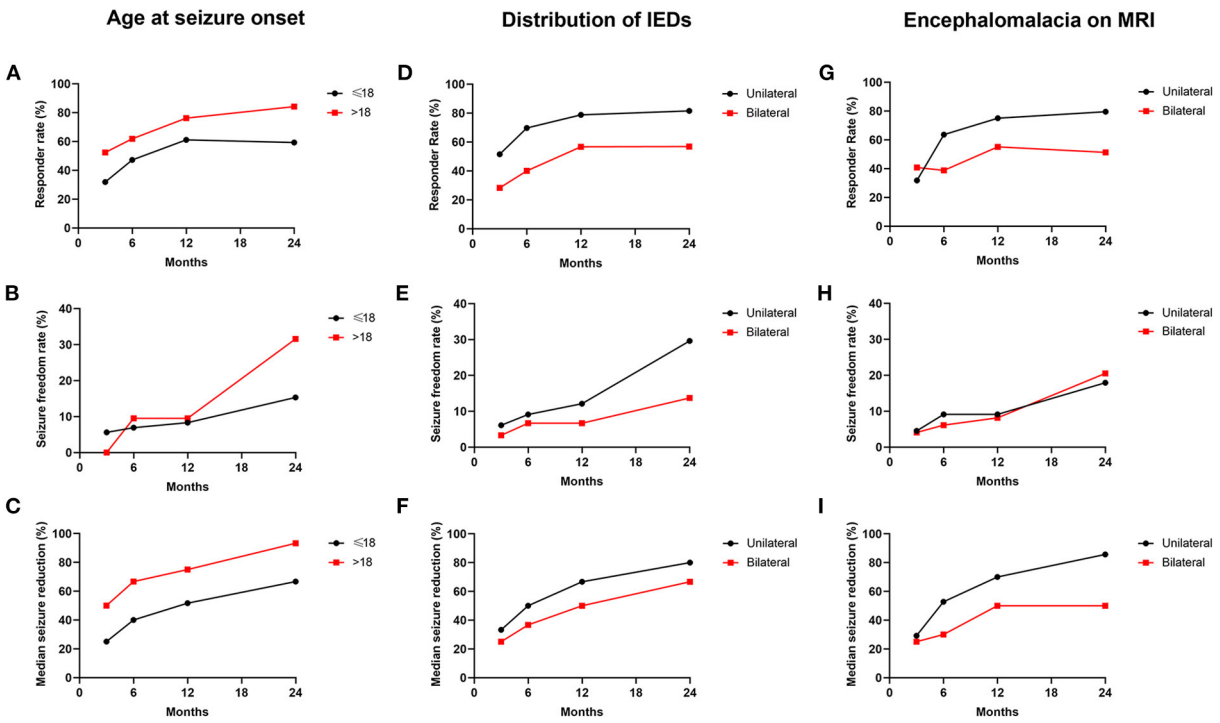

FIGURE 4
Seizure outcomes in patients classified by predictors of VNS effectiveness. **(A–C)** The responder rate **(A)**, seizure freedom rate **(B)**, and median seizure reduction **(C)** according to the classification of the age at seizure onset. **(D–F)** The responder rate **(D)**, seizure freedom rate **(E)**, and median seizure reduction **(F)** according to the classification of the distribution of IEDs. **(G–I)** The responder rate **(G)**, seizure freedom rate **(H)**, and median seizure reduction **(I)** according to the classification of the distribution of encephalomalacia on MRI.

TABLE 2 Seizure outcomes evaluated by modified Engel and McHugh seizure outcome classifications at the last follow-up (≥1 year).

Class	Modified engel description	No. of Pts (%)	McHugh description	No. of Pts (%)
I	Seizure-free; rare, non-disabling SPS	15 (16.2)	80–100% reduction in seizure frequency	42 (45.1)
II	>90% reduction in seizure frequency; rare CPS	14 (15.0)	50–79% reduction in seizure frequency	18 (19.4)
III	50–90% reduction in seizure frequency	31 (33.3)	<50% reduction in seizure frequency	7 (7.5)
IV	<50% reduction in seizure frequency	33 (35.5)	Magnet benefit only	0 (0.0)
V	/	/	No improvement	26 (28.0)

CPS, complex partial seizure; Pts, patients; SPS, simple partial seizure.

freedom occurred in 15 (16.1%) patients. During the follow-up time ranging from 1.0 to 12.0 years, the most frequently reported adverse events included voice hoarse, coughing, and throat pain, while all the side effects above were tolerable and transient. After device implantation, the responder rate, seizure freedom rate, and the median reduction of seizure frequency were all found to gradually increase over time. Those results were consistent with most studies involved VNS effectiveness in pharmacoresistant epilepsy (30, 31), which reported a reduction of or more than 50% in seizure frequency in 45–65% of patients as well as a progressive increase in the overall response to VNS therapy over time. Therefore, VNS therapy was demonstrated to be effective and safe in patients with epilepsy secondary to encephalomalacia. For those who are not suitable for resection surgery, VNS might be a promising therapeutic strategy.

Seizure freedom is generally considered a prominent predictor of life quality in patients with epilepsy. Unfortunately, complete seizure freedom is rarely obtained (6–8%) in patients who underwent VNS surgery (9–12). Among 93 patients with pharmacoresistant epilepsy secondary to encephalomalacia in the present study, 15 (16.1%) patients obtained seizure freedom at the last follow-up, which was higher than that observed in the general population of epilepsy. The relatively high rate of seizure freedom indicated that patients in the small cohort may achieve more improvements in the overall life quality *via* VNS therapy than those with other types of epilepsy. Further studies with

TABLE 3 Predictors of VNS effectiveness for pharmacoresistant epilepsy secondary to encephalomalacia on multivariate analysis.

Variables	OR	95% CI	*P*-value
Duration of epilepsy >15 years	2.250	0.757–6.686	0.144
Age at seizure onset >18 years old	0.236	0.059–0.949	0.042*
Bilateral IEDs	3.397	1.148–10.054	0.027*
Bilateral encephalomalacia on MRI	3.193	1.217–8.381	0.018*

CI, confidence interval; IEDs, interictal epileptic discharges; MRI, magnetic resonance imaging; OR, odds ratio; VNS, vagus nerve stimulation; *$P < 0.05$.

larger sample sizes are expected to focus on this problem in the future.

Although the VNS benefit was found more significant in the present cohort than in other types of pharmacoresistant epilepsy, our results confirmed that the complete seizure freedom rate was still less common with VNS than with resective surgery (3). In our previous study focusing on the surgical outcomes in patients with epilepsy secondary to encephalomalacia who received resective epilepsy surgery, ∼75.0% of the patients obtained seizure freedom 5 years after surgery (3). A study involving 17 patients with resection of frontal encephalomalacia for pharmacoresistant epilepsy reported that 12 (70%) patients were seizure-free or had only rare seizures after a median of 3 years of follow-up (6). The phenomenon also occurs in other neuromodulation treatments for pharmacoresistant epilepsy (32, 33). Therefore, current neuromodulation techniques are indeed not a substitute for resection therapy for pharmacoresistant epilepsy. However, epilepsy patients with widely distributed encephalomalacia which is involved in eloquent brain regions or bilateral hemispheres are not good candidates for resection. In such conditions, as a palliative treatment, VNS may help reduce the seizure frequency, as well as improve the overall life quality.

In addition to reducing seizure frequency, VNS may also benefit the quality of a patient's life by improving physical disability and neuropsychological disorders (34, 35). Patients with encephalomalacia on MRI usually have various types of initial etiologies, including brain trauma, perinatal hypoxia, meningoencephalitis, previous surgical procedures, and intracranial hematoma, any of which is associated with different degrees of brain damage (6). Therefore, those patients often suffer from neurological and neuropsychological impairments such as physical disability, depression, or anxiety (36, 37). In this study, 31.2% of patients reported a preoperative neurological deficit. Those deficits included hemiparesis, aphasia, ataxia, and persistent vegetative state. Modification of them was also a crucial step during the overall treatment. Multiple preclinical studies on ischemic stroke models have shown that VNS combined with rehabilitation training can significantly improve the recovery of forelimb motor function compared with rehabilitation training without VNS (34). Stimulation of the vagus nerve accelerates the release of neuromodulators, which can promote neuroplasticity throughout the cortex, such as acetylcholine and norepinephrine (38–40). Besides, it is well demonstrated that VNS therapy has benefits on mood, behavior, and cognition for epilepsy patients, independent of reducing seizures (35, 41). Thus, the potential benefits of VNS on psychological and neurological disorders in patients with pharmacoresistant epilepsy secondary to encephalomalacia cannot be ignored. Unfortunately, the neuropsychological disorders and the effectiveness of VNS for those symptoms were not presented in this study, which deserved further exploration in the future.

In the present study, we first evaluated the prognostic predictor of VNS effectiveness in patients with pharmacoresistant epilepsy secondary to encephalomalacia. After multivariate analysis, the age of the seizure onset >18 years was found to predict better effectiveness. Similar results have also been reported in previous studies. In a study recruiting 5,554 epilepsy patients with VNS therapy, the age of epilepsy onset >12 years was found to predict a higher rate of seizure freedom (10). A retrospective analysis of 158 patients with medically pharmacoresistant epilepsy reported that patients with age at seizure onset ≥15 years were ideal candidates for VNS (42). Thus, patients with seizure onset in adults (>18 years old) demonstrated more likely to benefit from VNS therapy than those who had seizure onset in children (≤18 years old). The potential mechanisms of the finding were still unclear. More studies with larger sample sizes are expected to further confirm the phenomenon and explore the underlying mechanisms in the future.

Among the recruited 93 patients, those with unilateral IEDs were found to have a higher rate of responder and seizure freedom, as well as higher median reduction of seizure frequency compared with those with bilateral IEDs at different follow-ups. The important role of EEG features in the prediction of VNS effectiveness for epilepsy has been demonstrated before (43–46). In our previous studies exploring the VNS effectiveness in 42 patients with pharmacoresistant post-encephalitic epilepsy with a follow-up ranging from 1.00 to 11.83 years, patients with focal IEDs were found to have better seizure outcomes than those with generalized IEDs at the last follow-up (18). A study including 144 patients with pharmacoresistant epilepsy reported a significant association between unilateral IEDs and a higher probability of seizure freedom after VNS surgery (44). Notably, it is also the case in resective surgery of patients with epilepsy. In patients with mesial temporal sclerosis who received surgical treatment, bitemporal IEDs indicated bitemporal epileptogenicity and predicted a worse seizure prognosis than unilateral-temporal spike foci (47, 48). The most recognized reason was probably that the bilateral IEDs represented an enlarged epileptogenic zone or a greater epileptogenicity, as the bilateral IEDs were usually accompanied by a bilateral seizure onset zone, a generalized seizure diffusion,

and a greater seizure frequency (49, 50). In addition, the bilateral IEDs arising from an interaction of multiple active foci presented a higher degree of epileptogenicity (51). Thus, whether for VNS effectiveness or resection surgery, the spatial distribution of IEDs could be considered a reliable assessment tool for the prognosis of seizure outcome. Besides, the distribution of encephalomalacia foci on MRI was also found associated with VNS effectiveness in the present study. Similar to bilateral IEDs, bilateral encephalomalacia might contribute to the worse seizure outcome *via* similar mechanisms, such as widely distributed brain lesions, generalized seizure propagation, and higher epileptogenicity. In addition, we also evaluated the association between the concordance of the IEDs and ictal onset rhythms or the IEDs and MEG findings with VNS effectiveness in the present study. However, no significant results were obtained after statistical analysis. The results might be biased by the small sample size (36 of 93 patients had MEG results). Further studies with larger sample sizes are expected to focus on this problem in the future.

It was important to acknowledge some limitations of the present study. First, the inherent biases and the relatively small sample size of this single-center retrospective study could not be ignored, and more prospective studies with a larger sample size need to be carried out in the future to make the findings more targeted. Second, some factors that may influence the comprehensive curative effect of VNS in the specific cohort were not included, such as the clinical assessments of neuropsychological problems, behavior disorders, and overall life quality. Third, the 1.5-T MRI equipment used in this study may result in an underestimation of the number of patients with mild encephalomalacia, potentially increasing selection bias. In spite of these limitations, this study suggested the effectiveness of VNS in reducing seizure frequency in patients with pharmacoresistant epilepsy secondary to encephalomalacia. In addition, the age of seizure onset, the spatial distribution of IEDs, and the spatial distribution of encephalomalacia foci on MRI might be independent predictors of VNS effectiveness.

5. Conclusion

The present study indicated that VNS therapy was effective in patients with pharmacoresistant epilepsy secondary to encephalomalacia, with an ideal tolerance in patients over a 1-year-follow-up period. Patients with seizure onset in adults (>18 years old), unilateral IEDs, or unilateral encephalomalacia on MRI were found to have better seizure outcomes after VNS therapy.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Non-identifying data are available from the corresponding author on reasonable request. Data were not placed in a repository due to the risk of re-identification of participants. Requests to access these datasets should be directed to TL, tianfuli@ccmu.edu.cn.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Sanbo Brain Hospital, Capital Medical University (SBNK-2017-15-01). Written informed consent to participate in this study was provided by the patients/participants or patients/participants' legal guardian/next of kin.

Author contributions

TL, GL, and MG contributed to the conceptualization. TL, GL, MG, JW, CT, JD, and JZha contributed to the methodology. MG, ZX, and XK contributed to the formal analysis and investigation. MG contributed to the writing—original draft preparation. TL, GL, MG, JW, CT, JD, JZha, XW, XK, YG, JZha, FZ, and ZX contributed to the writing—review and editing. YG, JZha, and FZ contributed to the investigation. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Conflict of interest

The 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1074997/full#supplementary-material

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DBS of the ANT for refractory epilepsy: A single center experience of seizure reduction, side effects and neuropsychological outcomes

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Objective: Evaluation of the antiseizure efficacy, side effects and neuropsychological effects of Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT). ANT-DBS is a treatment option for patients with difficult-to-treat epilepsy. Though several works outline the cognitive and/or mood effects of ANT-DBS for the treatment of epilepsy, data on the intersection between antiseizure efficacy, cognitive and undesired effects are scarce.

Methods: We retrospectively analyzed the data of our cohort of 13 patients. Post-implantation seizure frequencies were measured at 6 months, 12 months and last follow-up, as well as averaged throughout follow-up. These values were then compared with mean seizure frequencies in the 6 months before implantation. To address acute cognitive effects of DBS a baseline assessment was performed after implantation and before stimulation, and a follow-up assessment was conducted under DBS. The long-term effects of DBS on cognition were assessed by comparing the preoperative neuropsychological profile with a long-term follow-up under DBS.

Results: In the entire cohort, 54.5% of patients were responders, with an average seizure reduction of 73.6%. One of these patients achieved temporary seizure freedom and near-total seizure reduction during the entire follow-up. Seizure reduction of <50% was achieved in 3 patients. Non-responders suffered an average seizure increase of 27.3%. Eight of twenty-two active electrodes (36,4%) were off-target. Two of our patients had both electrodes implanted off-target. When removing these two patients from the analysis and averaging seizure frequency during the entire follow-up period, four patients (44.4%) were responders and three experienced a seizure reduction of <50%. Intolerable side effects arose in 5 patients, mostly psychiatric. Regarding acute cognitive effects of DBS, only one patient showed a significant decline in executive functions. Long-term neuropsychological effects included significant intraindividual changes in verbal learning and memory. Figural memory, attention and executive functions, confrontative naming and mental rotation were mostly unchanged, and improved in few cases.

Significance: In our cohort, more than half of patients were responders. Psychiatric side effects seem to have been more prevalent compared to other published cohorts. This may be partially explained by a relatively high occurrence of off-target electrodes.

KEYWORDS

deep brain stimulation, refractory epilepsy, cognition, side effects, neuropsychological assessment

Highlights

- Some multifocal and genetic epilepsies may respond well to ANT-DBS.
- Long-term neuropsychological outcomes are mixed.
- The most common side effects in our cohort were psychiatric.

Introduction

Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) is a treatment option for patients with difficult-to-treat epilepsy. ANT-DBS became an established therapy after the first (and only) prospective randomized controlled trial, the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial (1), showed promising results in its 3, 5 and 10-year follow-up studies (2, 3), with a 43% responder rate (≥50% reduction in seizure frequency) at 1 year ($n = 99$) and 74% at seven years ($n = 50$).

The antiseizure effects of ANT-DBS are thought to be based on the inhibition of seizure propagation through the thalamus (4) and modulation of the Circuit of Papez (5). Furthermore, increasing responder rates over the years have been attributed to long-term neuromodulation effects in neural networks.

Though several works (6, 7) outline the cognitive and/or mood effects of ANT-DBS for the treatment of epilepsy, data on the intersection between antiseizure efficacy, cognitive and undesired effects are scarce. We aimed to systematically evaluate the antiseizure efficacy, side effects and neuropsychological effects of ANT-DBS in epilepsy patients treated at our center.

Methods

We retrospectively analyzed the data of our cohort of 13 patients, stereotactically and transventricularly implanted between 2012 and 2014, who underwent DBS for refractory epilepsy (Medtronic Activa PC Models 37601, 3787). Data on seizure reduction and side effects were complete in 11 of 13 patients. We defined refractory epilepsy according to the 2017 ILAE guidelines as non-responding to ≥2 anti-seizure medications (ASMs). Stimulation was usually initiated 3–5 weeks after implantation. We initially used the parameters described in the aforementioned landmark SANTE (1) study (Impulse width 90 μsec, Frequency 145 Hz, stimulation voltage 5.0 V, cycle: stimulation for 60 s every 5 min). Monopolar stimulation was used in all patients except the one patient with active VNS. When seizure frequency increased or did not decrease, changes in stimulation parameters were preferred to changes in ASM in order to better isolate the therapeutic effects of DBS. The preferred order of these changes was firstly changes in voltage (increase by 0.5–1 V), secondly changes in cycle speed (e.g. stimulation for 60 s every 3 min), and thirdly change into bipolar stimulation. These changes were carried out similarly in case of side effects, beginning with voltage decrease in 0.5 V steps. Nevertheless, ASM changes happened when deemed clinically necessary.

Post-implantation seizure reductions were expressed as percentages and interquartile ranges (IQR) and measured at 6 months, 12 months and last follow-up, as well as averaged throughout follow-up. These values were then compared with mean seizure frequencies in the 6 months before implantation. Seizure frequencies were assessed using seizure diaries. Seizure semiology was classified according to 2017 ILAE guidelines, based on our video-EEG (vEEG) recordings and descriptions by patients or witnesses. We analyzed the cohort of 11 patients in its entirety, and calculated the average seizure reduction during follow-up including only the patients who had at least one electrode on-target ($n = 9$).

In the current study we analyzed acute as well as long-term effects of DBS on cognition. To address acute cognitive effects a baseline assessment was performed after implantation and before initiating stimulation, and a follow-up assessment was conducted under DBS. The cognitive screening focused on attention and executive functions [EpiTrack® (8)] and on verbal learning and episodic memory [short version of the Verbaler Lern- und Merkfähigkeitstest, VLMT (9)]. To analyze the long-term effects of DBS on cognition we compared the preoperative neuropsychological profile with a long-term follow-up under DBS. The neuropsychological assessment included tests on attention and executive functions [EpiTrack® (8)], episodic long-term memory, i.e. verbal and figural learning and memory [VLMT (10) and a revised version of the Diagnosticum für Cerebralschädigung, DCS-R (11)], confrontative naming [Boston Naming Test, BNT (12)], and mental rotation [Leistungsprüfsystem, LPS subtest 7 (13)]. A mild impairment was defined as a performance lower than 1 standard deviation below the mean of the normative sample, a severe impairment as a performance lower than 2 standard deviations below the mean of the normative sample. Given the small sample size, we analyzed the frequencies of statistically significant intraindividual changes under DBS, employing reliable change indices (RCIs).

Follow-up duration during stimulation ranged from 9 to 111 months (average 51.5 months), and was ongoing until deactivation in all cases where deactivation occurred.

Results

Patient characteristics

Demographics

Age at implantation ranged from 22 to 50 (mean 35.5) years. Age at epilepsy onset was mostly in childhood and ranged from 4 to 24 (mean 14.5) years. Our cohort was 63.6% assigned female at birth (Table 1).

Etiology

Among the 9 patients who experienced seizure reduction in the overall follow-up period, the etiology was most commonly unclear (5 patients, 55.5%), followed by structural origin. Five (55.5%) had multifocal epilepsy. Of the 2 patients with seizure increase, one had epilepsy of unknown etiology, the other structural epilepsy due to posttraumatic lesions. The patient who achieved seizure freedom had genetic generalized epilepsy. One of the responders with epilepsy of unknown origin, who underwent explantation due to polydipsia and the emergence of functional non-epileptic seizures, later underwent genetic testing that revealed a Dyamin-1 mutation suggesting a generalized encephalopathic epilepsy. Follow-up duration during stimulation ranged from 9 to 111 months (average 51.5 months), and is either ongoing, or continued until deactivation/explantation in all cases. Mean duration of stimulation (excluding the 3 patients with ongoing stimulation) was 52.6 months (range 10–97 months). When excluding the patient who underwent explantation before the 12 month follow-up mark due to intolerable side effects, all 7 patients underwent stimulation for at least 2 years and up to 6 years.

Anti-seizure medications

Patients were taking an average of 3.6 ASM at the time of implantation (range 2–5). Two patients underwent no changes in ASM during stimulation. Five patients, all of them DBS responders before the ASM change, underwent a substitution of one ASM due to side effects (exchange of one ASM for another), three patients were subject to more than one change in ASM (exchange, increase and/or reduction): two of these patients experienced a seizure increase during stimulation and underwent substitution and increase of one ASM, and one was a DBS responder (71% seizure decrease on average during entire follow-up) and underwent an exchange of one ASM due to side effects and a reduction of one ASM. One patient, who achieved temporary seizure freedom, was able to decrease the number of ASM. In two patients Perampanel was added, and in one Valproat was added, which may have influenced their psychiatric side effects, whether positively in the case of Valproate, or negatively in the case of Perampanel.

Concomitant VNS or prior surgeries

Presurgical evaluation including vEEG and/or stereo-EEG and 1.5 (due to VNS) or 3T MRI had taken place in all patients. Five of the patients in our cohort had undergone vagal nerve stimulation (VNS). Three of these were explanted at the time of initiating DBS, 1 remained implanted with an inactive VNS system, and 1 patient underwent simultaneous VNS (with constant stimulation parameters) and DBS stimulation. This patient suffered no side effects, and experienced a seizure reduction of 48.2% (average entire follow-up). One patient had undergone resective epilepsy surgery (lesionectomy of a left temporal cortical cavernoma) 12 years prior to implantation in another hospital. One patient had previously had a callosotomy 8 years prior.

Explantation and deactivation of DBS

Five patients remained implanted at the end of follow-up, and stimulation was ongoing in 3 patients (Figure 1). Causes for explantation or deactivation were: increased seizure frequency in 2 cases, side effects in 5 cases, and subjective insufficient seizure reduction in the remaining case.

Seizure reduction and side effects

Data on seizure control were complete in all 11 patients. When averaging seizure frequency during the entire follow-up period, six patients (54.5%) were responders (achieved seizure reduction of $\geq$50%) (average 73.6% reduction, range 50–94.9%, interquartile range (IQR) 49.75). One of these patients achieved temporary seizure freedom and near-total seizure reduction during the entire follow-up. Seizure reduction of $<$50% was achieved in 3 patients (average seizure reduction of 42.7%). Among these nine patients with seizure reduction, the average seizure decrease during entire follow-up was 58.7% (range 36.5–100%, IQR 44.85). The 2 remaining patients had a seizure frequency increase ranging from 21.3 to 33.3% (average 27.3%). During follow-up, all patients underwent neuropsychological testing and were explicitly asked about side effects, including mood disorders.

At 6 months, 10 of the 11 patients (90.9%) reported seizure frequency reduction (7%-99% reduction in seizure frequency, average 53.8%, IQR 60.8). Of these, 4 patients (36.4%) reported a seizure frequency reduction of $<$50% (7%-43%, IQR 21.95). One patient had a 33.3% seizure increase. The remaining 6 patients (54.5%) were responders. At this point in time, 2 patients presented with side effects, both of psychiatric nature (one patient presented with new-onset daily functional non-epileptic seizures, one patient showed an exacerbation of previously existing depression).

At 12 months, the device had been deactivated in 1 patient, who previously had experienced a seizure reduction of $>$80%, due to side effects (intolerable paresthesias along subcutaneous cable trajectory, exacerbation of pre-existing depression). Eight of the 10 patients (80%) reported seizure frequency reduction (range 28.6–100%, average 78.8%, IQR 12.9), seven of them of $>$50%, with one patient reporting seizure freedom (61.9–100%, average 76.9%, IQR 11.8). The two remaining patients, one of whom had previously reported an increase in seizure

TABLE 1 Patient characteristics.

Age at implantation	Sex assigned at birth	Etiology of epilepsy	Age at onset of epilepsy	ASM at implantation	VNS	Other epilepsy surgery	Side effects of DBS	Seizure reduction > 50% (avg during follow-up)
45	f	GGE	12	5	n	n	Anxiety, right temporal headache after cycle increase	>50%
50	m	Multifocal encephalopathic epilepsy, etiology unknown	21	4	y (inactive)	n	None	Seizure increase
30	f	Dynamin-1 Mutation (etiology unkown at implantation)	8	3	y (inactive)	n	Polydipsia, functional movement disorder, FNES	<50%
39	f	Unclear	12	4	n	y	None, wound problems	>50%
40	f	Perinatal left hemisphere substance defects, unclear origin	24	5	y (inactive)	y	Functional dysarthria and dysphagia	50%
29	f	Multifocal epilepsy, unclear origin	23	4	n	n	Initial concentration difficulties, immediate reversibility through voltage reduction. Paresthesias along cable	>50%
29	m	Post traumatic defect both superior frontal gyri	9	2	n	n	Delusional disorder	Seizure increase
22	f	Multifocal epilepsy, unclear origin	7	2	n	n	None	>50%
33	m	Suspected FCD left superior temporal gyrus	15	4	y (active during DBS)	y	None	<50%
44	m	Post herpes encephalitis	25	4	y (inactive)	y	None	<50%
30	f	Multifocal epilepsy, unclear origin	4	3	n	n	Burning dysesthesia around cable trajectory	>50%

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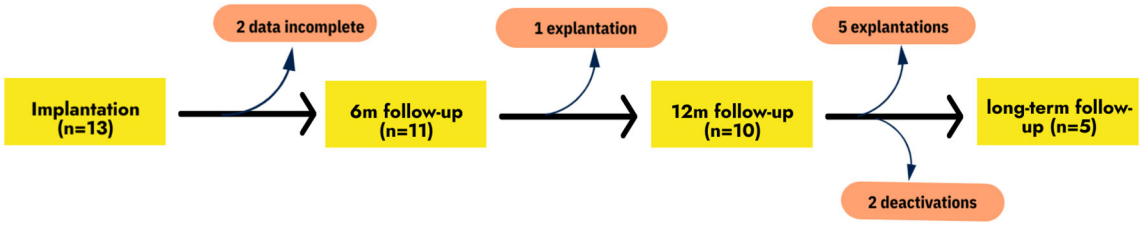

FIGURE 1
Study flowchart. Note: NPT is not detailed here.

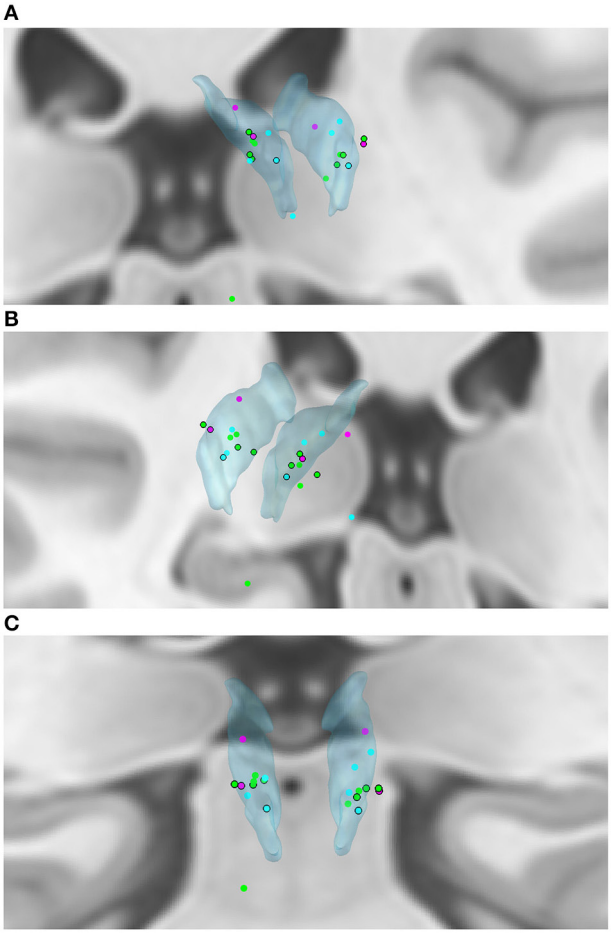

FIGURE 2
(A–C) Active electrode placements in the ANT (translucent blue). Blue dot—seizure reduction <50%; Green dot—seizure reduction ≥50%; Pink dot—seizure increase; Black ring around dot—intolerable side effects. Seizure outcomes displayed are averages over follow-up.

frequency, had dramatic seizure increases of more than double the preoperative seizure frequency (145 and 233% increase), leading to changes in anti-seizure medication. At this point in follow-up, 5 patients reported side effects (emergence of delusions and episodic agitation, functional non-epileptic seizures, burning dysesthesia along the cable trajectory, functional dysarthria and dysphagia, functional polydipsia and emergence of functional non-epileptic seizures). All side effects were reported by patients with seizure reduction during stimulation, except in the case of emergence of delusions and episodic agitation in a patient with seizure increase.

At last point of follow-up (beyond 12 months) of the ten patients who remained implanted and undergoing stimulation, seven patients (70%) reported a decrease in seizure frequency (43.3–100%, IQR 35.3), six of them of >50% (58.3–99.8%, IQR 33.1). The three remaining patients, including the 2 patients who had suffered a significant seizure increase at 12 months, had returned to their preoperative seizure frequency. All of the previously reported side effects persisted, and ultimately led to explantation or deactivation. No patients reported suicidal ideation at any time point.

Two of our patients had both electrodes implanted off-target. They had a seizure reduction of 71% and 50% during the entire follow-up. Both showed side effects (functional non-epileptic seizures and functional dysarthria and dysphagia) that ultimately led to deactivation and/or explantation. When removing these two patients from the analysis and averaging seizure frequency during the entire follow-up period, four patients (44.4%) were responders (average reduction 86.7%, range 65.6–94.9, IQR 18.97) and three experienced a seizure reduction of <50% (average reduction 42.6%, range 36.5–48.15, IQR 11.65). This cohort included the two patients with seizure increase as well as the patient that achieved temporary seizure freedom and near-total seizure reduction during the entire follow-up.

At their simplest, the outcomes in terms of side effects and seizure frequency in our cohort can be summarized as follows:

- one patient suffered a seizure increase and no side effects (etiology unknown)
- one patient suffered a seizure increase coupled with intolerable psychiatric side effects (structural posttraumatic etiology)
- four patients experienced a reduction in seizure frequency and no side effects (2 structural etiology, 1 genetic generalized epilepsy)
- one reported seizure reduction and tolerable side effects (etiology unknown)
- and the remaining four patients experienced seizure reduction coupled with intolerable side effects (etiologies unknown in 3 patients, structural 1, Dynamin-1 mutation 1).

Electrode placement

We created a model of electrode placement using the Lead-DBS toolbox for MatLab (14) (Figures 2A–C) with the DISTAL atlas

for 3D visualization (15, 16). Eight of twenty-two active electrodes (36.4%) were outside of the ANT, both electrodes in two patients and one electrode in four patients. Only two of these patients had intolerable side effects (Figures 2A–C, black-ringed dots).

Both patients with seizure increase had one active electrode outside of the ANT (the right electrode in both cases). The 4 remaining patients had seizure decreases of 43.3–86.3%. Two of these four patients had both electrodes off-target.

Cognitive effects

Data on cognitive effects was complete in 8 of the 13 patients.

Acute cognitive effects of DBS

At baseline, i.e., after implantation and before stimulation, 4 of the 8 patients showed impairment in attention and executive functions (1 mild, 3 severe; no floor effects). Under DBS, the one patient with mild impairment significantly deteriorated to a severely impaired level, the other 7 were unchanged according to RCIs. Regarding episodic memory, in 6 of the 8 patients a deficit was registered at baseline (3 mild, 3 severe; no floor effects). Although we did not observe any statistically significant intraindividual memory changes under DBS, there were some categorical changes, i.e., under DBS all patients showed an impairment (4 mild, 4 severe).

Long-term effects of DBS on cognition

To address the long-term effects of DBS on cognition we compared the preoperative neuropsychological profile with a long-term follow-up under DBS. The median interval between DBS implantation and follow-up assessment was 54.5 weeks. The preoperative cognitive profile of the 8 patients indicated deficits in attention and executive functions in 6 patients (2 mild, 4 severe), in verbal memory in 7 patients (2 mild, 5 severe), in figural memory in 6 patients (6 severe), in confrontative naming in 8 patients (1 mild, 7 severe), and in mental rotation in 3 patients (3 mild). Data did not indicate relevant floor effects that may have masked subsequent (significant) deteriorations. At the long-term follow-up, we observed significant intraindividual changes in verbal learning and memory in 5 of the 8 patients (3 deteriorated, 2 improved). In detail, 1 patient significantly declined in verbal learning and memory performance, 1 patient in verbal learning and recognition performance, and 1 in absolute delayed free recall. Regarding figural memory, none of the patients declined, 1 patient improved. The same is valid for attention and executive functions (1 improvement), confrontative naming (1 improvement, 2 missing), and mental rotation (1 improvement, 1 missing).

Discussion

In our cohort, 81.8% of patients treated with ANT-DBS for refractory epilepsy experienced seizure reduction, with an average seizure reduction during entire follow-up of 58.7% (36.5–94.9%). Two patients (18.2%) suffered an average seizure increase of 27.3% during entire follow-up, with a period of significant seizure increase at 12 months. Intolerable side effects arose in 5 patients, mostly psychiatric in nature, and most commonly the emergence of functional neurological disorders.

In our cohort, several patients with multifocal epilepsies benefit from ANT-DBS, in accordance with other centers' experiences (17). Patients with genetic generalized epilepsies may also benefit from DBS. Psychiatric side effects were more common in our cohort than in other published cohorts, and were occasionally severe enough to entail explantation. This may be explained by the fact that more than a third of our implanted electrodes were off-target, compared to approximately 10% in SANTE (1, 2). It is also relevant that, at the time of implantation, usage of electrode model Medtronic 3387 was widespread. In the years of its use, the 3387 electrode had 1.5 mm spacing, with fewer contacts in ANT, compared to the current electrode with 0.5 mm spacing. Additionally, it was not known at that time that it was optimal to target the region of termination of the mammillothalamic tract. Both patients with seizure increase had one active electrode outside of the ANT (the right electrode in both cases). Interestingly, the 4 remaining patients (two of whom had both electrodes off-target) had seizure decreases of 43.3% to 86.3%. This may be due to a variety of reasons: firstly, stimulation in the ANT or in close proximity may be similarly effective. Secondly, the modeling of electrode placement using software cannot be expected to be 100% accurate. Thirdly, interindividual anatomical variation of the exact placement of the ANT may pose a challenge for neurosurgical targeting (18). Furthermore, published data support the hypothesis that proximity to the ANT alone does not correlate with seizure reduction in ANT-DBS, whereas proximity to the mammillothalamic junction does (19). The electrode placement of patients with intolerable side effects seemed to form a cluster in the anterolateral segment of the ANT (Figures 2A–C, black-ringed dots). Interestingly, patients with $\geq$50% seizure reduction similarly seemed to cluster in a narrow band of the mid- to anterior segment of the ANT (Figures 2A–C, green dots).

Wound-related side effects including paresthesias occurred in our cohort and seem to be among the most common undesirable outcomes of DBS, as described in the SANTE studies (1, 2). It is now known that they usually result from use of the stimulator case as the anode, and that if turning down the current does not relieve the paresthesias, then switching to bipolar stimulation with the stimulator and extension leads taken out of the circuit usually does (1, 2).

Regarding the acute cognitive effects of DBS, only 1 of the assessed patients showed a statistically significant deterioration in executive functions. Although there were no significant changes in verbal memory, 2 patients showed a de novo deficit after a non-significant decline. Long-term neuropsychological effects included significant intraindividual deteriorations as well as improvements in verbal learning and memory. Figural memory, attention and executive functions, confrontative naming and mental rotation were mostly unchanged, and improved in few cases. Though these findings are meaningful, pinpointing their exact cause is challenging: several factors may be at play, such as stimulation programming, stimulation site, and the effect of seizure reduction on cognition, among others.

Due to lack of high-level evidence, there are currently no available standardized treatment guidelines for ANT-DBS with detailed evidence-based stimulation settings. Nevertheless, recently a European expert-panel consensus paper and an international consensus paper (20, 21) issued a series of recommendations and causes for concern, as well as experience-based opinions on the implementation of ANT-DBS. The majority of the panel agreed on broad aspects of stimulation settings (initial monopolar stimulation, most parameters according to the SANTE study). Currently, two main aspects seem decisive, but uncertain, in the effectiveness of ANT-DBS in published works (5, 17, 22–25): patient recruitment (more specifically etiology of epilepsy), and optimal stimulation settings. One of the largest single-center cohorts of patients treated with ANT-DBS (22) followed a systematic approach beginning with voltages under 5V and with minimal medication changes, and reported a responder rate of 73.9%. Lower voltages are coupled with decreased risk of side effects and longer battery life, though patients with higher impedances may need higher amplitudes. When deciding whether to apply monopolar or bipolar stimulation, it is important to consider that monopolar settings result in a wider range of stimulated tissue. When this is coupled with higher voltage, adverse reactions may arise.

Five patients in our cohort had undergone VNS. One patient received concomitant stimulation from the VNS and ANT-DBS. Though initially, it was common practice to require deactivation and/or removal of the VNS system before proceeding with ANT-DBS, recent data shows that here were no complications related to concomitant VNS and ANT-DBS, and removal of VNS does not appear to be necessary (26). Since ANT-DBS and VNS affect seizure control through different mechanisms, concomitant implantation may even be beneficial in certain patients.

Our study is limited by the small sample size and the heterogeneity in patient characteristics. This rendered subgroup analyses uninformative. Though we have strived to offer a more complete picture of life after implantation of DBS by including neuropsychological and side effect outcomes, a more nuanced approach including sleep disruption, subjective impact on quality of life, etc. is needed. Furthermore, all epilepsy studies based on patient-reported seizure frequencies probably suffer from seizure under-reporting (27), and ours is no exception.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Data availability statement

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

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 for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

KO: data curation (lead), data analysis (lead), statistical analysis (lead), MATLAB graphics (lead), writing—original draft preparation (lead), and writing—review and editing (equal). J-AW: neuropsychological data curation (lead), neuropsychological data analysis (lead), writing—original draft preparation (equal), and writing—review and editing (equal). RW: data curation (supporting) and writing—review and editing (equal). CH: supervision (equal), neuropsychological data analysis (supporting), writing—original draft preparation (supporting), and writing—review and editing (supporting). RS: supervision (equal), writing—original draft preparation (supporting), and writing—review and editing (equal). All authors contributed to the article and approved the submitted version.

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Conflict of interest

KO has received speaker fees from Eisai, unrelated to this work. RS has received fees as speaker or for serving on the advisory board from Angelini, Arvelle, Bial, Desitin, Eisai, Janssen-Cilag GmbH, LivaNova, Novartis, Precisis GmbH, UCB Pharma, UnEEG, and Zogenix. These activities were not related to the content of this manuscript.

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.

Publisher's note

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Deep brain stimulation for patients with refractory epilepsy: nuclei selection and surgical outcome

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Objective: By studying the surgical outcome of deep brain stimulation (DBS) of different target nuclei for patients with refractory epilepsy, we aimed to explore a clinically feasible target nucleus selection strategy.

Methods: We selected patients with refractory epilepsy who were not eligible for resective surgery. For each patient, we performed DBS on a thalamic nucleus [anterior nucleus of the thalamus (ANT), subthalamic nucleus (STN), centromedian nucleus (CMN), or pulvinar nucleus (PN)] selected based on the location of the patient's epileptogenic zone (EZ) and the possible epileptic network involved. We monitored the clinical outcomes for at least 12 months and analyzed the clinical characteristics and seizure frequency changes to assess the postoperative efficacy of DBS on the different target nuclei.

Results: Out of the 65 included patients, 46 (70.8%) responded to DBS. Among the 65 patients, 45 underwent ANT-DBS, 29 (64.4%) responded to the treatment, and four (8.9%) of them reported being seizure-free for at least 1 year. Among the patients with temporal lobe epilepsy (TLE, $n = 36$) and extratemporal lobe epilepsy (ETLE, $n = 9$), 22 (61.1%) and 7 (77.8%) responded to the treatment, respectively. Among the 45 patients who underwent ANT-DBS, 28 (62%) had focal to bilateral tonic-clonic seizures (FBTCS). Of these 28 patients, 18 (64%) responded to the treatment. Out of the 65 included patients, 16 had EZ related to the sensorimotor cortex and underwent STN-DBS. Among them, 13 (81.3%) responded to the treatment, and two (12.5%) were seizure-free for at least 6 months. Three patients had Lennox–Gastaut syndrome (LGS)-like epilepsy and underwent CMN-DBS; all of them responded to the treatment (seizure frequency reductions: 51.6%, 79.6%, and 79.5%). Finally, one patient with bilateral occipital lobe epilepsy underwent PN-DBS, reducing the seizure frequency by 69.7%.

Significance: ANT-DBS is effective for patients with TLE or ETLE. In addition, ANT-DBS is effective for patients with FBTCS. STN-DBS might be an optimal treatment for patients with motor seizures, especially when the EZ overlaps the sensorimotor cortex. CMN and PN may be considered modulating targets for patients with LGS-like epilepsy or occipital lobe epilepsy, respectively.

KEYWORDS

deep brain stimulation, refractory epilepsy, anterior nucleus of the thalamus, subthalamic nucleus, centromedian nucleus

1. Introduction

Epilepsy is a chronic neurological disorder that affects approximately 1% of the global population (1, 2). Currently, most patients can benefit from drug therapy, the first-line treatment for epilepsy. However, nearly 30% of patients suffer from drug-resistant epilepsy (3). In these patients, identifying the epileptogenic foci and performing resective surgery may help reduce or even control seizures completely (4). Noteworthily, epilepsy surgery remains challenging, including the difficulty of localizing the seizure focus, multiple seizure foci, and seizure focus close to the eloquent cortex (5, 6). Accordingly, not all patients with drug-resistant epilepsy may benefit from surgical resection. Therefore, alternative options are urgently needed (7).

Neurostimulation is an alternative treatment for patients who reap limited benefits from resective surgery (8). In the 1970s and 1980s, deep brain stimulation (DBS) emerged as an approach for treating epilepsy by stimulating a specific target (9, 10). Although the specific antiepileptic mechanism remains to be detailed, numerous clinical reports have confirmed the effectiveness of DBS against epilepsy. Gastaut and Broughton proposed that focal epilepsy is a cortico-subcortical disorder and suggested that subcortical structures participate in seizure initiation (11). Previous studies had documented that the thalamus had a widespread interactive connection with cortical regions and might, as a critical subcortical structure, participate in all focal epilepsies independently of the etiology or focus localization (12). Therefore, it seems reasonable to consider the thalamus as the stimulation target.

The famous SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) clinical study has demonstrated the safety and effectiveness of the anterior nucleus of the thalamus (ANT)-DBS (13). Subsequent studies confirmed the efficacy of ANT-DBS (14, 15). However, whether all patients would benefit from ANT-DBS remains a crucial clinical question. In other words, is the ANT the best modulating target for patients with different epilepsy or seizure types? In our opinion, due to the complexity of the thalamus anatomy and the functional network, one of the challenges of the DBS treatment for epilepsy is choosing the optimal stimulation target for specific epilepsy or different seizure types. According to limited clinical studies, DBS can also be effective on other nuclei, such as the subthalamic nucleus (STN) (16), the centromedian nucleus (CMN) (17), and the pulvinar nucleus (PN) (18). The present single-center study reports the effect of DBS on different thalamic nuclei for drug-resistant epilepsy. It provides new insights for selecting the optimal nuclei target for patients with refractory epilepsy.

2. Methods

2.1. Patient selection

All the participants were diagnosed with drug-resistant epilepsy at the Beijing Institute of Functional Neurosurgery, Xuanwu Hospital, between January 2012 and December 2021. In total, this study included 65 patients. Their mean age was 24.37 ± 9.56 years and 36.9% (24 subjects) were women. The mean duration of epilepsy was 12.76 ± 7.28 years. The mean follow-up duration was 39.4 ± 20.9 months (ranging from 12 to 108 months). Experienced neurologists and neurosurgeons discussed and designed the selection of the stimulation target and the surgical plan of the DBS for each patient.

The inclusion criteria were as follows: (1) Patients diagnosed with drug-refractory epilepsy were based on the ILAE Classification of Epilepsies (19). (2) The preoperative evaluation indicated that the patient was inoperable or had contraindications for resective surgery, such as widely distributed epileptogenic zones (EZ), EZ located in the functional cortex, failed resective surgery, or the patient refused to undergo the resective surgery.

2.2. Presurgical evaluation

We performed long-term scalp video electroencephalography (VEEG) to record at least three habitual seizures for each patient using a video EEG monitoring system (Micromed, Treviso, Italy). In some patients, we identified the EZ by performing stereotactic electroencephalography (SEEG). All patients underwent a high-resolution magnetic resonance imaging (MRI) protocol performed using a 3.0-T MR Scanner (Siemens, Verio, Germany) and consisting of conventional axial, sagittal, and coronal T1-weighted spin-echo sequences. In some patients, we identified the EZ by performing magnetoencephalography and positron emission tomography-computed tomography. The patients who underwent the DBS procedure after the special committee consultation excluded resective surgery based on their clinical data. For each patient, we selected the target thalamic nucleus for DBS (ANT, STN, CMN, or PN) based on the patient's epilepsy or seizure type and the location of the epileptogenic focus, as well as the possible epileptic network involved (20, 21). We defined the baseline for each patient as their mean seizure frequency over the 3-month pre-implant period.

2.3. Surgical method

We implanted the DBS electrodes (Model 3387 or 3389; Medtronic, Inc., Minneapolis, MN, USA) with the assistance of a frame-based, microelectrode-guided, stereotactic technique under general anesthesia. All the patients receiving ANT-DBS, CMN-DBS, and PN-DBS underwent bilateral electrode implantation. In patients with STN-DBS, some patients with specific epilepsy types (such as those with the possible EZ located in the unilateral hemisphere) underwent unilateral electrode implantation. With the help of the high-resolution T1-weighted images, we delineated the thalamus nuclei based on the Morel Stereotactic Atlas. We performed the surgical procedure of the implantation of the DBS leads and the pulse generator (Model 3628 screener, Medtronic, Inc., Minneapolis, MN, USA) based on previous studies (22). Postoperative computed tomography was performed and registered with the T1-weighted images to confirm the locations of the electrodes.

2.4. Postoperative follow-up and parameters adjustment

One month after the implantation procedure, the pulse generator was initiated to be activated and programmed. The outpatient review of each patient was carried out 3 months after the operation to identify the occurrence of long-term complications. In addition, the stimulation parameters and contacts were adjusted based on seizure frequency and clinical response. We categorized patients with a ≥50% decrease in seizure frequency (mean seizure frequency for the last 3 months of follow-up, compared with the baseline as responders and patients with a < 50% decrease in seizure frequency as non-responders. All of the patients were followed up monthly or trimonthly, and the seizure frequency was reported by the patient or the family members. Noteworthy, the post-operative seizure needs to be verified with the habitual seizure. The data were recorded from outpatient reviews, medical record reviews, patients' daily diaries, and telephone interviews. The postoperative program control details for each patient were also documented.

3. Results

Among the 65 patients, 45 underwent ANT-DBS, 16 underwent STN-DBS, three underwent CMN-DBS, and one underwent PN-DBS (Figures 1, 2). The demographic data and clinical characteristics of these patients are presented in Table 1 and Supplementary Table 1.

In our study, 46 of the 65 patients (70.8%) were responders (average decrease in seizure frequency 81.2%, ranging from 51.6% to 100%, interquartile range [IQR] 33.75). Among the 19 non-responders, nine patients experienced varying degrees of decrease in seizure frequency but <50% compared with the baseline (average 26.9%, range 9.1%−47.8%, IQR 25.75). Six patients reported no significant changes in seizure frequency. In total, four patients reported that their seizure frequency increased to various degrees (ranging from −25% to −220%).

Among the 45 patients who underwent ANT-DBS, 29 (64.4%) were responders (average decrease in seizure frequency 79.7%, ranging from 52.8% to 100%, IQR 31.99) and four (8.9%, patients 1, 5, 26, and 35) reported being seizure-free for at least 1 year. Based on the EEG, symptomatology, and other presurgical data, 36 of the 45 patients (80%) were diagnosed with temporal lobe epilepsy (TLE) and 22 of them (61%) were responders (average 80.2%, range 53.3%−100%, IQR 31.10). Among patients with TLE, nine (20%) were diagnosed with temporal plus (T-plus) epilepsy and eight of them (89%) were responders (average 84.8%, range 61.7%−100%, IQR 33.30). Based on the MRI images, 14 of the 36 patients (39%) with TLE had bilateral hippocampal sclerosis (HS) and eight of them (57.1%) were non-responders (ranging from −220% to 15%). Out of the 45 ANT-DBS patients, nine (20%) were diagnosed with extratemporal lobe epilepsy (ETLE), and seven of them (78%) were responders (average 78.2%, ranging from 52.8% to 100%, IQR 40.00). Among patients with ETLE, four were diagnosed with frontal lobe epilepsy, and three of them were responders (average 86.7%, ranging from 60.0% to 100%); five patients were diagnosed with multifocal epilepsy, and four of them were responders (average 71.9%, ranging from 52.8% to 91.7%, IQR 29.64). All of the patients' seizure types were focal seizures, and 28 of the 45 ANT-DBS patients (62%) had focal to bilateral tonic-clonic seizures (FBTCS). Among the 28 patients with FBTCS, 18 (64%) were responders (average 78.4%, ranging from 52.8% to 100%, IQR 31.88). Noteworthily, two non-responders with FBTCS reported that their seizure frequency was not significantly reduced, while their seizure severity was significantly improved (i.e., the duration of the seizures was reduced, and the patients quickly regained consciousness after the seizures).

In patients who underwent STN-DBS ($n = 16$), the etiologies were diverse, with cases of schizencephaly ($n = 5$), focal cortical dysplasia ($n = 5$), gray matter heterotopia ($n = 3$), and encephalitis ($n = 3$). One patient had both schizencephaly and focal cortical dysplasia. Noteworthily, the EZ of all patients was associated with the sensorimotor cortex, namely, with its centrofrontal ($n = 7$), centroparietal ($n = 2$), and frontoparietal ($n = 7$) lobes. Among the 16 patients, nine (56%) had motor seizures, while the seven others (44%) presented focal motor seizures and FBTCS. Moreover, 13 of the 16 patients (81%) were responders (average 87.1% reduction, ranging from 54.2% to 100%, IQR 27.58), and two patients (13%, patients 55 and 60) remained seizure-free for at least 6 months. Among the three non-responders, patient 50 suffered motor seizures and FBTCS; the aware motor seizures disappeared and the FBTCS increased after receiving the STN-DBS procedure, patient 57 reported a 25% increase in seizure frequency, and patient 61 reported a 43% decrease in seizure frequency.

For patients who underwent CMN-DBS ($n = 3$), the EZ was difficult to localize and, based on the EEG abnormalities and symptomatology, they were diagnosed with Lennox–Gastaut syndrome (LGS)-like epilepsy. The patients reported a 51.6%, 79.6%, and 79.5% reduction in seizure frequency at 76, 43, and 12 months of follow-up, respectively. Based on the presurgical evaluation, one patient was diagnosed with bilateral occipital lobe epilepsy, and the possible EZ was difficult to be removed surgically. Finally, the patient underwent PN-DBS. After the PN-DBS with elaborate postoperative program control, his seizure frequency was reduced by 69.7% at 13 months of follow-up.

4. Discussion

Deep brain stimulation is an emerging and promising treatment for epilepsy. The effectiveness of DBS is mainly related to the appropriate candidates, the optimal stimulation target, and the elaborate postoperative program control strategy. Currently, there are no specific stimulation target selection criteria for the treatment of epilepsy using DBS on the thalamus. Based on the symptomatology, VEEG/SEEG recordings, and imaging information, we inferred epilepsy or seizure type and EZ location for each patient, as well as the possible epileptic network involved. Next, we carefully selected a personalized stimulation target for each patient. We hope that documenting the surgical outcome of DBS in different thalamus nuclei will help clinical decision-makers select the optimal stimulation target for patients with refractory epilepsy.

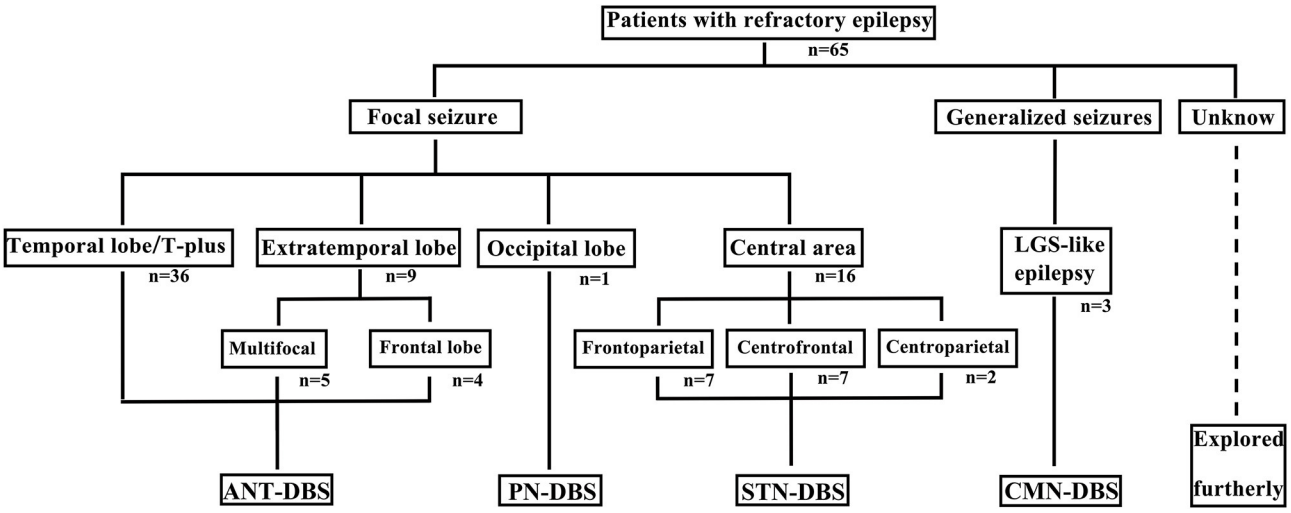

FIGURE 1
Different DBS procedures were selected for patients with various epilepsy or seizure types. T, temporal; LGS, Lennox–Gastaut syndrome.

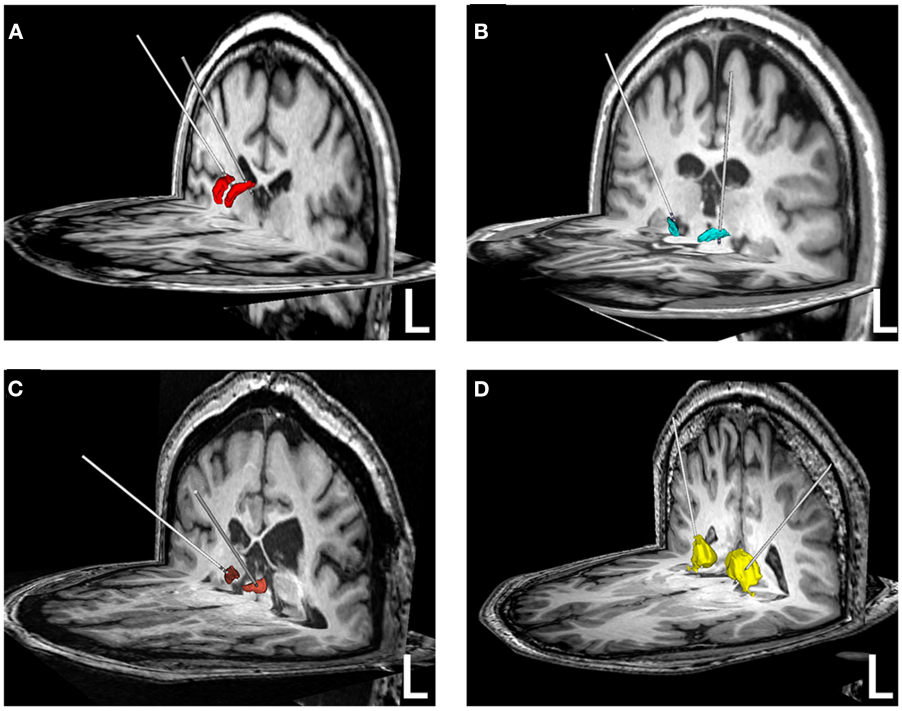

FIGURE 2
Reconstruction of electrodes in different brain nuclei. **(A)** ANT-DBS; **(B)** STN-DBS; **(C)** CMN-DBS; **(D)** PN-DBS. The ANT (red), STN (green), CMN (brown), and PN (yellow) were reconstructed based on the Morel Stereotactic Atlas.

4.1. ANT-DBS

The ANT is the most common stimulation target of DBS in epilepsy treatment (23). The unique anatomical relationship and the functional connection between ANT and the limbic system make this nucleus an ideal stimulation target for TLE treatment (24, 25). In our study, 80% of patients with ANT-DBS had TLE (including T-plus), and our results are in line with previous studies (13). Our previous SEEG study demonstrated that the ANT-DBS would desynchronize the epileptic network in patients with TLE. In addition, the position-specific correlation had also been reported between the DBS applied to the ANT and patients with TLE and EZ within the Papaz circuit or limbic system (26). Moreover, the ANT can receive the interictal period discharges that propagate from the

TABLE 1 Characteristics of the included patients.

Characteristics of patients ($n = 65$)	ANT-DBS ($n = 45$)	STN-DBS ($n = 16$)	CMN-DBS ($n = 3$)	PN-DBS ($n = 1$)
Age (y)	29.7 ± 9.59	19.56 ± 7.99	16.00 ± 4.00	23
Duration of epilepsy (y)	12.87 ± 7.80	12.29 ± 6.45	11.33 ± 4.04	20
Females[#]	15 (33%)	6 (37.5%)	3 (100%)	0
Mean follow-up (m)	44.24 ± 17.55	26.63 ± 23.02	43.6 ± 32.01	13
Seizure characteristic[*]				
Focal seizure	45 (69.2%)	16 (24.6%)	3 (4.6%)	1 (1.5%)
Focal to bilateral tonic-clonic seizures	28 (43.1%)	7 (10.8%)	3 (4.6%)	1 (1.5%)
Motor seizures	0	16 (24.6%)	0	0
Location of EZ[#]				
T/ T-Plus	36 (80%)	0	0	0
F-C/ C-P	4 (9%)	16 (100%)	0	0
O	0	0	0	1 (100%)
Multifocal	5 (11%)	0	Unknown	0
Surgical outcome[#]				
Responders	29 (64.4%)	13 (81.3%)	3 (100%)	1 (100%)
Seizure frequency reduction	37 (82.2%)	14 (87.5%)	3 (100%)	1 (100%)

[*]The proportion of individuals in total patients.
[#]The proportion of individuals in patients with specific DBS procedure.
T, temporal; T-Plus, temporal plus; F, frontal; C, central area; P, parietal; O, occipital; FBTCS, focal to bilateral tonic-clonic seizures; EZ, epileptogenic zone; y, year; m, month.

epileptogenic zones in neocortical temporal and mesial temporal epilepsy (27). Therefore, combined with the previous clinical studies, our data suggest that ANT is an optimal stimulation target for patients with TLE. Fasano et al. suggested that patients with frontal seizures also benefit from ANT-DBS (28). The long-term follow-up of the SANTE trial showed that frontal onset seizures also respond well to ANT-DBS (14). In our study, patients with frontal epilepsy showed a good response to ANT-DBS. In addition, patients with multifocal epilepsy also benefited from the ANT-DBS. Previous studies suggested that ANT plays a role in a wider cortical network (29, 30), and other epilepsy types could be treated through ANT stimulation.

In patients with FBTCS, ANT-DBS showed good efficacy, which may be because ANT-DBS modulates the epileptic network excitability. Previous studies suggested that the ANT participates in the organization and maintenance of seizure activity (21). In addition, Tyvaert et al. observed a synchronous activity between the ANT and generalized epileptogenic network in patients with generalized epilepsy, indicating that the ANT is a potential propagation point (31). We speculate that, on the one hand, ANT-DBS might reduce the epileptic network excitability to some extent and raise the seizure threshold, making the seizure less likely to occur. On the other hand, the reduced network excitability might limit the propagation of the epileptic excitatory signal. This hypothesis is also supported by the reduced severity of postoperative seizures in patients with FBTCS. Therefore, based on the mechanism studies and the clinical results, ANT-DBS is also an alternative treatment for patients with FBTCS.

The reasons why some patients have poor responses to ANT-DBS are complex. In our study, ANT-DBS turned out to be poorly effective for patients with bilateral HS. We speculate that the EZ of these patients has excessive excitability, and ANT-DBS may have a relatively weak inhibitory effect on the sclerotic hippocampus. A previous epilepsy study reported that hippocampal DBS was less effective in patients with HS than in patients with normal MRI profiles (32). According to previous studies, the sclerotic hippocampus was related to neuronal reduction, which may prevent the hippocampus to provide enough available tissue for modulation (33). In addition, the sclerotic hippocampus might have an increased impedance and require a more intense stimulus (32). Regarding ANT-DBS in patients with bilateral HS, indirect stimulation based on the specific network may further weaken the regulation effect on the sclerotic hippocampus. Noteworthy, the aberrant circuits may be involved in patients with bilateral HS, which would induce inefficacy or even the paradoxical effect when the ANT-DBS was applied.

Currently, identifying patients who would benefit from ANT-DBS is difficult. Our results indicate that some epilepsy types would be refractory to this treatment. Therefore, different stimulation targets and corresponding surgical indications need to be explored further for patients with refractory epilepsy.

4.2. STN-DBS

In some patients with drug-resistant epilepsy, resective surgery would be contraindicated due to the EZ being located in the primary motor cortex. Responsive brain stimulation (34) and ANT-DBS (13) offer an alternative treatment for these patients, but the response is not always satisfactory. In 2002, Benabid et al. first applied STN-DBS to treat epilepsy in a patient with focal centroparietal dysplasia and reported an 80.7% reduction in seizure frequency (16). Subsequent studies confirmed the safety and effectiveness of STN-DBS in patients with motor seizures (35, 36). Regarding the mechanism, our team's prior study demonstrated the interaction between STN and the motor cortex. In addition, STN-DBS with high-frequency stimulation suppressed the interictal spikes and high-frequency oscillations in patients with motor seizures (37).

Based on existing clinical evidence and our knowledge of the mechanism, we choose STN as the target for patients with an EZ overlapping the sensorimotor cortex. STN-DBS significantly reduced motor seizures in these patients in concordance with previous studies (38). Therefore, STN-DBS can be a potent treatment option for patients with motor seizures. Nevertheless, STN-DBS needs to be further investigated in large-scale randomized controlled trials and specific regulative mechanism studies. Notably, patient 57 reported a seizure frequency increase (four times per month) after the STN-DBS, which might be related to the lower baseline (2–3 times per month) and require further stimulation parameter adjustment and follow-up. The EZ of patient 50 was located in the frontoparietal region with focal motor seizures and FBTCS. After STN-DBS, his focal seizures disappeared, and the FBTCS frequency decreased non-significantly; the pulse generator was removed after 14 months due to an increase in FBTCS frequency. We speculated that the poor response may be due to improper stimulation parameters and contacts. Therefore, even when selecting the optimal stimulation target, elaborate postoperative program control is particularly important.

4.3. CMN-DBS and PN-DBS

Patients with LGS present specific EEG abnormalities and multiple seizure types, such as generalized tonic seizures (17). Previous studies recorded epileptiform EEG activity in the CMN of patients with generalized tonic seizures from LGS (39). In addition, CMN has diffuse connections with the diffuse frontal areas, brainstem, and striatum, which prompted us to choose the CMN rather than the ANT, as the stimulation target in LGS or LGS-like epilepsy cases (40). Velasco et al. performed CMN-DBS on five patients with drug-resistant epilepsy and reported a significant reduction in secondary generalized tonic-clonic seizures (GTCS) frequency (41). Subsequent randomized controlled and small open-label studies reported significant efficacy for CMN-DBS in generalized seizures, especially in patients with primary or secondary LGS (17, 42). Based on this encouraging clinical data, we performed CMN-DBS in three patients with LGS-like epilepsy and also observed a good response. Therefore, we consider CMN-DBS to be an alternative treatment for patients with generalized-onset epilepsy.

As the largest thalamus nucleus, the PN has extensive connections with areas of the cortex, such as the mesial temporal lobe, the parietal cortex, and the occipital lobe (43–45). The anatomical features of the PN indicate that it is a potential neuromodulation target to treat epilepsy. Compared with the other targets, clinical reports on the stimulation of PN for the treatment of epilepsy are relatively rare. Filipescu et al. investigated PN stimulation on temporal lobe seizures and first suggested that PN-DBS could be a well-tolerated and effective approach for drug-resistant epilepsy (44). In a study of responsive neurostimulation targeting the PN to treat epilepsy, it was effective for drug-resistant epilepsy with posterior quadrant origin (18). In our study, we performed PN-DBS on one patient with bilateral occipital lobe epilepsy, significantly reducing seizure frequency. Although this is only one case, PN does seem to be an alternative target for neuromodulation to treat occipital lobe epilepsy.

4.4. Conclusion

Based on our single central clinical results, we summarized empirical guidance for the selection of stimulation targets for patients with refractory epilepsy. Our results show that ANT-DBS is effective for patients with either TLE (including T-plus) or ETLE (including FLE and multifocal epilepsy). However, in patients with bilateral HS, ANT-DBS should be applied with more caution. In addition, ANT-DBS is effective for patients with FBTCS. For patients with motor seizures, especially with the EZ overlapping the sensorimotor cortex, STN-DBS might be a powerful treatment. CMN-DBS and PN-DBS might be alternative options for patients with LGS-like epilepsy and occipital lobe epilepsy, respectively.

4.5. Limitation

The small cohort of our study prevented the investigation of the efficacy of DBS in a wider variety of epilepsy and seizure types. In addition, we only reviewed the efficacy of DBS in different thalamus nuclei. In future studies, we would investigate the details of postoperative program control, such as the parameter settings and side effects and the influence factors of surgical outcome.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Capital Medical

University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

HY, XW, TY, and LR designed the study. WS, CX, and RG contributed to the analysis of data. XZ, DN, and LQ contributed to the data acquisition. All authors contributed to the manuscript revision and read and approved the submitted version.

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Conflict of interest

The 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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Publisher's note

Supplementary material

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Effects of altered excitation–inhibition imbalance by repetitive transcranial magnetic stimulation for self-limited epilepsy with centrotemporal spikes

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Objectives: Patients with self-limited epilepsy with centrotemporal spikes (SeLECTS) with electrical status epilepticus in sleep (ESES) have generalized cognitive impairment, yet treatment options are limited. Our study aimed to examine the therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) on SeLECTS with ESES. In addition, we applied electroencephalography (EEG) aperiodic components (offset and slope) to investigate the improvement of rTMS on the excitation–inhibition imbalance (E-I imbalance) in the brain of this group of children.

Methods: Eight SeLECTS patients with ESES were included in this study. Low-frequency rTMS ($\leq$1 Hz) was applied for 10 weekdays in each patient. To assess the clinical efficacy and changes in E-I imbalance, EEG recordings were performed both before and after rTMS. Seizure-reduction rate and spike-wave index (SWI) were measured to investigate the clinical effects of rTMS. The aperiodic offset and slope were calculated to explore the effect of rTMS on E-I imbalance.

Results: Five of the eight patients (62.5%) were seizure-free within 3 months after stimulation, with treatment effects decreasing with longer follow-ups. The SWI decreased significantly at 3 and 6 months after rTMS compared with the baseline ($P = 0.0157$ and $P = 0.0060$, respectively). The offset and slope were compared before rTMS and within 3 months after stimulation. The results showed a significant reduction in the offset after stimulation ($P < 0.0001$). There was a remarkable increase in slope after the stimulation ($P < 0.0001$).

Conclusion: Patients achieved favorable outcomes in the first 3 months after rTMS. The ameliorative effect of rTMS on SWI may last up to 6 months. Low-frequency rTMS could reduce firing rates in neuronal populations throughout the brain, which was most pronounced at the site of stimulation. A significant reduction in the slope after rTMS treatment suggested an improvement in the E-I imbalance in the SeLECTS.

KEYWORDS

self-limited epilepsy with centrotemporal spikes, repetitive transcranial magnetic stimulation, excitation-inhibition imbalance, spike-wave index, electrical status epilepticus in sleep

1. Introduction

Self-limited epilepsy with centrotemporal spikes (SeLECTS) is the most common focal syndrome in childhood epilepsy (1). Most children with SeLECTS have a good prognosis, but a small percentage may evolve into epileptic encephalopathy with spike-and-wave activation in sleep (EE-SWAS). The EEG pattern associated with EE-SWAS is known as electrical status epilepticus in sleep (ESES) (2). The nearly constant epileptiform activity of slow-wave sleep is usually accompanied by significant regression in cognitive or behavioral function. All cognitive domains may be affected, including language and communication, temporospatial orientation, attention, and social interaction. However, existing treatments remain very limited in their ability to effectively reduce functional impairment in SeLECTS patients with ESES.

Repetitive transcranial magnetic stimulation (rTMS), as a focal, non-invasive technique, has therapeutic potential in the field of epilepsy (3). Low-frequency rTMS ($\leq$1 Hz) inhibits cortical excitability, increases cortical silent period duration, and reduces motor-evoked potential amplitudes (4). The rationale for using low-frequency rTMS to suppress seizures is related to the fact that it is promising to interrupt synaptic potential and focal cortical excitability. Real-world evidence suggests that low-frequency rTMS using a figure-8-coil may be an effective therapy for drug-resistant epilepsy in pediatric patients, resulting in a 30% reduction in seizure frequency (5). Ren et al. found that rTMS acted as a novel approach to behavioral problems that are highly prevalent in patients with SeLECTS (6). Although a Cochrane review found rTMS to be safe and effective in reducing epileptiform discharges, the evidence for the efficacy of rTMS for seizure reduction is still lacking (7).

The imbalance between excitatory and inhibitory properties (E-I imbalance) in SeLECTS has been identified as contributing to seizures and cognitive impairment (8). The inhibitory network involves both sensorimotor and subcortical networks, which manifest as a dissociation of the corresponding functions. However, the effect of rTMS on improving the E-I imbalance in SeLECTS patients is unclear. We hypothesized that rTMS would reduce seizure frequency and E-I imbalance in SeLECTS. To address our hypothesis, two requirements need to be met: (1) whether seizure frequency and epileptiform discharges are reduced after rTMS and (2) whether the E-I imbalance can be improved by rTMS.

2. Methods

2.1. Patient selection

This study was a retrospective analysis of patients with SeLECTS who visited the Sanbo Brain Hospital from January 2015 to December 2020. The inclusion criteria were as follows: (1) age of onset between 3 and 15 years; (2) appropriate seizure semiology which suggested focal onset (9); (3) centrotemporal spikes on EEG and unilateral spike-wave index (SWI) >80% or bilateral SWI >50%; (4) the neuropsychology test showed that intelligence quotient (IQ) was lower than normal intellectual development; (5) TMS treatment; and (6) at least one EEG exanimation after TMS. We excluded children with a history of prematurity (<35 weeks), abnormal magnetic resonance imaging (MRI) of the brain, other epilepsy syndromes, neurosurgery, and severe brain injury. This study was approved by the Ethics Committee of Sanbo Brain Hospital, Capital Medical University.

2.2. EEG recordings

The EEGs were recorded based on the standard international 10–20 system, with 19 scalp electrodes. The recording system used was Nicolet. EEG recordings during sleep and awake were obtained. The EEG signal was recorded at 512 Hz or 1,024 Hz. Impedance levels for each electrode were at or below 50 kΩ during data collection. EEG was referenced online to the central midline electrode site (Cz). The SWI was reviewed by an independent epileptologist blinded to the clinical data.

2.3. Neuropsychological evaluation

All patients underwent evaluation for intellectual and behavioral impairment using standard assessment procedures. The Wechsler Intelligence Scale for Children, fourth edition (WISC-IV), was used to measure the intelligence level of children at the baseline.

2.4. rTMS procedure

In our study, rTMS was performed on all patients using Magstim (Company Ltd.). The figure-8-coil plane targeting the stimulation site was tangential and was kept parallel to the scalp. The stimulus parameters were as follows: frequency $\leq$1 Hz; intensity, reference resting motor threshold; and the number of stimuli, 500/1,000/1,500 per site, depending on the frequency. The treatment lasted for 10 weekdays. The stimulation site was the central region (C5 or C6). The determination of the stimulation site was based on a combination of seizure symptoms, EEG, and abnormalities of positron emission tomography (PET) metabolism in the brain.

2.5. EEG data analysis

The EEGLAB toolbox in MATLAB was used to analyze the raw EEG data. The EEG was re-referenced to the average of all electrodes. We applied a 1 Hz bandpass filter and 80 Hz cutoff to the data. Independent components analysis was used to correct eye blink artifacts for correction.

The power spectral density (PSD) was calculated at 0.5 Hz increments from 1 Hz to 40 Hz using Welch's method (10 s time window, 0.5 s window length, 50% overlap). The "Fitting Oscillations and One-Over-f" (FOOOF) toolbox was used to calculate the aperiodic component (offset and slope). The PSD slope is equivalent to the negative exponent when measured in log–log space due to aperiodic activity having a 1/f-like distribution with exponentially decreasing power across increasing frequencies (10).

The E-I ratio could be estimated from the PSD slope. The steeper the slope is, the lower the E-I ratio (11). A more negative slope indicates that relatively more inhibition occurs in the underlying neuronal populations (12). The power spectrum, P, was modeled using three parameters:

$$P = L + \sum_{n=0}^{N} G_n \,, \tag{1}$$

where L is the aperiodic "background" signal, with N total peaks extracted from the power spectrum and Gaussians (Gn) fitted to each peak. The peaks were iteratively fitted by Gaussians:

$$G_n = a * \exp\left(\frac{-(F-c)^2}{2w^2}\right), \tag{2}$$

with an amplitude, center frequency, c, the bandwidth, w, of the Gaussian G, and the input frequencies, F. The aperiodic signal L was modeled by

$$L = b - \log\left(k + F^{\chi}\right), \tag{3}$$

where b is the broadband offset, x is the slope, and k is the "knee" parameter, which was set to 0. The FOOOF model was fitted for the frequency range of 1–40 Hz.

2.6. Follow-up program

Each patient was assessed for seizure frequency, SWI, WISC-IV, offset, and slope before treatment and observed after 10 working days of low-frequency stimulation. Seizure frequency, SWI, offset, and slope were assessed at 3 months post-treatment. Seizure frequency and SWI were measured at 6 months and 12 months post-treatment.

2.7. Statistical analysis

To test whether there were significant differences between baseline measurements before rTMS and follow-up measurements after rTMS, the pairwise comparison method was applied. First, a normality test was performed. If all groups met the normality and the variation between the two groups was homogeneous, a paired t-test was used. A non-parametric Wilcoxon matched-pairs signed rank test was considered if all groups did not meet the normality test. P-values < 0.05 were considered to be statistically significant. P-values were corrected with the original false discovery rate (FDR) method of Benjamini and Hochberg.

3. Results

3.1. Clinical information

Eight patients with SeLECTS were enrolled, 4 female and 4 male patients. Follow-up visits were scheduled at 3, 6, and 12 months after rTMS. The follow-up schedule is shown in Supplementary Figure S1. The mean age at the onset of epilepsy was 4.5 years (range 3–7), and the mean age at the first visit was 5.9 years (range 4–7). Two children (patients 2 and 4) had a previous history of febrile convulsions. The mean SWI before rTMS was 86.58% (range 74.33–97.67%). MRI was normal in all of them. The mean IQ was 76.5 (range 67–84). Detailed information is listed in Table 1 and Supplementary Tables S1, S2.

3.2. Treatment effects after rTMS

3.2.1. Seizure frequency reduced by rTMS

Five of the eight patients (62.5%) were seizure-free within 3 months after stimulation, and the other three had <50% reduction in seizure frequency. Within 6 months after rTMS, four patients had a reduction in seizure frequency of more than 50%, two patients had a reduction of about 30%, one patient returned to baseline and one patient had an increase in seizure frequency. Within 12 months after rTMS, three patients had achieved complete seizure-free status, three had seizure reduction by more than 50%, and two had a decrease by approximately 30% (Figure 1).

3.2.2. SWI before and after rTMS

The SWI at 3 months was reduced significantly by rTMS ($P = 0.0157$) (Figure 2A). The SWI at 6 months after rTMS was remarkedly lower than that before rTMS ($P = 0.0060$) (Figure 2B). There was no significant difference in SWI at 12 months after rTMS and before rTMS (Figure 2C).

3.3. Evolution of excitability after rTMS

3.3.1. Aperiodic offset before and after rTMS

We evaluated whether rTMS could alter the PSD offset. The offset of all scalp electrodes before rTMS was compared with that at 3 months after rTMS. A significant decrease was observed after stimulation ($P < 0.0001$) (Figure 3A). We further analyzed whether differences existed in different brain regions. It was found that the most significant changes were in brain areas around the stimulation sites (Figure 3B).

3.3.2. Aperiodic slope before and after rTMS

We assessed whether rTMS could change the E-I imbalance. The PSD slope of all scalp electrodes before rTMS and 3 months after rTMS was compared. It was found that there was a significant increase in PSD slope after stimulation ($P < 0.0001$) (Figure 4A). To analyze the differences in different brain regions, we observed that the most prominent alteration was in the scalp electrodes at the stimulation site (Figure 4B).

4. Discussion

The present study aimed to evaluate whether rTMS could clinically benefit SeLECTS patients and modify E-I imbalance. To

TABLE 1 Patients' clinical information.

Pt/No.	Gender	Epilepsy onset	Age at rTMS	Previous history	Frequency (Seizures per month)	SWI before rTMS (%)	MRI	ASMs
1	Female	5	7	Normal	2	97.67	Normal	ZNS, CZP, steroids
2	Female	5	7	Febrile convulsion	0.5	75.33	Normal	VPA, LEV, CZP, steroids
3	Male	5	5	Normal	30	90	Normal	VPA, TPM
4	Female	4	7	Febrile convulsion	30	74.33	Normal	VPA, LEV, steroids
5	Male	4	5	Normal	2	91.33	Normal	LCM, TPM, OXC
6	Male	3	5	Normal	3	94.67	Normal	VPA, LEV, CLB, steroids
7	Male	3	4	Normal	4	82	Normal	VPA, LEV, CZP
8	Female	7	7	Normal	2	87.33	Normal	VPA, LEV

ASMs, anti-seizure medications; ZNS, zonisamide; CZP, clonazepam; VPA, valproate; LEV, levetiracetam; TPM, topiramate; LCM, lacosamide; OXC, oxcarbazepine; CLB, clobazam.

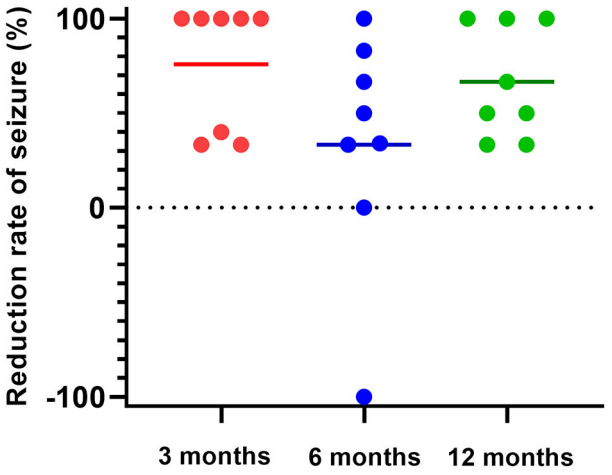

FIGURE 1
Seizure frequency reduced by rTMS. Five of the eight patients (62.5%) were seizure-free within 3 months after stimulation, and the other three had less than a 50% reduction in seizure frequency (red). Within 6 months after rTMS, seizure frequency was reduced by more than 50% in four patients, and approximately 30% in two patients, returned to the baseline level in one patient, and increased in one patient (blue). Within 12 months after rTMS, three patients had achieved complete seizure-free, three had seizure reduction by more than 50%, and two decreased by approximately 30% (green).

achieve this goal, our research was divided into two parts. In the first part, we assessed the clinical efficacy of TMS. Seizure-reduction rate and SWI were compared before and after rTMS. The results found that rTMS reduced seizure frequency for at least 3 months. The SWI was decreased by rTMS at 3 and 6 months. In the second part, we applied a special parametric approach to analyze the aperiodic offset and slope. We observed a significant reduction in aperiodic offset after rTMS, reflecting a decline in the spiking rate of cortical neurons. Among all channels, the most dramatic changes occurred around the rTMS stimulation site. The aperiodic slope after rTMS was increased, suggesting that the E-I imbalance was altered by stimulation. Similarly, the most obvious change was around the rTMS site.

4.1. Excitation–inhibition imbalance in SeLECTS

SeLECTS is characterized cardinally by sensory-motor seizures, oro-pharyngo-laryngeal symptoms, speech arrest, and hypersalivation, which are associated with abnormal discharges in the Rolandic areas (13, 14). Children with SeLECTS have a less stable network of areas involved in sensorimotor function (15). The function of bilateral sensorimotor areas is disorganized, as evidenced by a significant delay in motor control and impaired language function (16). The diseased neuronal networks are less efficient and may cause language impairments (17). The deficits in the language domain may be a downstream effect of altered motor cortex function possibly due to diffusion of activity to areas involved in language processing and/or as a result of motor execution difficulties, such as tongue immobility (17–19).

The concept of epilepsy as a spectrum disorder is increasingly acknowledged and patients frequently exhibit comorbid cognitive and behavioral impairments (20). Patients with SeLECTS with ESES exhibit an onset of symptoms during a critical period of brain development, which is the most vulnerable time for cognitive function. In addition to seizures, this group of patients is often associated with reduced cognitive function and impaired executive function (21, 22). Of the numerous factors that influence executive dysfunction in patients with SeLECTS, the most significant correlations are observed with the age of onset, frequency of intermittent discharges, and alterations in brain networks (22). During early childhood, the brain exhibits high levels of neuroplasticity and relatively low functional specificity of neural networks. Seizures at this stage can significantly impact children's executive and memory functions (23). The effect on the child's attentional network varies with the frequency of intermittent discharges and is more pronounced if the onset occurs at a younger age of onset (24). Functional and structural brain connections may be altered in children with SeLECTS, resulting in cognitive

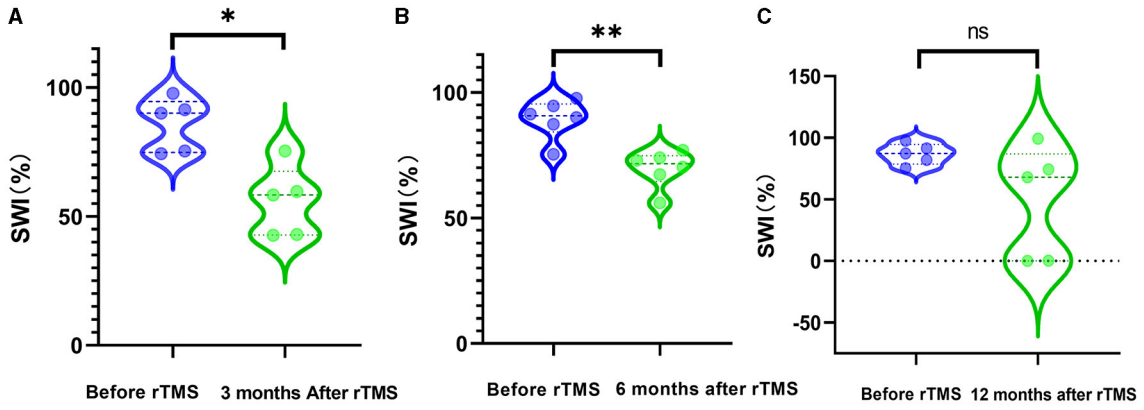

FIGURE 2
SWI before and after rTMS. **(A)** SWI before rTMS and 3 months after rTMS. **(B)** SWI before rTMS and 6 months after rTMS. **(C)** SWI before rTMS and 12 months after rTMS.

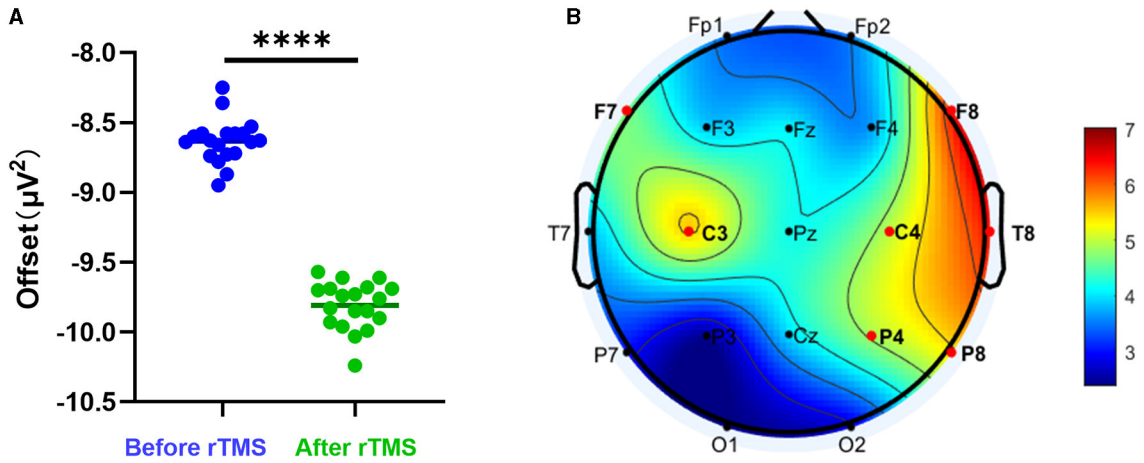

FIGURE 3
Aperiodic offset before and after rTMS. **(A)** PSD offset before rTMS and 3 months after rTMS. There was a significant reduction in PSD offset after stimulation ($P < 0.0001$). **(B)** T-value distributed in different brain regions.

dysfunction, particularly executive function abnormalities (25, 26). Relevant evidence derived from resting-state functional MRI also suggests that reduced functional connectivity in Rolandic areas may exert an impact on the wider brain network (27).

Numerous studies have shown that the balance between excitatory and inhibitory electrical activity of neurons in the brain is dynamically regulated under normal conditions. However, in patients with epilepsy, the balance is disturbed, resulting in a relative increase in excitatory neuronal activity, either directly or indirectly (28, 29). Studies based on support vector machine models of Granger causal density have revealed abnormalities in connectivity both between and within different networks in patients with SeLECTS (30). Frequent intermittent epileptic discharges can lead to irreversible reconfiguration of neural networks, resulting in an imbalance between excitation and inhibition (31). The excitation–inhibition imbalance in brain networks further leads to cognitive dysfunction and seizures (20, 32), making it a potential biological marker for SeLECTS (8).

4.2. RTMS improves E-I imbalance in SeLECTS

TMS exhibits diagnostic and therapeutic potential in the field of epilepsy. As an assessment tool, TMS can be combined with EMG to provide biological markers for indicators of cortical excitation and inhibition associated with epilepsy and antiepileptic drugs (33). Therapeutically, low-frequency rTMS (≤1 Hz) can effectively prolong postsynaptic inhibition and reduce brain excitability. During both interictal and ictal periods, TMS can be utilized to varying degrees to reduce the frequency or severity of seizures or even terminate them (3). However, few studies are using EEG signals to evaluate the improvement of the cortical excitation–inhibition ratio by TMS. The present study may serve as a supplementary and guiding reference for rTMS treatment in epilepsy.

Studies of intracranial local field potential have shown that broadband power offsets are positively correlated with the firing

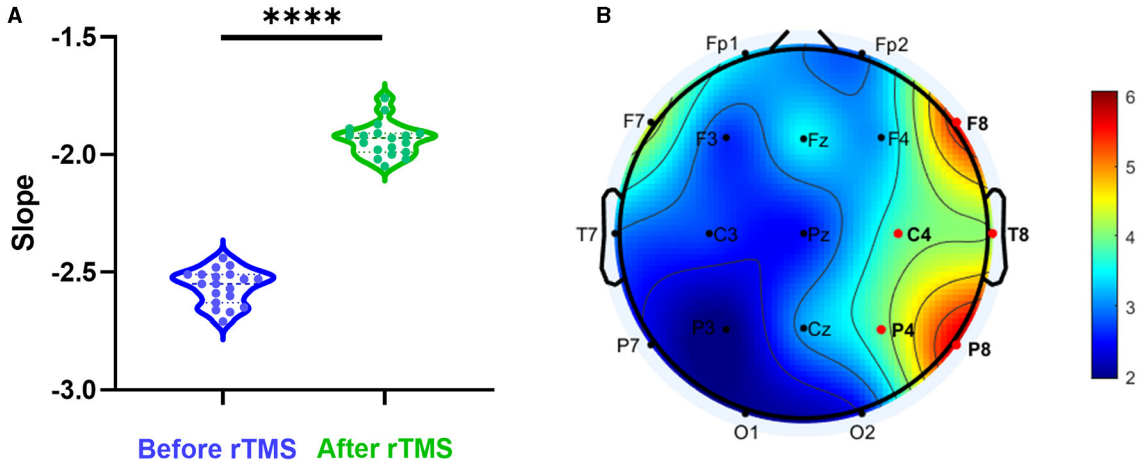

FIGURE 4
Aperiodic slope before and after rTMS. **(A)** PSD slope before rTMS and 3 months after rTMS. There was a significant reduction in PSD slope after stimulation ($P < 0.0001$). **(B)** T-value distributed in different brain regions.

rate of neuronal populations (34). Similar results have been observed in macaque studies correlating neuronal action potentials with instantaneous changes in broadband local field potentials (35). Other studies have shown that whole-brain aperiodic offset is inversely correlated with age, and it is speculated that this phenomenon may be due to a decrease in the firing rate of cortical neurons as the brain matures with age (36). In the present study, the PSD offset decreased after rTMS, reflecting the reduction in cortical neuronal firing and the suppression of action potentials in neuronal populations. Although this was observed on all electrodes, it tended to be more pronounced near the stimulated area. However, the explanatory relationship between the observed phenomenon and the mechanism of TMS remains speculative, and a more precise causal relationship requires further experimental confirmation.

The excitation–inhibition imbalance may lead to hyper-synchronization of the electrical activity of neurons in epileptic networks (29). The slope of the aperiodic PSD signal reflects the balance between excitation and inhibition (11). With an increase in age, the aperiodic slope tends to decrease. In studies of visual working memory tasks, older adults show a relatively flat slope, whereas younger adults show a steeper slope (37). Relevant evidence suggests that an increase in excitation–inhibition ratio may result in a flatter PSD slope, indicating a reduced synchronization of neuronal firing (38). A positive correlation was found between the excitation–inhibition ratio and the PSD slope, while a stronger correlation was found between the synaptic density of inhibitory neurons and the PSD slope. In the present study, the increase in PSD slope after rTMS treatment might be due to the increased application of stimulation effects to inhibitory neurons, resulting in improved function of the SeLECTS inhibitory loop and, thus, a reduction in the excitation–inhibition imbalance. However, this is conjecture, and further studies are needed to elucidate the cytological and molecular mechanisms involved.

5. Limitations

There are some limitations in the present study. The sample size was 8, and there was some individual variation that may have influenced the results. The number of EEG electrodes was 19, which may have led to a lack of accuracy in the spatial sampling of electrical brain activity. We did not assess the Wechsler Intelligence Scale for post-treatment assessment and thus cannot yet determine whether rTMS can improve cognitive performance. The most important and difficult point is that since the study is limited to the processing of EEG signals, the results are presented as phenomena and we are not yet able to explain the mechanism of action of rTMS. We have established a more standardized process to compensate for the above limitations to allow for more discoveries in the future.

6. Conclusion

Favorable clinical outcomes are observed in patients within the initial 3-month period following rTMS treatment. After treatment, the patient's SWI is significantly reduced, and the effect lasts for up to 6 months. Low-frequency rTMS induces a reduction in neuronal firing, particularly at the site of stimulation. The E-I imbalance can be improved in SeLECTS after rTMS intervention.

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 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.

Author contributions

TL and MW contributed to the conception and design of the study. YY and YH contributed to the writing and preparation of the figures. YH and YZ contributed to analyzing the data. JW contributed to reviewing the EEG data. DC contributed to interpreting the results. All authors contributed to the acquisition and analysis of data, reviewed, and revised the manuscript for intellectual content.

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Conflict of interest

The 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1164082/full#supplementary-material

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Modulation of the thalamus by microburst vagus nerve stimulation: a feasibility study protocol

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Vagus nerve stimulation (VNS) was the first device-based therapy for epilepsy, having launched in 1994 in Europe and 1997 in the United States. Since then, significant advances in the understanding of the mechanism of action of VNS and the central neurocircuitry that VNS modulates have impacted how the therapy is practically implemented. However, there has been little change to VNS stimulation parameters since the late 1990s. Short bursts of high frequency stimulation have been of increasing interest to other neuromodulation targets e.g., the spine, and these high frequency bursts elicit unique effects in the central nervous system, especially when applied to the vagus nerve. In the current study, we describe a protocol design that is aimed to assess the impact of high frequency bursts of stimulation, called "Microburst VNS", in subjects with refractory focal and generalized epilepsies treated with this novel stimulation pattern in addition to standard anti-seizure medications. This protocol also employed an investigational, fMRI-guided titration protocol that permits personalized dosing of Microburst VNS among the treated population depending on the thalamic blood-oxygen-level-dependent signal. The study was registered on clinicaltrials.gov (NCT03446664). The first subject was enrolled in 2018 and the final results are expected in 2023.

KEYWORDS

vagus nerve stimulation, drug-resistant epilepsy, focal epilepsy, generalized epilepsy, feasibility study

1. Introduction

Device-based therapies for epilepsy aim to leverage intrinsic circuits to either interrupt or suppress epileptic activity. Two invasive, cranial procedures exist that are currently approved as adjunctive therapies to lessen the frequency of seizures in patients in whom multiple trials of anti-seizure medications (ASMs) have failed: responsive neurostimulation (RNS) and deep-brain stimulation (DBS). While DBS is an open loop device approved for the treatment of focal onset epilepsy with anterior nucleus of the thalamus as the therapy target (1), some researchers have implanted the stimulation electrodes in other thalamic nuclei e.g., centro-median nucleus (2). RNS, a closed-loop system, is currently FDA-approved for the treatment of focal onset epilepsy (3). However, similar to DBS, this system has also been implanted in patients with generalized epilepsies, including idiopathic generalized epilepsies (4) and Lennox-Gastaut Syndrome (LGS) (5), with specific trials for both indications registered with clinicaltrials.gov. Both approaches directly target brain structures with electrical energy.

These approaches have been demonstrated to reduce seizure frequency by over 50% in more than 40% of patients in the first year of therapy with additional improvements observed over time. However, they carry the risk of rare but potentially severe adverse events due to the invasiveness of the implantation procedure (1, 3, 6, 7). VNS is considered a less invasive, peripheral approach to change epileptic networks, and it has been previously demonstrated to modulate epilepsy-associated brain structures (8).

The first VNS Therapy™ System received approval for the adjunctive treatment of medically refractory epilepsy in 1994 in Europe and in 1997 in the United States and consists of an implantable pulse generator (IPG) that supplies intermittent electrical stimulation to the left vagus nerve. The specific mechanism of action by which the VNS Therapy reduces seizure frequency is not precisely understood, because the physiological effects of VNS are documented as multifaceted (8). Modulation of vagus nerve firing rates has been shown to subsequently modulate central nervous system activity with this central modulation being required for the anti-seizure effect of VNS in epilepsy (9, 10).

In the early 2000s, an experimental VNS stimulation paradigm was developed that consists of high-frequency bursts of stimulation, herein called "Microburst VNS" (μVNS) (Figure 1). While the mechanism of traditional VNS was believed to be mediated by the nuclei closer to the brainstem, such as the nucleus of the tractus solitarius (NTS) and the nucleus of the locus coeruleus (LC), existing evidence suggests that μVNS can be employed to modulate other brain areas, including the thalamus (11, 12).

High frequency burst VNS, eventually labeled "Microburst" VNS, was first examined in primates in the early 2000s (11, 12). This stimulation protocol is similar to the one implemented in transcranial magnetic stimulation called intermittent theta burst stimulation (iTBS) that is known to affect long-term potentiation and induce cortical plasticity (13, 14). In the original experiments, standard VNS and high frequency bursts of VNS were used to evoke responses in the parafascicular nucleus of the thalamus, measured by simultaneous electrophysiological recordings. Only paired pulses of 1.5 mA at 400 μs (∼5x the threshold charge density), delivered at 300 Hz, elicited a vagal evoked potential in the parafascicular nucleus that had not been previously detected in the mapping studies of vagal evoked potentials (11). Ito and Craig advocated that this effect could be due to paired pulse excitation or inhibition mechanics in the ascending vagus nerve circuits. Following this discovery, the experiment was replicated with multiunit discharges recorded in the parafascicular nucleus and the basal ventromedial nucleus (12). A series of studies in beagles and rats followed the initial primate work and investigated the impact of μVNS on imaging and biochemical markers in experimental epilepsy models (15–17). In beagles, standard VNS parameters were not associated with cerebral blood flow alterations, while μVNS caused significant hypoperfusion of the left frontal lobe and the right parietal lobe. Moreover, both standard VNS and μVNS were associated with a significant increase of norepinephrine release, suggesting evoked activation of the coeruleo-fugal pathways (15, 16). In rodents, both standard and μVNS increased the electrographic seizure threshold of pentylenetetrazole-kindled seizures, but decreased stimulus intensity may have contributed to microbursts not reaching a level of statistical significance (17). Most recently, and concurrently with the clinical feasibility study described herein, μVNS has returned to primate study in a naturally occurring model of genetic generalized epilepsy in baboons. In these animals, μVNS reduced the frequency of generalized tonic-clonic seizures except when the baboons received output currents of 0.25 mA for extended periods, suggesting a dose-response relationship (18). Baboons tolerated μVNS well, and this approach was not associated with cardiac or behavioral changes. However, transient regular muscle contractions could be detected during VNS on-times consistent with the 0.5-s interburst intervals that were not noted during wakefulness (18).

Vagus nerve stimulation is an MRI-conditional product, meaning that the collection of MRI images in patients with VNS therapy is safe provided certain use limitations are followed. One such restriction is the deactivation of the VNS device prior to introducing an implanted patient into an area of a strong magnetic field. The primary rationale for this particular restriction is the activation of a magnetically-sensitive component in the pulse generator, which could respond to the MRI's magnetic fields in a variety of ways.

However, investigators have demonstrated that it is possible to record the Blood Oxygen Level Dependent (BOLD) response of different brain regions to VNS, with the device being active during scanning. After the first demonstration of an MRI-compatible positioning of the device that avoids deactivation while the patient lies supine within the scanner (19) (only suitable for devices without "Magnet Mode"), an investigative team examined VNS-evoked BOLD responses in subjects receiving investigational VNS as therapy for treatment-resistant depression. In initial feasibility work, the team demonstrated that the phase lag from the onset of stimulation to the onset of the hemodynamic response was variable for each affected brain region but tended to be ∼ 4–7 s with a similarly variable washout time of 15–25 s (20). The VNS-evoked BOLD response was dose dependent, with lower VNS charge densities resulting in significantly weaker BOLD responses (21, 22). BOLD response was diffuse and not always consistent between patients, but the most common areas of BOLD response were the thalamus, amygdala and insular cortex (20–23).

Following the preclinical history of microburst VNS investigations, and with some understanding of its mechanism of action and how that mechanism can be objectively studied, we designed a prospective, open-label, multicenter phase I clinical trial to investigate the potential risk-benefit profile of μVNS in humans. The study, registered as NCT03446664, examined over 12 months two cohorts of treatment-resistant epilepsy patients with focal-onset (including those with progression to bilateral tonic-clonic seizures) or primary (idiopathic/genetic) generalized-onset tonic-clonic seizures (PGTC). In addition to traditional outcome measures of epilepsy studies, an investigational fMRI protocol was executed in all subjects to offer personalized titration and measure the impact of μVNS on the thalamus.

2. Methods and analysis

This prospective, non-randomized, interventional, open-label phase I clinical trial was designed to collect data on up

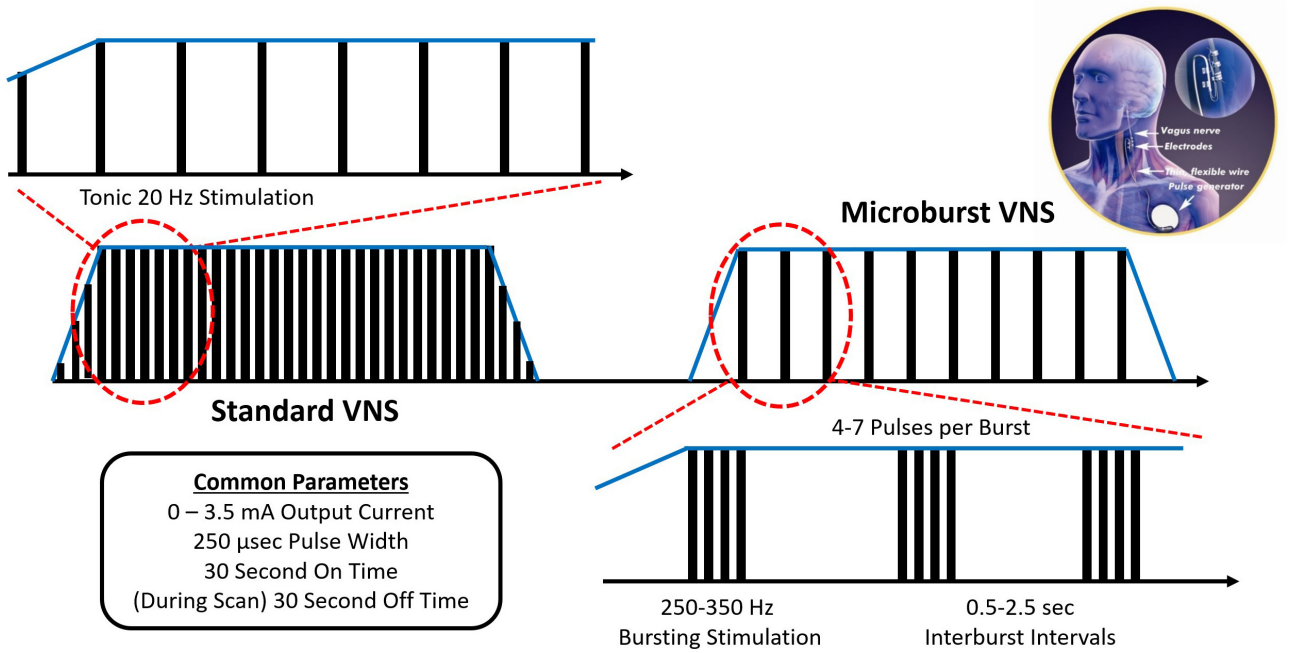

FIGURE 1
Microburst VNS consists of short bursts of pulses separated by brief off-times called interburst intervals (IBIs). The µVNS waveform incorporates 7 stimulation parameters with a range of available settings (Table 3). On compatible pulse generators, µVNS can be selected as a stimulation setting for the normal mode, the magnet mode, or the autostim mode, which can be set to different levels to deliver VNS (traditional or µVNS) at a regular cadence or based on a specific triggering event. In its current embodiment, µVNS can be delivered from standard VNS Therapy leads and implantable pulse generators with form factors similar to existing VNS devices.

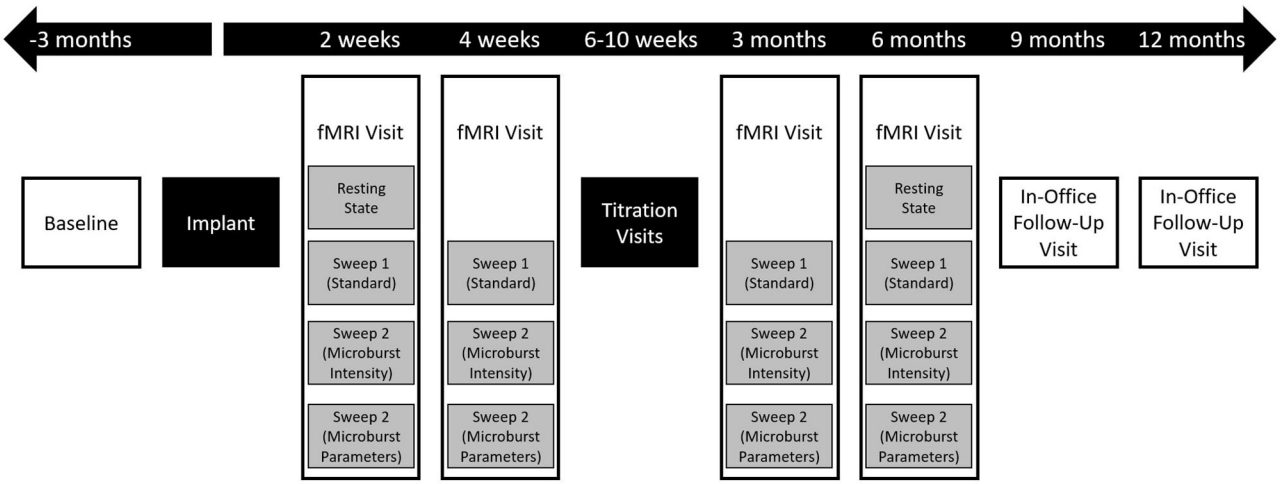

FIGURE 2
Flow chart of overall study events. After screening and consent, enrolled patients underwent a 3-month prospective baseline period followed by implantation. All subjects were then followed for up to 12 months, with the first 6 months including an intensive, imaging-guided titration program and the last 6 months including telephone and in-office visits. Clinical outcome measures were collected at all boxes shown in white, though reports of adverse events could be collected at any time, including outside of study visits. During fMRI visits (Figure 3), study outcome measures were collected sporadically during rest periods between scans to minimize the impact of the duration of the visit on the subject's schedule.

to 40 subjects (20 PGTC and 20 focal onset) implanted with an investigational µVNS delivering therapy over 12 months of follow-up (Figure 2). The study was registered on clinicaltrials.gov (NCT03446664) and approved by the Institutional Review Boards and Ethics Committees of all study sites. All research procedures were conducted in accordance with the ethical principles of informed consent and the Declaration of Helsinki. All participants received care in academic hospitals from epileptologists trained in the use of the VNS Therapy System (Table 1).

TABLE 1 Microburst study sites, site investigators, and date of site authorized to start recruitment.

Site	Site investigator	Date of site initiation
University of Colorado—Denver	Cornelia Drees Mesha Gay-Brown Danielle McDermott Lesley Kaye	05 NOV 2018
Rush University Medical Center	Rebecca O'Dwyer	27 FEB 2018
Northwestern University	Michael Macken	07 JUN 2018
Duke University	Muhammad Zafar	25 APR 2019
Mayo Clinic Florida	William Tatum	02 JUL 2019
University of Alabama at Birmingham	Zeenat Jaisani	16 JAN 2019
University of Ghent Hospital	Kristl Vonck	04 JUN 2019
Weill Cornell Medical College	Pegah Afra	17 DEC 2018
University of Utah Health Science	Blake Newman	23 AUG 2018

TABLE 2 Additional inclusion and exclusion criteria for the Microburst Feasibility Study.

Inclusion criteria	Exclusion criteria
1) Must be on adjunctive anti-seizure medications. 2) Willing and capable to undergo multiple evaluations with fMRI, EEG, and ECG. 3) 12 years of age or older. 4) Male or non-pregnant female adequately protected from conception. Females of childbearing potential must use an acceptable method of birth control. 5) Provide written informed consent-assent/Health Insurance Portability and Accountability Act (HIPAA) authorization and self-reported measures with minimal assistance as determined by the investigator.	1) Currently using, or are expected to use, short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy. 2) A VNS Therapy System implant would (in the investigator's judgement) pose an unacceptable surgical or medical risk for the subject. 3) A planned procedure that is contraindicated for VNS Therapy. 4) A history of implantation of the VNS Therapy system. 5) Currently receiving treatment from an active implantable medical device. 6) Presence of contraindications to MRI per the MRI subject screening record. 7) Known clinically meaningful cardiovascular arrhythmias currently being managed by devices or treatments that interfere with normal intrinsic heart rate responses (e.g., pacemaker dependency, implantable defibrillator, beta adrenergic blocker medications). 8) History of chronotropic incompetence (commonly seen in subjects with sustained bradycardia). 9) Any cognitive or psychiatric deficit found in the investigator's judgement that would interfere with the subject's ability to accurately complete study assessments. 10) History of status epilepticus within 1 year of study enrollment. 11) Dependent on alcohol or narcotic drugs as defined by DSM IV-TR within the past 2 years, based on history. Tests for drug or alcohol use will not be administered. 12) Currently being treated with prescribed medication that contains cannabis or cannabis-related substances, including recreational use. 13) Any history of psychogenic non-epileptic seizures. 14) Currently participating in another clinical study without the written approval of LivaNova.

2.1. Patient selection

Patients were recruited into a cohort based on their seizure history, baseline characteristics, and satisfaction of the inclusion criteria without meeting any of the exclusion criteria. No specific methods for patient recruitment were employed, and each site investigator was responsible for identifying appropriate patients in their practice to screen for the study. Patients recruited in the focal-onset seizure cohort had to have a clinical diagnosis of medically refractory epilepsy with focal-onset seizures, which could include seizures that secondarily progressed to bilateral tonic-clonic seizures, and had to have an average of at least three countable seizures per month during the 3-month baseline period without any seizure-free interval >30 days during the baseline period. Patients recruited into the PGTC seizure cohort had to have a clinical diagnosis of medically refractory idiopathic/genetic generalized epilepsy with generalized-onset tonic-clonic seizures, though they may also have other seizure types, and must have at least three countable seizures during the 3-month baseline period. Clinical diagnosis of PGTC seizures was required to be confirmed by historical EEG within the past 3 years by the investigator. If no historical EEG was available, a prospective EEG could be collected to verify the diagnosis by independent review.

Other inclusion criteria and exclusion criteria are described in Table 2.

2.2. Intervention

The VNS Therapy System is approved for use in epilepsy as an adjunctive treatment in reducing seizure frequency for adults and children 4 years of age or older (in Europe, all ages) with drug-resistant focal epilepsy (in Europe, also generalized epilepsy).

TABLE 3 VNS settings, microburst and standard VNS on the M3000C investigational VNS programming system.

	Output current (mA)	Pulse width (μsec)	Signal on time (sec)	Signal off time (min)	Signal frequency (Hz)	Interburst interval (sec)	Number of pulses
Standard VNS	0–2 in 0.125 mA increments; 2–3.5 in 0.25 mA increments	100, 130, 150, 200, 250, 300, 350, 400, 450, 500	7, 14, 21, 30, 60	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3, 5–55 (by 5), 60–180 (by 30)	1, 2, 5–30 in 5 Hz increments	N/A	N/A
Microburst VNS	0–2 in 0.125 mA increments; 2–3.5 in 0.25 mA increments	100, 130, 150, 200, 250, 300, 350, 400, 450, 500	7, 14, 21, 30, 60	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3, 5–55 (by 5), 60–180 (by 30)	100–350 in 50 Hz increments	0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6	2, 3, 4, 5, 6, 7

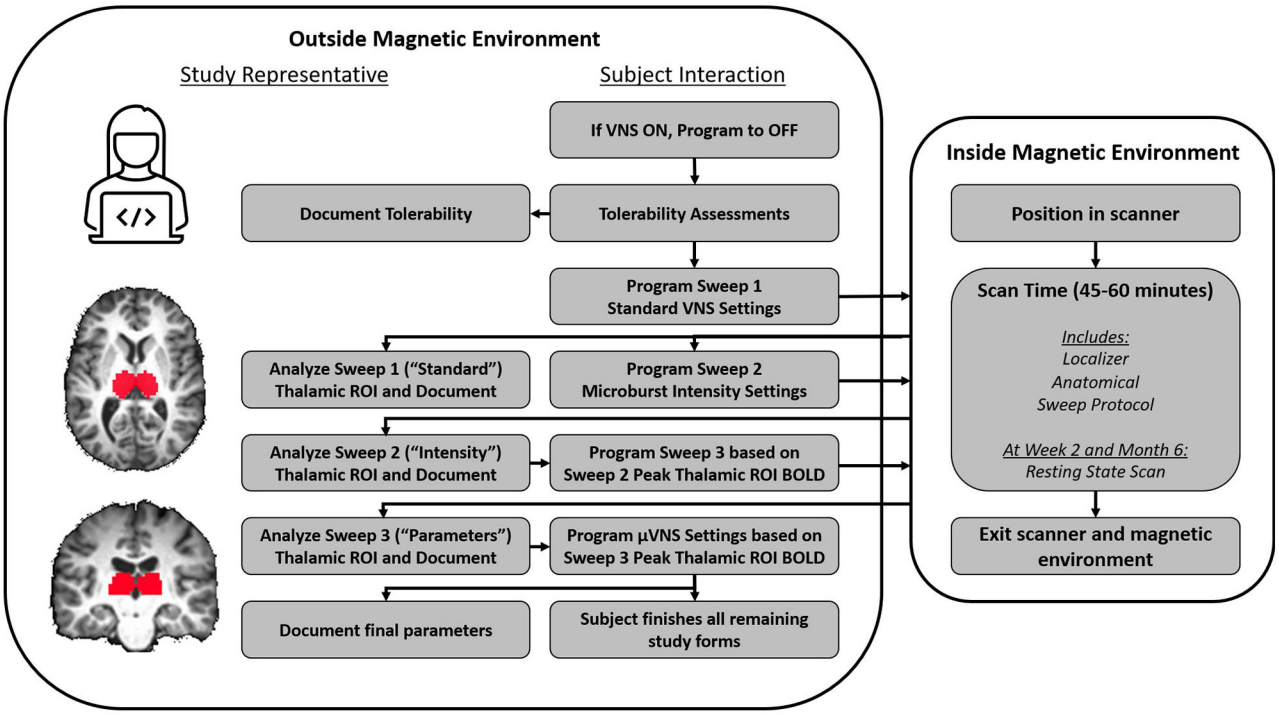

FIGURE 3
Flow chart of activities during an fMRI titration visit. The device was initially deactivated, and then, a tolerability protocol was followed. The purpose of the tolerability protocol was to identify VNS and μVNS intensities that evoked intolerable side effects so that side effects that induced involuntary movement (e.g., cough) could be avoided in the scanner. Based on the tolerability assessments, a maximum intensity was determined for VNS (Sweep 1) and μVNS (Sweeps 2 and 3). A study representative then programmed the Sweep 1 parameters into the device's "Parameter Sweep Mode", which is an investigational function that allows the pulse generator to sequentially modify programming settings at a future time (e.g., in the scanner). The subject was then positioned into the scanner, and multiple functional and anatomical scans were collected. When Sweep 1 concluded, the subject was removed from the scanner and study representatives programmed Sweep 2 based on the tolerability assessment and re-admitted the subject to the scanning environment. While Sweep 2 was underway, study representatives analyzed the Sweep 1 fMRI data to identify the settings associated with the peak BOLD response in the thalamic ROI. When Sweep 2 concluded and the subject was removed from the scanner, study representatives analyzed the Sweep 2 fMRI results similar to the procedure for the Sweep 1 results; however, when programming the subject for Sweep 3, the optimal μVNS intensity identified in the Sweep 2 results was used. When Sweep 3 concluded, a final analysis was completed by study representatives to identify the μVNS parameters that the subject would leave the clinic with.

The principal components of the system are an implantable VNS Therapy generator, a lead, and an external programming system used to change stimulation settings. The pulse generator is housed in a hermetically sealed titanium case and is powered by a single battery. Electrical signals are transmitted to the left cervical vagus nerve through the lead. The system is manufactured by LivaNova USA, Inc.

Subjects enrolled in this study received the investigational M1000C μB SenTiva™ VNS Therapy System along with a commercial, FDA approved VNS Therapy System lead, either the M302, M303, or M304. The M1000C unit was programmed to provide investigational "microburst" stimulation patterns (Figure 1). Microburst stimulation consists of short bursts of pulses separated by brief off-times called "interburst intervals" (IBI) (13). The microburst waveform can be fully described by 6 stimulation parameters with a range of available settings: Output Current, Pulse Width, Signal Frequency, Duty Cycle, Interburst Interval, and Number of Pulses (Table 3). The M1000C investigational VNS

TABLE 4A Programming table for parameter Sweep 2, using an exemplar tolerability value of 1 mA.

Step	Output	PW (μsec)	SF (Hz)	IBI (s)	Pulses	ON (s)	OFF (min)
1	0 mA	VNS off. Step 1 used to position subject in scanner					.
2	0.375 mA	250	300	2.5	7	30	0.5
3	0.500 mA	250	300	2.5	7	30	0.5
4	0.625 mA	250	300	2.5	7	30	0.5
5	0.75 mA	250	300	2.5	7	30	0.5
6	0.875 mA	250	300	2.5	7	30	0.5
7	1.00 mA	250	300	2.5	7	30	0.5

TABLE 4B Programming table for parameter Sweep 3.

Step	Output	PW (μsec)	SF (Hz)	IBI (sec)	Pulses	ON (sec)	OFF (min)
1	0 mA	VNS off. Step 1 used to position subject in scanner.					
2	Optimal intensity setting selected from Sweep 2 analysis.	250	250	1.5	4	30	0.5
3		250	300	1.5	4	30	0.5
4		250	300	0.5	4	30	0.5
5		250	300	0.5	7	30	0.5
6		250	300	2.5	7	30	0.5
7		250	350	2.5	7	30	0.5

Therapy system provided all the basic functionality of previous VNS Therapy models as well as the new microburst feature under investigation.

In addition to the μVNS settings, the M1000C VNS Therapy System includes a "parameter sweep" feature that is designed to allow for the stimulation of the vagus nerve using up to 7 sets of existing parameter values (e.g., the choice of a value for each VNS parameter creates one set) over a short period of time. The parameter sets were delivered sequentially at pre-defined intervals (e.g., 5 min of parameter set 1, 5 min of parameter set 2, and so on). Simultaneously, the parameter sweep feature disengaged the functionality of the reed switch, which is an electrical component that responds to the presence of a strong magnetic field by opening or closing a circuit. Disengaging the reed switch allowed the M1000C VNS Therapy system to deliver stimulation inside the bore of a MRI scanner for investigational purposes.

All patients received an active VNS implant. There was no group with inactive or intentionally low output μVNS.

2.3. Titration strategy

A critically important element to the design of this study was the fMRI-guided titration strategy (Figure 3). Post-implant, at weeks 2, 4, 12, and 24, patients were required to return to their study site for a follow-up visit that included a personalized, BOLD-driven titration protocol. Subjects proceeded directly to an MRI scanning facility at the hospital for these visits, where they met with the site investigator, a sponsor's clinical engineer, and other MR facility personnel. First, tolerability of both standard VNS and μVNS was assessed to determine the maximum tolerability output current and pulse width for that study visit. Following the maximum tolerability determination, the subject's device was programmed using the parameter sweep function to deliver up to seven unique parameter sets over the course of the following 45–60 min (see Tables 4A, B for examples). The subject was then placed into the MRI scanner while the parameter sweep function was active. Each patient underwent a series of three fMRI scans with parameter sweeps per visit, totaling 45–60 min per scan or up to 180 min of scanning per visit day.

The principal objective of each 45–60 min scan was to examine the BOLD signal within a region of interest (ROI) centered over the left and right thalamus. After completion of the structural scanning protocol (structural voxel size not larger than 1 mm^3 isotropic), a 30-min fMRI sequence was initiated at the same time as the first set of pre-programmed parameters from the parameter sweep (functional voxel size not larger than 4 mm^3 isotropic). The parameter sweep programmed VNS settings in a 30 s ON/30 s OFF manner and switched to a new group of VNS settings every 5 min. This paradigm permitted a later off-line analysis of BOLD signal in the ON vs. OFF state for each pre-programmed group of settings. Maximal BOLD signal increases from each 45–60 min MR session within the thalamic ROI were used to identify settings for the next parameter sweep, refining the VNS programming with each scanning session. Settings for the next scan were determined by identifying settings in the preceding scan that resulted in the greatest thalamic ROI BOLD intensity and by the maximum *t*-value calculated from at least 2 contiguous voxels.

The first scan of a visit day assessed standard VNS settings, and the output current was the only parameter that varied during the fMRI session. Subjects started with a resting scan

with no stimulation (VNS inactive) and then proceeded from a low-intensity stimulation to a higher intensity stimulation, as determined by the tolerability assessment from that visit day. After the scan, the subject was given a short break while the sponsor's engineer analyzed the fMRI data using a customized processing pipeline utilizing the Analysis of Functional NeuroImages (AFNI) software (24) to determine the output current associated with peak thalamic ROI BOLD signal increase. The subject was then programmed for a μVNS sweep that also assessed output current, starting from low intensities and moving to higher intensities limited by the tolerability. Patient tolerance to stimulation was assessed separately for both standard VNS and μVNS, so the output current settings were not always the same between the first and second parameter sweep protocols. After the second scan, the subject again exited the scanner and the sponsor's engineer analyzed the data. For the third scan, the patient's parameter sweep was programmed to the output current intensity of the thalamic ROI BOLD peak from the second scan. At that intensity, the other μVNS settings of IBI, number of pulses, and signal frequency were adjusted. After this scan was completed, the sponsor's engineer again analyzed the fMRI data using the custom fMRI processing pipeline. The pulse generator was programmed to the intensity (output current and pulse width) resulting from the second scan and the μVNS settings that drove peak thalamic ROI activation in the third scan. The patient left the clinic with these settings.

After the 4-week MRI visit, patients were asked to visit the clinic once every 2 weeks for titration of their output current, up to the 12-week MRI visit. While the relationship between standard VNS titration and μVNS titration is not fully understood, interim titration visits to adjust output current were performed so that patients would be more likely to achieve a dose range associated with effectiveness for standard VNS, likely between 1.5 mA and 2.25 mA at 250–500 μs (25). Output current increases during these titration visits were not aided by fMRI.

2.4. Outcome measures and data collection

The primary effectiveness endpoint was the percent change in seizure frequency per month (over a 3-month period) compared to the seizure frequency per month (over the 3-month period) calculated at baseline, at 6 months post-implant, and 12 months post-implant. The primary safety endpoint was the occurrence of stimulation-related adverse events in the first 6 months after implant and in months 6 to 12 thereafter.

The study also assessed other secondary outcome measures related to seizure severity (Seizure Severity Questionnaire; SSQ), quality of life (Quality of Life in Epilepsy scales; QOLIE-31P, QOLIE-AD-48), medication load (prescribed daily dose/defined daily dose), and suicidality (Columbia Suicide Severity Rating Scale).

During the MRI scanning days, at the 2-week and 6-month visits, resting state fMRI was also collected from each patient as an exploratory outcome. This was collected at the beginning of the scanning day, shortly after the tolerability assessment but before any other MRI procedures were performed.

Study data were collected by site investigators or their designees and were entered into a custom-built, 21 CFR Part 11 compliant electronic data capture system managed by the study sponsor for subsequent analysis.

2.5. Statistical analysis methods

This clinical study was exploratory in nature. All the inferential statistics should be considered hypothesis-generating in nature and not confirmatory. Cohorts were not powered for the purpose of confirmatory statistical testing, and the population characteristics of each cohort are not expected to be suitable for a clinically meaningful comparison. Each cohort will be analyzed separately as soon as each cohort completes the relevant recruitment and subjects reach the expected follow-up threshold. Descriptive statistics (mean, standard deviation, median, mode, range, and confidence intervals, as appropriate) will be used to describe the population outcome of within-subject changes between baseline and each follow-up visit.

We plan for an intermediate analysis at the time of all subjects completing their 6-month follow-up visit. The final analysis was conducted when all subjects completed the study at the 12-month visit.

2.6. Withdrawal of consent and study exit

Subjects were permitted to withdraw their consent for the study at any time. Withdrawal of consent could be made through not signing a study-related form, through checking a box on that form indicating the subject's intention to withdraw their consent, or by emailing a representative of the sponsor directly if the subject was not actively completing study related forms.

Study investigators were also empowered to withdraw subjects from the study if they perceived a developing or active safety concern.

3. Discussion and design limitations

The study was designed to demonstrate the safety and potential efficacy of the investigational μVNS stimulation paradigm. In addition to this primary objective, an investigational fMRI protocol was employed to guide patients to an appropriate personalized dose of the therapy. The presence of two investigational variables in this study may increase the difficulty of assigning treatment effect sizes.

There were also risks to the study outcome driven by choices made in the design of the fMRI protocol. At the time of study design, the best choice of target ROI for standard vs. microburst was not clear; hence, a decision was made to use a thalamic ROI as the target measure of VNS response with adjustments based on the peak of BOLD responses. The selection was grounded in the data from the available literature including previous VNS neuroimaging studies (20–22, 26). It was also unclear at that time whether the peak is the best measure and whether, e.g., the volume of activated tissue in the thalamus or the volume of the overall activated brain should be used instead. The VNS cycle time in the scanner also created risks, as there is little available evidence in humans to confirm the validity of the 30 s off-time for washing out VNS effects in

the central nervous system. Further, it was not feasible to analyze all available options for parameters; thus, it was possible to have missed an optimal parameter. Finally, randomization of treatment settings (intensity, or other μVNS parameters) was not conducted within each scan in order to reduce the risk of side effects that would impact the imaging procedure (e.g., a participant coughing during fMRI acquisition). Regarding the risk of bias driven by patient selection, there were no indications from the literature on whether the VNS treatment targets should be different between focal epilepsies and idiopathic/genetic generalized epilepsies.

Due to the complicating factor of the investigational fMRI titration paradigm, the investigators proposed a publication plan that specifically addresses subject outcomes during the titration phase separately from the longer-term outcomes. A pair of study outcomes manuscripts will be developed to address these matters in the future. In addition, one or more manuscripts focused on the potential mechanism of μVNS and its impact of resting state functional networks will be developed using the fMRI data.

Ethics statement

The studies involving human participants were reviewed and approved by Northwestern University Biomedical IRB, Rush University Medical Center IRB, University of Utah IRB, Weill Cornell Medical College IRB, Western Institutional Review Board, Mayo Clinic Institutional Review Board, and Ethisch Comite UZ Gent. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Microburst Study Group

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Author contributions

RV, JS, KV, and GG equally contributed to the initial draft of the manuscript. JA provided additional feedback during the draft revision process. The remainder of the Microburst Study Group offered critical review and feedback. All authors contributed to the article and approved the submitted version.

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Conflict of interest

RV and GG are employees of LivaNova PLC or a subsidiary, and own stock and/or stock options with the sponsor of this study. KV was an investigator on the Microburst Feasibility Study. JS and JA developed the imaging protocol for this study under a consulting agreement with LivaNova USA, Inc. KV, JA, and JS have active consulting agreements with LivaNova PLC or its subsidiary businesses, related to advisory services, speaking services, and/or research activities. The Microburst Study Group consists of site investigators from each clinical study site. These investigators received some funding from LivaNova USA, Inc. to execute the Microburst Feasibility Study. No author was compensated for time spent writing this manuscript, and the content reflects the views of the authors and not LivaNova PLC or a subsidiary.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1169161/full#supplementary-material

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A multicenter retrospective study of patients treated in the thalamus with responsive neurostimulation

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Introduction: For drug resistant epilepsy patients who are either not candidates for resective surgery or have already failed resective surgery, neuromodulation is a promising option. Neuromodulatory approaches include responsive neurostimulation (RNS), deep brain stimulation (DBS), and vagal nerve stimulation (VNS). Thalamocortical circuits are involved in both generalized and focal onset seizures. This paper explores the use of RNS in the centromedian nucleus of the thalamus (CMN) and in the anterior thalamic nucleus (ANT) of patients with drug resistant epilepsy.

Methods: This is a retrospective multicenter study from seven different epilepsy centers in the United States. Patients that had unilateral or bilateral thalamic RNS leads implanted in the CMN or ANT for at least 6months were included. Primary objectives were to describe the implant location and determine changes in the frequency of disabling seizures at 6months, 1year, 2years, and >2years. Secondary objectives included documenting seizure free periods, anti-seizure medication regimen changes, stimulation side effects, and serious adverse events. In addition, the global clinical impression scale was completed.

Results: Twelve patients had at least one lead placed in the CMN, and 13 had at least one lead placed in the ANT. The median baseline seizure frequency was 15 per month. Overall, the median seizure reduction was 33% at 6months, 55% at 1year, 65% at 2years, and 74% at >2years. Seizure free intervals of at least 3months occurred in nine patients. Most patients (60%, 15/25) did not have a change in anti-seizure medications post RNS placement. Two serious adverse events were recorded, one related to RNS implantation. Lastly, overall functioning seemed to improve with 88% showing improvement on the global clinical impression scale.

Discussion: Meaningful seizure reduction was observed in patients who suffer from drug resistant epilepsy with unilateral or bilateral RNS in either the ANT or

CMN of the thalamus. Most patients remained on their pre-operative anti-seizure medication regimen. The device was well tolerated with few side effects. There were rare serious adverse events. Most patients showed an improvement in global clinical impression scores.

KEYWORDS

centromedian nucleus of thalamus, anterior thalamic nucleus, neuromodulation, responsive neurostimulation (RNS), drug-resistant epilepsy (DRE), epilepsy surgery

1. Introduction

Neuromodulation is now recognized as an epilepsy surgery treatment alternative for drug resistant epilepsy (DRE) patients who are not resective or ablative surgical candidates. Candidates for neuromodulation include those with multifocal epilepsy, seizure foci in eloquent cortex, as well as those with generalized epilepsy. Vagal nerve stimulation (VNS), responsive neurostimulation (RNS), and deep brain stimulation (DBS) are neuromodulatory approaches used for DRE. VNS and DBS provide a continuous or pre-fixed electrical stimulation cycle. In VNS, extra stimulation can be delivered with the patient magnet or in response to tachycardia. On the other hand, RNS is a closed-loop device activated by abnormal electrocorticography patterns in or near the seizure focus (1). Because epilepsy is thought to involve corticothalamic networks, DBS and RNS have been increasingly applied to the thalamus (1–20).

Discussion of the thalamus in epilepsy dates to Wilder Penfield in the 1950s (21–23). Penfield posited that the thalamus was involved at the onset of absence and generalized tonic clonic seizures and may be rapidly engaged in seizures of temporal and frontal onset. Although resective or ablative epilepsy surgery is the best chance for cure, not every patient is a candidate as the seizure onset zone may be more extensive or in eloquent cortex. In the pivotal clinical trial, the RNS device treated patients with two seizure foci or with a seizure onset in eloquent cortex with electrodes as close to the onset zone as possible (24). Interrupting the seizure via the thalamic network responsively is a novel concept and while implemented at multiple level four epilepsy centers, has not been written about extensively.

Neuromodulation has been used in several nuclei of the thalamus to interrupt and modulate the neural networks with the objective of seizure reduction. The centromedian nucleus of the thalamus (CMN) is involved in wakefulness and has broad cortical projections. This network is related to seizure initiation, propagation and loss of consciousness (24). The anterior nucleus of the thalamus (ANT) is a key node in the limbic (circuit of Papez) and frontotemporal networks (25). DBS placement in the ANT or CMN is thought to modulate corticothalamic pathways (20, 26). A potential limitation of DBS is the continuous electrical stimulation regardless of the patient's ictal state (27). Although less readily available to the practicing clinician, local field potential power spectral analysis is now available with DBS systems and can allow for assessment of seizures over time. RNS on the other hand provides stimulation that recognizes seizure patterns before delivering stimulation and keeps a fairly detailed record of seizure events (24).

We retrospectively reviewed and characterized patients treated with thalamic RNS across seven centers. Our main objectives were to describe clinical changes in disabling seizures, the thalamic nuclei implanted and whether the approach was bilateral or unilateral. Our secondary objectives were to assess seizure free periods of greater than 3 months, anti-seizure medication (ASM) regimen changes, stimulation side effects, serious adverse events, and the overall global clinical impression.

2. Methods

A retrospective multicenter study across seven epilepsy centers in the United States was performed including Mount Sinai Hospital, NYU Langone Medical Center, Emory University, Yale University, Brown University/Rhode Island Hospital, Corewell Health, and Medical College of Wisconsin. A waiver of informed consent and a HIPPA waiver were obtained from the IRB at all sites granting permission to access medical records for observational research purposes. Inclusion criteria included any patients that received at least one thalamic RNS lead at least 6 months prior to February of 2020. At all centers, the thalamic nuclei were targeted based on volumetric T1 MPRAGE and/or FGATIR MRI sequences. Placement was often confirmed with a post-op volumetric CT (Figure 1). Patients that received the RNS system for off-label indications, for example a pediatric patient or patients with generalized epilepsy, were not excluded from the study. Primary objectives were to describe the implant location and determine changes in the frequency of disabling seizures at 6 months, 1 year, 2 years, and at the >2 year visit. Secondary objectives included documenting seizure free periods of greater than 3 months, ASM regimen changes, stimulation side effects, and serious adverse events. In addition, the global cognitive impression scale (GCI-I) was performed.

Patient demographics were collected including gender, age at implant, duration with epilepsy, and etiology of the epilepsy. Comprehensive presurgical workup prior to the RNS implant was collected including MRI, scalp EEG, and intracranial EEG data when performed. Patient's surgical history was explored as well as prior or concurrent use of other neuromodulatory treatments like VNS. Information regarding RNS implantation and therapy was collected for each patient. The specific nucleus of the thalamus and other targets of stimulation and detection were recorded. Descriptive statistics were used for analysis. Seizure reduction was estimated according to patient and clinician subjective report at each follow-up visit. Several cases included here were described in previous reports (1–3, 8).

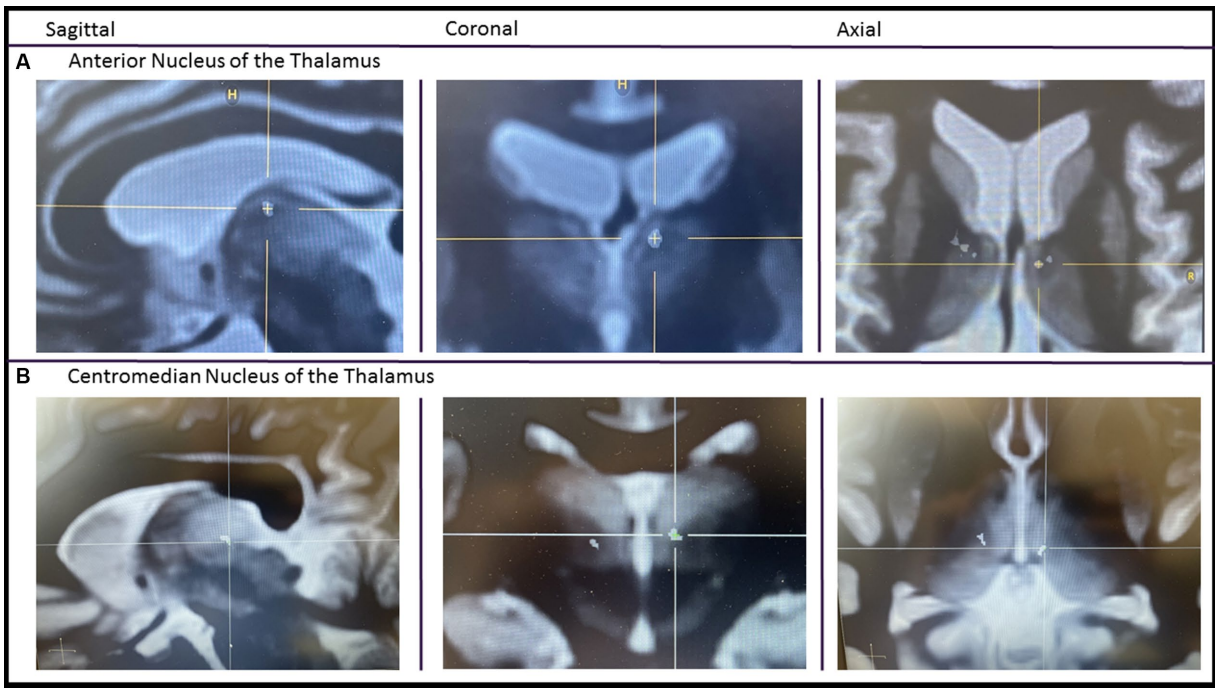

FIGURE 1
Imaging of thalamic RNS. A pre-op FGATIR MRI used for targeting is fused with a post-op volumetric CT. After fusion, the CT scan is made translucent except for the contacts. Imaging centered on the most internal contact of the left anterior thalamic lead **(A)** and centromedian lead **(B)**.

3. Results

3.1. Patient demographics

A total of 25 DRE patients (14 M, 11F) were enrolled in the study. The age at implant ranged from 9 to 53 years with a mean age of 27.2 (Table 1). All 25 subjects had been treated with RNS for a minimum of 6 months, 20 patients for 1 year, 18 patients for 2 years, and 10 patients for >2 years. Of note, no patients were lost to follow up. Thirteen (52%) had previous epilepsy surgery (six temporal lobe resections, two corpus callosotomies, two frontal resections, one frontal/parietal resection, one frontal/temporal resection, and one hemispheric resection). Duration of epilepsy ranged from 7 to 39 years (mean duration 19.4 years). Ten patients had no known cause for their epilepsy, 11 had a structural cause, three had a genetic cause, and one had an infectious cause. Of the structural causes, four patients had polymicrogyria, two patients had unilateral mesial temporal sclerosis (MTS), one patient had bilateral MTS, one patient had periventricular nodular heterotopia, one patient had tuberous sclerosis, one patient had post traumatic injury, and one patient had Dyke-Davidoff-Masson syndrome (Table 1).

3.2. Seizure characteristics

Baseline seizure frequency ranged from 3 to 2,250 disabling seizures per month (median 15). All patients had seizures captured on scalp EEG. Five patients had seizures with a generalized onset and 20 patients had seizures with focal onset. Of the patients with focal onset, 11 had greater than three foci, four had two foci, and five had a single focus. Onset zones on scalp were varied and as follows: Frontal (12), parietal (7), occipital (4), temporal (13), and mesial temporal (2). The majority had an intracranial EEG (20). Onsets on intracranial EEG were slightly different from prior scalp EEG and as follows: Frontal (12), parietal (10), occipital (4), temporal (9), mesial temporal (7), and insula (2). Two of the generalized onset patients had juvenile myoclonic epilepsy, two had Lennox Gastaut Syndrome and one likely had generalized epilepsy with tonic clonic seizures alone. Three of the patients with generalized onset underwent an intracranial EEG prior to RNS placement (Table 1).

3.3. Location of implant, detection and stimulation

Twelve patients had at least one lead placed in the CMN, 13 had at least one lead placed in the ANT. Four patients had bilateral thalamic depths and 21 patients had unilateral thalamic depths with another RNS strip or depth in various regions throughout the brain (Table 1). The thalamic lead(s) were used for detection in 18 patients whereas detection was solely non-thalamic in seven patients. Stimulation was delivered on the thalamic depths in 24 patients. In one patient, the thalamic lead was used for detection only and not stimulation.

3.4. Seizure reduction

For patients with thalamic depths there was a median seizure reduction of 33% at 6 months, 55% at 1 year, 65% at 2 years, and 74%

TABLE 1 Participant data.

Gender age at RNS implant	Epilepsy duration	Previous respective epilepsy surgery Y/N	Previous VNS Y/N	Epilepsy type (Focal/ Generalized)	Etiology (description)	RNS location
M40	7	N	Y	Focal	Infectious (Coxsackie B meningoencephalitis)	B CMN
F26	15	N	Y	Generalized	Genetic (JME with Jeavon's syndrome)	B ANT
F30	22	N	Y	Generalized	Genetic (JME)	R ANT, L F
M53	21	Y (R ATL)	Y	Focal	Structural (Polymicrogyria)	L ANT, L HCP
F36	36	Y (L ATL)	Y	Focal	Structural (Bilateral MTS)	R ANT, R HCP
M29	10	N	N	Focal	Structural (L MTS)	L ANT, L HCP
F38	37	Y (R selective medial temporal resection)	Y	Focal	Structural (L MTS)	L ANT, L HCP
M32	20	N	N	Focal	Structural (Periventricular nodular heterotopia)	R CMN, R P
M9	9	Y (CC)	N	Focal	Unknown	L CMN, R F
F24	24	N	Y	Generalized	Unknown	R ANT, R SMA
F14	14	Y (R hemispheric resection)	Y	Generalized	Unknown (LGS)	L CMN, R F
M16	16	Y (see *)	Y	Focal	Unknown	L ANT, R T
M31	27	N	Y	Focal	Structural (Dyke-Davidoff-Masson Syndrome)	B CMN
M12	4	N	N	Generalized	Genetic (Dup 15q, LGS)	B CMN
M19	11	N	N	Focal	Structural (Polymicrogyria)	R ANT, R T
F10	10	Y (CC)	N	Focal	Unknown (LGS)	L CMN, R HCP
F11	11	Y (R TL and disconnection)	N	Focal	Unknown	R ANT, L HCP
M28	27	Y (Partial R T resection)	N	Focal	Structural (Polymicrogyria)	R CMN, R P
F25	24	Y (L FP resection)	N	Focal	Structural (Tuberous Sclerosis)	L CMN, L F
M31	17	N	N	Focal	Structural (Post-traumatic)	L CMN, L P operculum
F47	28	Y (L F resection)	N	Focal	Unknown	L CMN, L post F
F44	39	Y (R ATL)	N	Focal	Unknown	L CMN, L T
M28	25	N	Y	Focal	Structural (pathogenic variant SPAST)	L ANT, L T
M23	23	Y (partial F and T resections)	Y	Focal	Unknown	R ANT, R posterior central region
M24	9	N	N	Focal	Unknown	L ANT, L P

ATL, anterior temporal lobectomy; ANT, anterior nucleus of the thalamus; B, bilateral; CC, corpus callosotomy; CMN, central median nucleus; F, frontal; FP, frontoparietal; Hippo, hippocampus; L, left; LGS, lenox-gastaut syndrome; MTS, mesial temporal sclerosis; P, parietal; R, right; and T, temporal.*R frontal lobe resection, CC, VNS, anterior comissurotomy L temporal lobectomy L parietal-occipital disconnection L orbital-frontal resection.

at >2 years (Figure 2A). Twenty-one patients (84%) reported a reduction of seizures at every visit. Nine patients reported at least 3 months of seizure freedom. Overall, eight patients (32%) reported an interval of at least 6 months with a greater than 90% seizure reduction. One patient reported worsened seizure frequency at 2 years and at the most recent visit. Three patients reported no change in seizure frequency at every follow up visit.

Seizure reduction was further analyzed based on lead location (ANT vs. CMN), type of epilepsy (generalized vs. focal), and unilateral vs. bilateral thalamic stimulation. Those with ANT leads (13) had

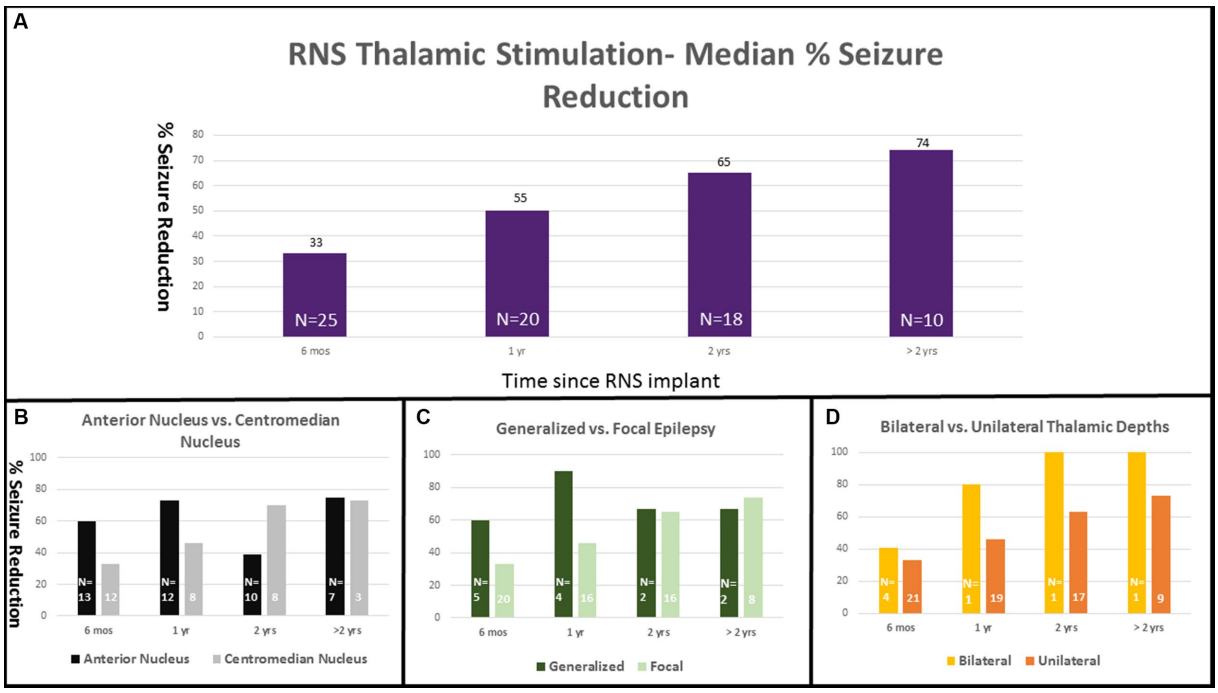

FIGURE 2
RNS thalamic stimulation—Median % Seizure Reduction with Subgroup Comparison. Percent seizure reductions was 33% at 6months (n =25), 55% at 1year (n =20), 65% at 2years (n =18), and 74% at >2years (n =10; **A**). Percent response is separated into subgroup comparisons with anterior nucleus vs. centromedian nucleus **(B)**, generalized vs. focal epilepsy **(C)**, and unilateral vs. bilateral thalamic depths **(D)**.

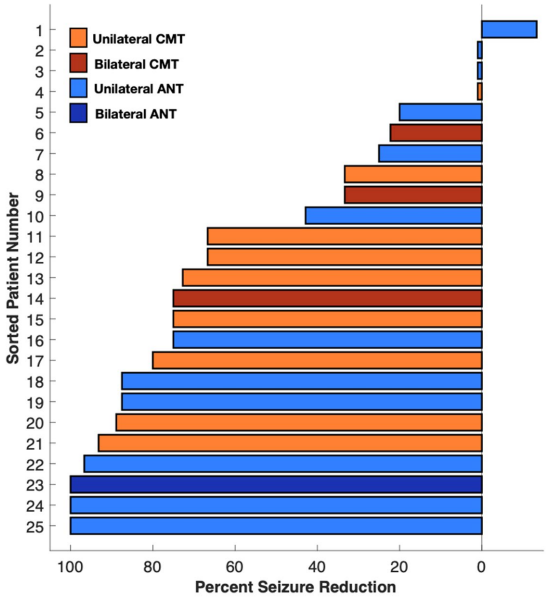

FIGURE 3
Median percent seizure reduction in ANT, CMN, bilateral, and unilateral depths at most recent visit.

median reductions of 60, 74, 39, and 75% at 6 months, 1 year, 2 years, and > 2 years respectively, compared with a median reduction of 33, 46, 70, and 73% in the CMN group (12) (Figure 2B). The single patient who experienced a worsened seizure frequency had an ANT lead. The seizure reduction in the ANT group was more heterogeneous including the patient with worsened seizure control at the 2 year mark, two patients who did not show any change and two patients who were super responders with 100% seizure control at the most recent follow up. Those with generalized onset epilepsy (5) had a median seizure reduction of 60, 90, 67, and 67% at 6 months, 1 year, 2 years, and > 2 years compared to reductions of 33, 46, 65, and 74% in the focal epilepsy group (20) (Figure 2C). Patients with bilateral thalamic leads (4) experienced a median seizure reduction of 41, 80, 100, and 100% at 6 months, 1 year, 2 years, and > 2 years compared to median seizure reduction of 33, 50, 63, and 73% in the unilateral (21) group (Figure 2D). Seizure reduction at the most recent visit is summarized in Figure 3.

3.5. Anti-seizure medications

The mean number of ASMs at the start of the study, prior to implant was 2.64 compared with 2.52 at the most recent visit. Of the 25 patients, 15 (60%) patients did not have a change in the number or type of ASMs. Three patients (12%) were on reduced ASMs at the most recent visit. Six patients (24%) had medication adjustments which resulted in the same number of ASMs and one patient (4%) was on one more ASM at the most recent visit compared to prior to implant (Figure 4).

3.6. Stimulation side effects and serious adverse events

No stimulation side effects outside of the clinic were reported. Two patients had events that qualified as serious adverse events: One patient had asystole within the first 6 months of having the RNS

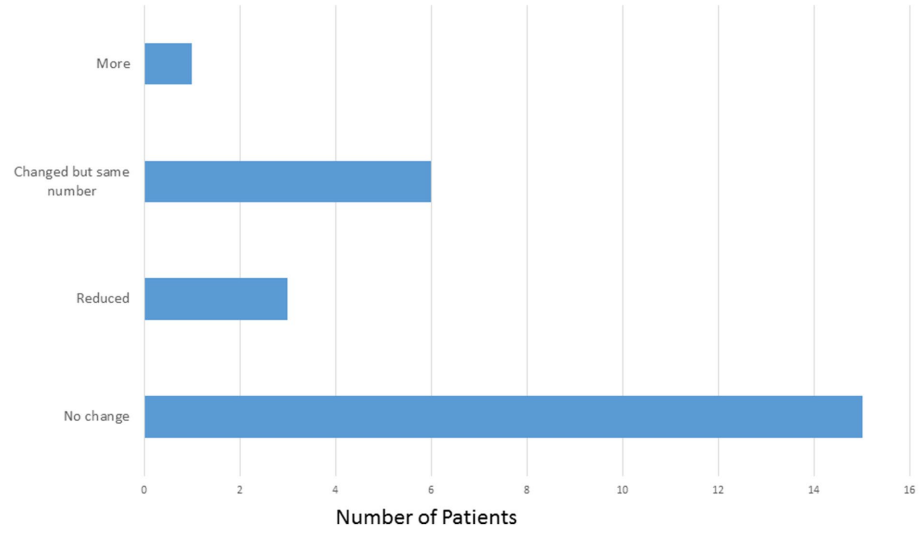

FIGURE 4
Anti-seizure medication changes with thalamic stimulation.

implanted, likely caused by a seizure, followed by syncope resulting in a hospitalization. This was unlikely to be related to the RNS device. A second patient had a left intraventricular hemorrhage at the time of implant noted on an intraoperative MRI and post-operative CT. This was asymptomatic without chronic sequelae. The patient left the hospital on post-operative day 2 in good condition.

3.7. Global clinical impression

The GCI-I was assessed for all patients by the care team. This assessment evaluates the overall quality of life. Nine patients were very much improved, six patients were much improved, seven patients were minimally improved, and three patients had no change. No patients assessed were clinically worse post-RNS.

4. Discussion

The thalamic nuclei with their widespread connections across cortical and subcortical regions hold promise to exert multi-focal or global influence on the brain, if harnessed properly. Original reports of thalamic stimulation and its effect on seizures date back to cat and human models in the 1950 and 1960s (28–30). Chronic stimulation in the thalamus has been shown to cause as well as abort seizure activity. Specific thalamic nuclei and their wider connections to other brain regions have been widely investigated. The CMN is an "intralaminar" nucleus that broadly affects the cortex (sensorimotor, premotor) with prominent connections to the cerebellum and basal ganglia and is likely involved in arousal and attention (31–33). Meanwhile, the ANT is part of Papez circuit which links medial frontal cortex with medial temporal lobe structures and is believed to underlie aspects of emotional and mnemonic function (34, 35). Up until now, several case reports of ANT and CMN responsive neurostimulation have been published in the literature (1–14). Reports on neuromodulation involving other thalamic nuclei, including the pulvinar, have been examined as well (36, 37). To date this case series is the largest involving the CMN and ANT. While there are no randomized controlled data comparing nucleus selection for thalamic stimulation in epilepsy, the current convention is to select the thalamic nucleus with connections most involved in the patient's epilepsy network. For example, ANT was often selected based on limbic involvement and the CMN where motor/frontal involvement seemed most prominent. The working theory is that the thalamic stimulation, given at the onset of a potential seizure, can de-synchronize the electrical activity by spreading to areas involved in the seizure network.

The patients included in this study should be conceptualized as among the most refractory patients. The choice of nuclei selected was based on seizure semiology and electrographic seizure signature. When an extensive seizure network is involved, thalamic neuromodulation appears the most attractive option after medications and in many instances, previous resections have failed.

In this multicenter review, the 25 RNS patients with thalamic RNS leads had seizure reduction profiles similar to that of the larger group of patients with cortical (non-thalamic) RNS studied in the long-term prospective open label trial (38). Here, at the time of the >2 year visit the median seizure reduction was 74%. In the long-term prospective trial, the median reduction at 9 years was 75%. Similarly, DBS in the ANT was shown to have a 75% median seizure reduction at 10 years (27). RNS in the thalamus appears to be a safe and well tolerated procedure. One of the two patients with serious adverse events was unrelated to the device and the other was an asymptomatic intraventricular hemorrhage. Thalamic RNS seems to have few side effects and no long term cognitive or mood changes were observed. In fact, most patients showed a general improvement in overall functioning.

5. Limitations

This study has several important limitations: this was a retrospective review with a relatively small number of

heterogeneous patients and there was no blinded period or placebo control (AKA sham stimulation period). Parameters of stimulation pathway, stimulation duration, and stimulation intensity were not pre-set and were up to the individual clinician or group. Furthermore, seizure frequency was determined by patient report and expert clinician assessment, rather than by device-based measurements, (serial RNS-based measures of seizure frequency are typically confounded by changes in detection thresholds during programming visits). These factors prevent a more objective and controlled analysis of seizure reduction in this retrospective series. The seizure etiology and target nucleus of the thalamus varied among this heterogeneous cohort, limiting power for subgroup analysis in this initial case series. We included specific outcome data for the subgroups (bilateral vs. unilateral stimulation, ANT vs. CMT, generalized vs. focal epilepsy). While these numbers are far too small to be significant, we believe these are important subgroups to consider in future prospective study design.

Additionally, most patients (21/25) had thalamic and non-thalamic stimulation. It is not known what portion of the benefit came from the thalamic stimulation. The purely thalamic stimulation group was only four patients (the bilateral thalamic subgroup) and therefore not large enough for substantive conclusions. While the GCI-I tool was used to obtain a gross assessment of overall functioning, more detailed and validated neuropsychological tools would be of significant benefit to measure mood and cognitive functioning with greater precision.

Overall, this work suggests that RNS treatment in the thalamus is safe and effective at reducing seizure frequency and improving quality of life in patients with difficult seizure types that often would not typically be amenable to further neurosurgical intervention. However, larger, prospective studies with stricter controls and assessments are needed to determine optimal treatment strategies for this highly refractory group of patients.

Author's note

CS conducted the research as an epilepsy fellow at Icahn School of Medicine at Mount Sinai.

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 IRB at Mount Sinai Hospital, NYU Langone Medical Center, Emory University, Yale University, Brown University/Rhode Island Hospital, Corewell Health, and Medical College of Wisconsin. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

MF, LM, CS, and PD conceptualized the project. OE, MF, and CS constructed the database and questionnaire. MF, LM, and CS drafted the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

KB receives salary support from Neuropace. FP and LM are a speaker for Neuropace.

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.

Publisher's note

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Effect of vagus nerve stimulation against generalized seizure and status epilepticus recurrence

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Objective: Vagus nerve stimulation (VNS) is a palliative surgery for drug-resistant epilepsy. The two objectives of this study were to (1) determine the seizure type most responsive to VNS and (2) investigate the preventive effect on status epilepticus (SE) recurrence.

Methods: We retrospectively reviewed 136 patients with drug-resistant epilepsy who underwent VNS implantation. We examined seizure outcomes at 6, 12, and 24 months following implantation of VNS as well as at the last visit to the Juntendo Epilepsy Center. Univariate analysis and multivariate logistic regression models were used to estimate the prognostic factors.

Results: 125 patients were followed up for at least 1 year after VNS implantation. The percentage of patients with at least a 50% reduction in seizure frequency compared with prior to VNS implantation increased over time at 6, 12, and 24 months after VNS implantation: 28, 41, and 52%, respectively. Regarding overall seizure outcomes, 70 (56%) patients responded to VNS. Of the 40 patients with a history of SE prior to VNS implantation, 27 (67%) showed no recurrence of SE. The duration of epilepsy, history of SE prior to VNS implantation and seizure type were correlated with seizure outcomes after VNS implantation in univariate analysis ($p = 0.05$, $p < 0.01$, and $p = 0.03$, respectively). In multivariate logistic regression analysis, generalized seizure was associated with VNS response [odds ratio (OR): 4.18, 95% CI: 1.13–15.5, $p = 0.03$]. A history of SE prior to VNS implantation was associated with VNS non-responders [(OR): 0.221, 95% CI: 0.097–0.503, $p < 0.01$]. The duration of epilepsy, focal to bilateral tonic–clonic seizure and epileptic spasms were not significantly associated with VNS responders ($p = 0.07$, $p = 0.71$, and $p = 0.11$, respectively).

Conclusion: Following 125 patients with drug-resistant epilepsy for an average of 69 months, 56% showed at least 50% reduction in seizure frequency after VNS implantation. This study suggests that generalized seizure is the most responsive to VNS, and that VNS may reduce the risk of recurrence of SE. VNS was shown to be effective against generalized seizure and also may potentially influence the risk of further events of SE, two marker of disease treatment that can lead to improved quality of life.

KEYWORDS

vagus nerve stimulation, generalized seizure, status epilepticus, drug-resistant epilepsy, response rate

1. Introduction

Vagus nerve stimulation (VNS) has been approved in Japan since 2010 and has been used for patients with drug-resistant epilepsy. Indications for VNS are drug-resistant epilepsy patients for whom curative surgery is difficult because the epileptic focus is difficult to detect or the epileptic focus is in an eloquent area. It is estimated that 45 to 65% of patients achieve at least a 50% reduction in seizure frequency by VNS (1–10). Previous studies have reported a variety of good VNS response factors (1–10). Although there have been reports on the efficacy of VNS for each seizure type, such as focal onset seizure, focal to bilateral tonic–clonic seizure (FBTCS), generalized seizure, and epileptic spasms, the best response candidates for seizure type still remains inconclusive (11–16).

Status epilepticus (SE) is a neurological emergency with a mortality rate of 3.45 to 22% (17, 18). The prevention of SE recurrence is important for reducing seizure burden, improving quality of life and developmental outcome in patients with drug-resistant epilepsy. The effect of VNS on SE still remains unclear. The effect of VNS on acute SE has been reported (19–21). For 38 acute-phase SE patients, seizures stopped in 28 patients in an average of 18 days after VNS implantation. However, the effect of VNS for SE remains unclear, not only in the acute-phase SE but also in the long-term prevention of SE recurrence.

The purpose of this study was to (1) determine which seizure type is most responsive to VNS and (2) investigate the protective effect on SE recurrence.

2. Materials and methods

2.1. Patient selection

Between 2010 and 2022, 136 patients with drug-resistant epilepsy who underwent VNS implantation at the Juntendo Epilepsy Center were retrospectively reviewed. All patients underwent a detailed preoperative examination at the Juntendo Epilepsy Center and were determined not to be candidates for curative epilepsy surgery. In our epilepsy center, video electroencephalography, magnetic resonance imaging, fluorodeoxyglucose-positron emission tomography, and neuropsychological testing, and, when necessary, magnetoencephalography were performed. Based on these results, a multidisciplinary conference was held to evaluate the indications for epilepsy surgery. The eligibility criteria for VNS implantation were as follows: (1) the epileptic focus could not be identified, (2) presence of multiple epileptic foci; and (3) the epileptic focus was located in an eloquent area. The implanted VNS devices implanted were either models with cardiac-based seizure detection (model AspireSR® 106, LivaNova) between 2017 and 2022 or without cardiac-based detection (models 103, 105) between 2010 and 2017. Patients who were followed up at the Juntendo Epilepsy Center for at least a year after VNS implantation were included in this study. Adjustments in antiseizure medication (ASM) and changes in VNS parameters were made in accordance with the decisions of the epileptologist.

2.2. Study ethics

This study was approved by the ethics committee of Juntendo University (No.16–163). Written informed consent was obtained from all the patients or their parents.

2.3. Seizure outcome

Outpatient charts at follow-up were used to assess seizure outcomes after VNS implantation. Postsurgical seizure outcomes were evaluated according to the McHugh classification (22). We defined the patients with class I to II as the "responder group" and the patients with class III to V as the "non-responder group" (Table 1). We collected data on seizure outcomes at 6, 12, and 24 months after VNS implantation. The overall seizure outcome was defined as the frequency of seizures at the last visit. In case of patients who underwent the epilepsy surgery after VNS implantation were considered to have the period immediately preceding the epilepsy surgery as the overall seizure outcome.

2.4. Statistical analysis

All statistical analyses were performed using the SPSS Statistics 25 (IBM Corp., Chuo-ku, Tokyo, Japan). We performed the Mann–Whitney U test and Steel-Dwass test after testing for data normality using the F test. The chi-squared test or Fisher's exact test was used to compare the categorical variables. Statistical significance was set at p value <0.05. Univariate analysis and multivariate logistic regression models were used to analyze the correlations between the seizure outcomes and the clinical characteristics.

3. Results

3.1. Clinical profiles

A total of 136 patients who underwent a primary VNS implantation between 2010 and 2022 at the Juntendo Epilepsy Center. Eleven patients were excluded because of insufficient follow-up and unavailable data ($n = 8$), removal less than 1 month after implantation due to infection ($n = 2$), or implantation impossible due to cardiac arrest caused by intraoperative trial stimulation ($n = 1$). Table 2 summarizes the clinical profiles of 125 patients (60 male, 65 female) who met the inclusion criteria enrolled in this study. 40 patients (32%)

TABLE 1 Classification of seizure outcome after VNS implantation.

Class	McHugh classification	This study
1	80–100% reduction in seizure frequency	Responder
2	50–79% reduction in seizure frequency	Responder
3	<50% reduction in seizure frequency	Non-responder
4	Magnet benefit only	Non-responder
5	No improvement	Non-responder

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TABLE 2 Clinical profiles.

	$n = 125$
Gender (Male: Female)	60: 65
Age at seizure onset (years)	13.2 ± 13.5
Age at VNS (years)	29.2 ± 15.4
Duration of epilepsy (years)	16.0 ± 12.9
Duration of follow-up period (months)	69.4 ± 42.2
Model of VNS (103/105: 106)	85: 40
History of epilepsy surgery prior to VNS	53 (42%)
Seizure type	
Focal onset seizure	110 (88%)
Focal to bilateral tonic–clonic seizure	65 (52%)
Epileptic spasms	22 (17%)
Generalized seizure	16 (12%)
Etiology	
Structural	57 (45%)
genetic	27 (22%)
infectious	16 (13%)
unknown	25 (20%)
History of SE prior to VNS	40 (32%)

SE, status epilepticus.

had history of SE prior to VNS implantation. The most common etiology of epilepsy was structural ($n = 57$, 45%), followed by genetic ($n = 27$, 22%), unknown ($n = 25$, 20%), and infectious ($n = 16$, 13%). The structural group of 57 consisted of 21 patients with bilateral temporal lobe epilepsy, 17 with unilateral temporal lobe epilepsy, 10 with focal cortical dysplasia, 3 with post-stroke and ectopic gray matter, and 1 each due to trauma, tumor, or hemangioma. The 27 genetic groups consisted of 7 Lennox–Gastaut syndrome, 7 Sturge–Weber syndrome, 6 with tuberous sclerosis complex, 3 with West syndrome, and 1 case of each of dentatorubral-pallidoluysian atrophy and cardiofaciocutaneous syndrome and CHARGE syndrome and Angelman syndrome.

3.2. Seizure outcome after VNS implantation

Seizure outcomes according to McHugh classification at several follow-up points are shown in Figure 1. At 6, 12, and 24 months of follow-up, McHugh classification class I was achieved in 21 (17%), 24 (19%), and 30 (29%) patients, respectively. At 6, 12, and 24 months of follow-up, McHugh classification class II was achieved in 14 (11%), 28 (22%), and 24 (23%) patients, respectively. At 6, 12, and 24 months of follow-up, McHugh classification class III was achieved in 38 (30%), 39 (31%), and 25 (24%) patients, respectively. At 6, 12, and 24 months of follow-up, McHugh classification class V was achieved in 52 (42%), 34 (27%), and 24 (23%) patients, respectively. Overall seizure outcome, McHugh classification class I was achieved in 39 (31%), II in 31 (25%), III in 30 (24%), and V in 25 (20%). At 6, 12, and 24 months of follow-up, the number of responder patients (the total of all patients in class I and class II) was 35 (28%), 52 (42%), and 54 (52%). As the

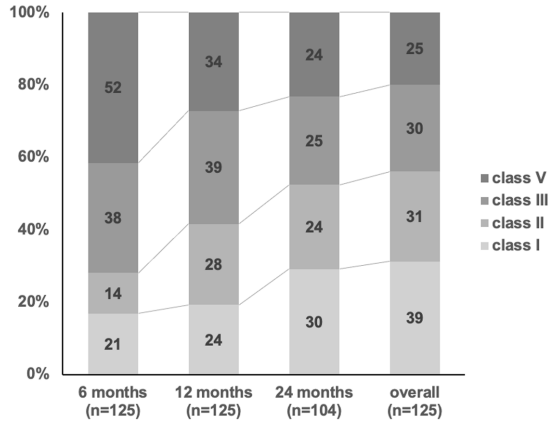

FIGURE 1
Seizure outcome after VNS implantation. The response rates (> 50% reduction, McHugh classification I-II) at 6, 12, 24 months and overall outcome after VNS implantation has increased from 28, 41, 52, and 56%.

overall seizure outcome, the number of responder patients was 70 (56%).

Of the 40 patients with a history of SE before VNS implantation, 27 (67%) showed no recurrence of SE after VNS implantation. SE did not appear after VNS implantation in 83 of the 85 (98%) patients without a history of SE prior to VNS implantation.

3.3. Predictors of VNS responder

Table 3 shows that the duration of epilepsy, history of SE prior to VNS implantation, and seizure semiology were associated with seizure outcome after VNS implantation in the univariate analysis ($p = 0.05$, $p < 0.01$, $p = 0.03$, respectively). In the multivariate logistic regression analysis, Generalized seizure was associated with VNS response [odds ratio (OR), 4.18; 95% CI: 1.13–15.5, $p = 0.03$] (Table 4). A history of SE prior to VNS implantation was associated with non-responders to VNS (OR: 0.221, 95% CI: 0.097–0.503, $p < 0.01$). Duration of epilepsy, FBTCS and epileptic spasms were not significantly associated with VNS responders ($p = 0.07$, $p = 0.71$, and $p = 0.11$, respectively).

4. Discussion

4.1. VNS for generalized seizure

This study demonstrated the preventive effects of VNS against generalized seizure. This positive outcome in patients with generalized seizure was consistent with previous research (23). Patients with generalized seizures achieving $a > 50\%$ reduction in seizure frequency 1 and 2 years after VNS implantation were 46 and 49%, respectively. On the other hands, focal seizures are more likely to respond to VNS than generalized seizure (24). Although it is still controversial which type of seizure VNS is effective for, involvement of the thalamus in seizure onset suggests a mechanism for the effect of VNS on generalized seizure. According to a previous report, the thalamus is responsible for seizure onset based on a reduction in the N-acetyl

TABLE 3 Univariate analysis.

	Responder ($n = 70$)	Non-responder ($n = 55$)	p value
Gender (Male: Female)	32: 38	29: 26	0.27
Age at seizure onset (years)	14.7 ± 13.4	11.3 ± 13.6	0.09
Age at VNS (years)	29.0 ± 14.2	29.5 ± 16.9	0.43
Duration of epilepsy (years)	14.4 ± 12.1	18.2 ± 13.7	0.05*
Duration of follow-up period (months)	73.6 ± 42.8	64.1 ± 41.2	0.11
Model of VNS (103/105: 106)	47: 23	38: 17	0.49
History of epilepsy surgery prior to VNS	25	28	0.06
Seizure type			0.03*
Focal onset seizure	56	54	
Focal to bilateral tonic–clonic seizure	35	30	
Epileptic spasms	7	15	
Generalized seizure	13	3	
Etiology			ns
structural	32	25	
genetic	12	15	
infectious	9	7	
unknown	17	8	
History of SE prior to VNS	13	27	<0.01*

SE, status epilepticus; ns, not significant.

TABLE 4 Multivariate logistic regression analysis.

	p value	OR	95%CI
Duration of epilepsy (years)	0.07	0.97	0.94–1.002
Seizure type			
Focal onset seizure	Ref		
Focal to bilateral tonic–clonic seizure	0.71	1.125	0.61–2.08
Epileptic spasms	0.11	0.45	0.17–1.19
Generalized seizure	0.03*	4.18	1.13–15.5
History of SE	<0.01*	0.221	0.097–0.503

SE, status epilepticus; Ref, reference category; OR, odds ratio; CI, confidence interval.

aspartate/creatine ratio in the thalamus in patients with generalized seizure (25). Because VNS affect the bilateral thalamus (26), it is considered that VNS is effective against generalized seizure. We did not investigate as to which type of generalized seizure is effective because the number of patients with generalized seizure in this study was too small. Further studies are required to elucidate the mechanisms of the effectiveness of VNS against generalized seizure.

4.2. VNS for SE

In this study, we observed good outcomes for the recurrence of SE after VNS implantation. However, we found that the patients with a history of SE had a poor response to VNS as an overall outcome regarding the response rate of all seizure types compared to the patients without a history of SE. The outcome of VNS in SE has been reported to be favorable (27). They reported that the patients with a history of repeated episodes of SE showed improved SE and seizure frequency. VNS implantation was performed in 8 patients with episodes of SE, and 4 patients (50%) had a recurrence of SE after VNS implantation. To our knowledge, this is the first report of the preventive effect of SE in patients with episodes of SE prior to VNS implantation. However, these patients showed less than a 50% reduction in the seizure frequency of the other seizure types except SE after VNS implantation.

The mechanism of VNS against SE has not been fully elucidated. It is thought that the pathophysiological roles of γ-aminobutyric acid, glutamate, the inflammatory cascade, and hypoxia lead to SE (28). Moreover, the breakdown of the blood–brain barrier, inflammation, and increase may occur during the development of SE (28). This hypothesis is supported by previous studies showing some changes caused by VNS. Henry et al. showed that VNS increases cerebral blood flow, mainly in the bilateral thalamus (26). VNS-induced changes in the thalamus are significantly correlated with seizure suppression (29).

In terms of inflammatory responses, VNS was associated with a marked increase in the levels of circulating anti-inflammatory circulating cytokines (30). This cytokine response after VNS implantation may play an important role in reducing SE (31). Based on these studies, VNS may be effective against SE. It is reasonable to perform VNS implantation even if the seizure frequency, except for SE, does not improve. This study suggests a potential protective effect of VNS on SE recurrence; however, neuromodulation, such as DBS and RNS, may be an option for patients who still have other seizure types remaining.

5. Limitation

The present study had some limitations. This study was conducted using a retrospective survey of outpatient medical records. In addition, the assessment of seizure outcomes after VNS implantation is based on the McHugh classification, which is primarily based on seizure frequency. If the severity of the seizure is improving but the frequency of the seizure is unchanged, the McHugh classification becomes class V. Seizure outcome assessment based on classification with emphasizing the seizure severity as well as the seizure frequency may be needed in the future studies.

The next limitation is the effect of VNS on preventing the reoccurrence of SE. In this study, 27 of the 40 patients who had experienced SE prior to VNS implantation were free of SE recurrence at an average follow-up of more than 5 years. However, because SE is a rare event for most patients who experience SE, larger and longer studies are needed to determine the precise effect of VNS on the long-term risk of the recurrence of SE.

This study did not examine the relationship between seizure outcomes and ASM is not mentioned. In particular, the withdrawal of ASM may need to be considered. The present study had an average follow-up of more than 5 years and > 50% of the patients were VNS responders. In these patients, it is expected that reducing ASM can

be considered, and the relationship between the seizure outcome and ASM withdrawal in patients with VNS requires further investigation.

6. Conclusion

A total of 125 patients with drug-resistant epilepsy were followed up for an average of 69 months, with 56% showing a good response to VNS. This study suggests that the seizure type most responsive to VNS is generalized seizure. It has also been suggested to potentially prevent the recurrence of SE in drug-resistant epilepsy patients with a history of SE prior to VNS implantation. VNS was shown to be effective against generalized seizure and also may potentially influence the risk of further events of SE, two marker of disease treatment that can lead to improved 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.

Ethics statement

The studies involving humans were approved by the ethics committee of Juntendo University (No.16–163). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

All authors made substantial contributions to the conception, validation, design, acquisition of data, or analysis and interpretation of data.

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Conflict of interest

The 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. The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Clinical outcomes following responsive neurostimulation implantation: a single center experience

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Background: Responsive neurostimulation (RNS) is an implantable device for persons with medically refractory focal-onset epilepsy. We report a single-center experience for RNS outcomes with special focus on stereoelectroencephalography (sEEG) for seizure onset localization.

Methods: We performed retrospective review of patients with drug resistant focal epilepsy implanted with the RNS System for a minimum of six months between July 2014 and July 2019. Records were reviewed for demographic data, epilepsy duration, seizure frequency, number of prior antiepileptic drugs (AEDs), number of AEDs at RNS System implantation, prior epilepsy surgery or device use, previous seizure localization with sEEG, and RNS system information. Clinical response was defined as a 50% reduction in seizures. Differing response rates were calculated using Fisher Exact test.

Results: 30 patients met inclusion criteria. Seventeen (57%) underwent previous sEEG. Average clinical follow up was 3.0 years. Overall response rate was 70%. Median seizure reduction was 74.5%. Response rate was 82.3% for patients with sEEG compared to 53.8% without ($p = 0.08$); 37.5% for prior epilepsy surgery compared to 81.8% without ($p = 0.02$); 70% for mesial temporal onset; 50% for previous vagal nerve stimulator compared to 77.3% without ($p = 0.13$).

Conclusion: Our response rates match or surpass outcome metrics of previous studies. Although limited by small study size, subpopulation analyses show positive response rates in patients with previous sEEG versus no sEEG and in temporal versus extratemporal pathology. Additional research is needed to evaluate efficacy of RNS in patients with previous epilepsy surgery, and utility of sEEG in this population.

KEYWORDS

epilepsy, RNS, responsive neurostimulation, StereoEEG, neuromodulation

1. Introduction

More than 30% of persons with epilepsy develop medically refractory disease, meaning they will continue to have seizures despite adequate trials of two appropriate anti-epileptic drugs (AEDs) (1). Responsive neurostimulation (RNS) is readily available to patients with medically refractory focal-onset epilepsy. Real-world RNS efficacy has outpaced the original treatment responses seen in clinical trials, with possible explanations including improved detection and

stimulation programming with increased clinical experience (2). Use of stereotactic electroencephalography increases the accuracy of seizure onset localization and thus may improve treatment outcomes with RNS. The goal of the current paper is to analyze treatment responses at a center experienced in stereoelectroencephalography (sEEG).

2. Background

The RNS (NeuroPace) system is approved for the treatment of medically refractory focal-onset epilepsy. Patients are typically considered for RNS if seizures are localized to 1 or 2 foci and there are at least three or more disabling seizures per month on average despite AEDs (these may include focal motor, focal onset with impaired awareness, and secondarily generalized tonic–clonic seizures). The system is comprised of a cranially implanted programmable neurostimulator allowing implantation of a maximum of four leads – depth electrodes or subdural strips. However, there is a limitation of two that can be connected for recording and stimulating the patient's specific seizure focus. The neurostimulator continually senses electrocorticographic activity and delivers stimulation in response to abnormal activity according to parameters specified by the physician. Both seizure detection and stimulation parameters are tailored to the patient and modified over time for optimal seizure control (3).

RNS efficacy was established in the randomized, multicenter, double-blinded, sham-stimulation controlled pivotal trial, with final results of up to 2 years postimplant follow-up data released in 2014 (4). The blinded assessment period lasted 12 weeks, during which time the treatment group experienced a significantly greater reduction in total disabling seizures compared to sham group (41.5% and 9.4% reductions respectively). During the open label period, median percent reduction reached 44% at 1 year, and 53% reduction at 2 years. The overall responder rate, the percentage of patients with at least a 50% reduction in clinical seizure frequency, was 54%. The study was not powered for subgroup analysis but descriptively found no major differences based on mesial temporal lobe onset or changes in anti-seizure medications. Quality of life outcome measures were also favorable. Subsequent real-world experience with RNS has demonstrated median seizure frequency reduction of 67% at 1 year and 75% at 2 years. Responder rate was 66% at 1 year.

The advantages of RNS include safety compared to traditional epilepsy surgery in eloquent cortex, preservation of or even improvement in cognition over time, comparable hemorrhage and infection rates to other intracranial surgeries, overall excellent long-term tolerability (2, 4), and potentially favorable patient perception of invasiveness. As with any new procedural therapy, the primary disadvantage is accessibility.

Traditional indications for intracranial EEG include localization of seizure foci in (a) nonlesional epilepsy, (b) large/deep/multifocal lesions, (c) epileptic zone in proximity to eloquent cortex, and (d) previous failed surgery. SEEG offers less coverage of superficial cortical areas compared to subdural strip- or grid-electrodes; however, it does allow bilateral symmetric implants for better sampling of epileptic networks and precise mapping of deep cortical areas. SEEG is also usually better tolerated and carries a lower rate of clinically significant complications. Use of sEEG has improved study of large, deep, and multifocal lesions including polymicrogyria and heterotopic gray matter, and in surgical planning of suspected bitemporal lobe epilepsy (5). There have been some studies highlighting patterns on sEEG that might predict response to RNS (6), however the role for sEEG in preoperative evaluation for RNS if resection is not intended remains unclear. We hypothesized that precise seizure onset localization using sEEG could guide RNS implantation and improve RNS response rates.

3. Methods

3.1. Patient selection

We performed retrospective review of patients with drug resistant focal epilepsy who were implanted with the RNS System for a minimum of 6 months between July 2014 and July 2019 at the Pennsylvania State University Hershey Medical Center (PSUHMC), a comprehensive level 4 epilepsy center. Patients required at least six months of outcomes data after implantation to ensure that the "implant effect" from surgery was bypassed (3). All implanted patients with the minimum six months of post-implantation data were included in the analysis. Electronic medical records were reviewed for age, sex, epilepsy duration, seizure frequency, number of prior antiepileptic drugs, number of AEDs at RNS System implantation, prior epilepsy surgery or device use, previous seizure localization with sEEG, and RNS system information including lead type and location. All patients were discussed at an interdisciplinary epilepsy case conference prior to implantation of the RNS System. Guidelines for consideration of RNS at PSUHMC adhere to the selection criteria in the pivotal trial (3, 4), including a minimum of 3 disabling seizures per month. We consider RNS placement in patients with lower-frequency events meeting certain exceptional circumstances: if seizures present with severe injury or status epilepticus and (a) other interventions such as VNS, laser ablation, or resective surgery have already failed or (b) the patient is not a candidate for resection or ablation.

3.2. Data collection and analysis

Baseline clinical seizure frequency was the patient-reported number of seizures with impaired awareness with and without secondary generalization prior to RNS System implantation. Focal aware seizures were not counted when determining seizure frequency. Clinical seizure frequency was retrospectively assessed based on documentation by treating providers at each outpatient follow up visit based on seizure diaries and/or self-report from the patient or caregiver. Rates of seizure reduction or increase for each patient were determined and then compiled into response categories of increased seizures, seizure freedom, and seizure reduction quartiles ranging from 0% to 99%. Responder rate of patients with at least a 50% reduction in clinical seizure frequency is taken at last observation.

Statistical tests used for data analysis are indicated in the text. For all comparisons α was set to $p < 0.05$ for statistical significance. Subpopulation analysis of response rates was completed for patients with mesial temporal onset including mesial temporal sclerosis (MTS), sEEG, prior epilepsy surgery, and previous vagus nerve stimulator (VNS).

4. Results

Over a five-year period, a total of 31 patients were implanted with the RNS System at PSUHMC and carried a diagnosis of medical refractory localization related epilepsy with disabling seizures. However, there were two pediatric patients (age < 18 years) at the time of implantation for which the device is not approved. Three patients underwent revision of RNS leads due to a single lead break, one of whom was excluded due to less than six months of outcomes data following revision. Specific clinical characteristics for each patient are provided in Table 1. Of the 30 remaining patients, 40% ($n = 12$) were female. Mean age at time of RNS System implantation was 33.4 years ±10.7 (range 14–55). Mean duration of epilepsy was 20.5 ± 9.4 years (range 7–41 years). Patients were taking a mean of 3.0 ± 1.0 (range 1–6) antiepileptic drugs at the time of implantation with a mean of 4.7 ± 1.6 (range 2–9) antiepileptic drugs tried previously. The majority of patients (20, 66.7%) had onset of seizures from the mesial temporal region and 13 patients (43.3%) had two seizure foci. Seventeen of 30 patients (57%) had prior intracranial monitoring for seizure localization with stereotactic EEG (sEEG). There were a small cohort of patients who previously underwent either resection or laser ablation (8, 27%), vagal nerve stimulator placement (8, 27%), or both (2, 6.7%). Grouped characteristics for 30 implanted patients can be found in the Supplementary material.

A total of 60 leads were implanted of which 16 were strips and the remaining 44 were depth leads accounting for 19 dual depth systems, 5 dual strip systems, and 6 combination systems with both depth and strip leads. The majority of leads were implanted in the mesial temporal lobe ($n = 33$) with other locations consisting of the frontal ($n = 11$), parietal ($n = 4$), lateral temporal ($n = 10$), occipital ($n = 1$), and insular regions ($n = 1$).

4.1. Seizure reduction

The median baseline seizure frequency prior to implantation of the RNS device was 10 (range 0.5–90) per month. There were 4 patients with seizure frequency of <2 per month and 2 patients with <1 seizures per month. Three of these 4 patients with low baseline seizure frequency were selected for RNS due to continued disabling seizures following lobectomy. One patient (number 23 in the table) had a seizure frequency of up to 4 per month at the time of epilepsy surgery conference, and seizure frequency declined in the interim before RNS System implantation as medications were adjusted. All patients were followed for a minimum of six months with a mean follow up of 3.0 years and a cumulative of 90 patient implant years.

The responder rate (percent of subjects with at least a 50% reduction in seizure frequency) was 70% with a median reduction of 74.5%, and median seizure frequency of 3.9 (range 0–15) per month. For the group with less than a 50% response rate, there was an equal percentage of patients with increased seizure frequency and a 25%–49% seizure frequency reduction while 3% had less than a 25% reduction in seizures (Figure 1). Non-responders were on average slightly younger (mean 32.5 years) with a similar epilepsy duration (20.8 years).

4.2. Subpopulations

The 17 patients who underwent sEEG for seizure localization just prior to RNS implantation have a responder rate of 82.3% in comparison to 53.8% for the patients with no prior invasive monitoring for seizure localization (one-tailed Fisher exact test, $p = 0.08$; Figure 1). The median seizure reduction was 86.4%, and median seizure frequency fell from 10.5 to 3.7. There were four patients (13%) with at least a 95% reduction in seizures and two patients (6.7%) with no seizures for at least six months. One patient (0.6%) experienced an increase in seizure frequency from 12 to 15 per month. Outcomes for specified subpopulations are summarized in Table 2.

The eight patients who had a prior history of epilepsy surgery (including 7 lobectomies and 1 ablation) have a responder rate of 37.5%, compared to 81.8% for the patients with no history of prior epilepsy surgery (Fisher exact test, $p = 0.02$). The median seizure reduction was 37.5%, and median seizure frequency fell from 6.5 to 5. Maximum seizure reduction was 81.3%, and two patients with relatively low seizure frequency at baseline (<1 per month) experienced an increase in seizure frequency. Only two patients underwent sEEG prior to implantation in this group. Both experienced a decrease in seizure frequency but in only one patient was the decline >50%.

The 20 patients with mesial temporal localization included 13 patients with imaging findings consistent with MTS, 1 patient with hippocampal cortical dysplasia, and 6 patients with normal imaging. This group had an overall responder rate of 70%, equal to the population as a whole. The 13 patients with MTS have a 61.5% response rate compared to 85.7% response rate in the non-MTS group (Fisher exact test, $p = 0.23$). The median seizure reduction was 70.3% overall, 66.3% in the MTS group, and 81.3% in the non-MTS group. Median seizure frequency fell from 9.6 overall, 9.2 in the MTS group, and 10.5 in the non-MTS group to 4.1, 4.3, and 3.7, respectively. There were two patients in the MTS group (16.7%) and one in the non-MTS group (12.5%) with at least a 95% reduction in seizures, and one patient (12.5%) in the non-MTS group with no seizures for at least six months. Three MTS patients with relatively low seizure frequencies at baseline experienced an increase in seizure frequency. Nine patients underwent sEEG prior to implantation, with an 88.9% response rate compared to 54.5% response rate without prior sEEG (Fisher exact test, $p = 0.11$), with similar rates between the MTS and non-MTS groups.

The eight patients with previous vagal nerve stimulator have a responder rate of 50%, compared to 77.3% for the patients without prior VNS (Fisher exact test, $p = 0.13$). Median seizure frequency fell from 41 to 5.1 seizures per month. There were two patients (25%) with a >95% seizure reduction, and one patient with a slight increase in seizure frequency.

5. Discussion

In comparison to the results of the pivotal trial, our cohort experienced increased 1- and 2-year responder rates, a somewhat increased 1-year median percent reduction, and an increased 2-year median percent reduction (see Table 3). Our overall rates of seizure improvement, seizure freedom, and increase in seizures were similar (2, 4).

In comparing the two populations, age, sex, duration of epilepsy and rates of sEEG implantation were similar. Our population had fewer patients with prior epilepsy surgery, somewhat lower rates of multiple seizure foci, and an overall lower baseline seizure frequency. The finding in the pivotal trial that patients with increase in seizure

TABLE 1 Individual patient characteristics.

Case no.	Years with epilepsy	AED no.	Baseline seizure frequency	Prior surgery	Prior VNS	Foci no.	sEEG	RNS location (strip/depth)	Current seizure frequency	Percent reduction
1	18	6	10	Lobectomy	Y	1	N	S – L Post Basal Temporal S – L Inf Lat Temporal	7.1	29.00
2	13	4	13.5	N	N	2	Y	D – Bil Mesial Temporal	4.5	66.67
3	29	3	75	N	N	1	N	D – L Ant Temporal D L Post Temporal	7.8	89.60
4	19	3	8	N	N	2	Y	D – L Mesial Temporal S – R Mid Temporal Gyrus	2.7	66.25
5	10	3	32	N	N	2	Y	D – Bil Mesial Temporal	5	84.38
6	13	2	10	N	N	1	N	D – R Mesial Temporal S – R Inf Occipital	4.25	57.50
7	8	4	3	N	N	2	Y	D – Bil Mesial Temporal	0	100.00
8	7	4	30	N	N	1	Y	D – R Ant Inf Parietal S – R Inf Parietal	1	96.67
9	24	3	6	N	Y	1	Y	S – L Mid Frontal Gyrus	3.7	38.33
10	10	4	80	N	Y	1	Y	S – L Frontal (Motor) L Sup Temporal Gyrus	10.75	86.56
11	30	5	70	N	Y	2	Y	D – Bil Mesial Temporal	6.5	90.71
12	26	4	75	Lobectomy	N	1	N	D – L Mesial Temporal	14	81.33
13	41	3	95	N	Y	2	N	D – Bil Mesial Temporal	1.5	98.42
14	34	3	8	Lobectomy	N	1	Y	D – R Post Orbitofrontal D – R Frontal (Premotor)	2.3	71.25
15	8	4	28	N	N	2	Y	S – Bil Mid Frontal Gyrus	3.8	86.43
16	25	3	2.5	N	N	1	Y	S – L Orbitofrontal S – L Frontal Operculum	0	100.00
17	36	3	5.5	N	N	2	Y	D – L Mid Frontal Gyrus D – L Mesial Temporal	0.5	90.91
18	25	3	45	N	N	1	N	D – L Mesial Temporal	5	88.89
19	10	2	0.75	Ablation	N	1	N	D – L Mesial Temporal	6	−700.00
20	20	4	5	Lobectomy	Y	2	N	D – L Mesial Temporal	1.3	74.00
21	34	2	1.3	Lobectomy	N	1	N	D – R Mesial Temporal	0.7	46.15
22	15	2	90	N	Y	1	Y	D – L Mesial Temporal S – L Lat Temporal	0.71	99.21
23	16	1	1.5	N	N	1	N	D – R Mesial Temporal	12.5	−733.33
24	14	2	6	N	N	2	N	D – Bil Mesial temporal	1.5	75.00
25	17	2	10.5	N	N	1	Y	D – R Mesial Temporal S – R Temporal	3.7	64.76
26	28	2	4	N	N	2	Y	D – L Insulotemporal D – R Mesial Temporal	0.5	87.50
27	8	2	20	N	N	2	N	D – Bil Mesial Temporal	15	25.00
28	27	3	12	N	Y	2	Y	D – R Post Cing Gyrus S – R Frontal (Motor)	15	−25.00
29	24	3	0.5	Lobectomy	N	1	N	D – R Mesial Temporal	4	−700.00
30	27	1	9.2	Lobectomy	N	1	Y	D – L Post Sup Temporal Gyrus D – R Mesial Temporal	7.8	15.22

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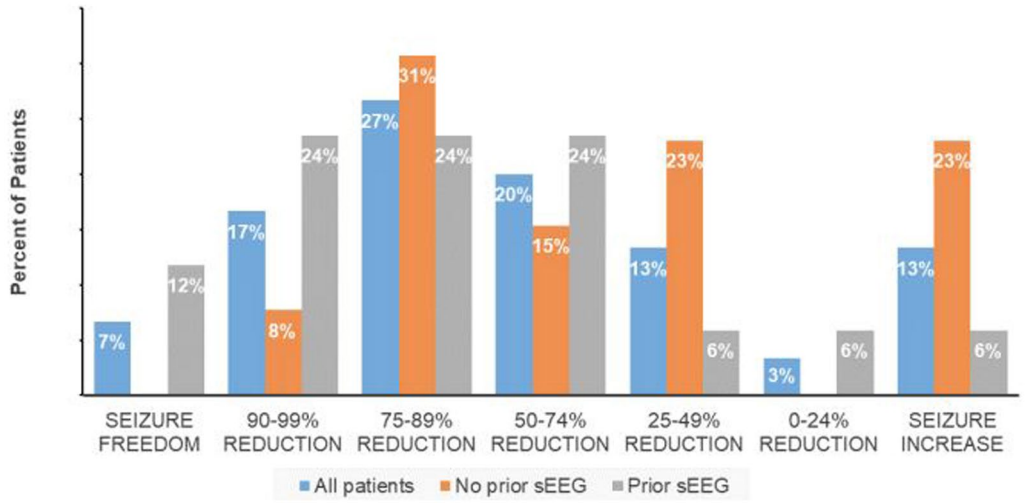

FIGURE 1
Response quartiles (all implanted vs. sEEG localization).

TABLE 2 Subpopulation analysis.

Subpopulation	50% responder rate (%)	Median % reduction	Minimum % reduction	Maximum % reduction	*p*-value (responder rate)
Total participants ($n = 30$)	70	74.5	−733.3	100	
sEEG ($n = 17$)	82.3	86.4	−25	100	0.08
Prior surgery ($n = 8$)	37.5	37.5	−700	81.3	**0.02**
Mesial temporal onset ($n = 20$)	70	70.3	−733.3	100	
Radiographic mesial temporal sclerosis ($n = 13$)	61.5	66.3	−733.33	99.2	0.35
Prior VNS ($n = 8$)	50	80.3	−25	99.2	0.13

Statistically significant result is shown in bold.

TABLE 3 Comparison of study cohort to previous trials.

	Comparison of study cohort to results of previous trial data[2,4]		
	Pivotal *N* = 191	Razavi et al. *N* = 150	Current cohort *N* = 30
1 year responder rate	43%	66%	70%
2 year responder rate	54%	77%	87%
1 year median percent reduction	44%	67%	57%
2 year median percent reduction	55%	75%	81%
Some improvement in seizures	82%		87%
Seizure freedom	9%	18%	7%
50% or greater increase in seizures	7%		10%

frequency had a tendency to younger age (4) was not borne out in the present cohort.

In comparison to real-world data, our cohort had a lower proportion of patients with prior epilepsy surgery and higher rates of mesial temporal localization. Although only 57% of our patients underwent intracranial monitoring prior to implantation compared to 82% in the Razavi study (2), all our intracranial monitoring was performed with sEEG in contrast to a mix of sEEG and subdural grid and strip electrodes. Our cohort therefore is amongst the largest study of sEEG in RNS to date, where 73% of leads implanted were depth leads, compared with only 46% in the Razavi study.

Initial stim settings 200 Hz, 160 ms pulse width, 100 ms burst duration for charge density 0.5 uC are unchanged between the pivotal trial, the real-world data, and our cohort. Our subsequent programming was per provider discretion based on data from the original pivotal trial.

5.1. Subpopulation analysis

Subpopulation data was not reported in the pivotal trial except for mesial temporal onset. Subpopulation real-world data analysis found no difference in seizure frequency reduction depending on patient age, age at epilepsy onset, duration of epilepsy, location of seizure, brain MRI abnormalities, prior intracranial monitoring, prior epilepsy surgery, or prior VNS treatment.

Although our subpopulation analyses also largely did not reach significance, observational trends are relevant to guide future research. In evaluating the nine patients who were non-responders, 5 had undergone previous epilepsy surgery, 3 had prior VNS, and one had both. Age and

epilepsy duration were similar between responders and non-responders. Additionally, all of the patients with baseline seizure frequency < 2/month were non-responders, including 3 with >700% increases in seizure frequency. This suggests there may be little room for improvement in this subgroup, and risk of worsening must be carefully considered.

Use of sEEG has a trend toward improved response rates, however this does not reach significance in either the total population or mesial temporal subpopulation analysis. The hypothesis that more accurate seizure localization prior to RNS implantation is based on the proposed therapeutic mechanism of RNS delivering stimulation to the site of ictal onset to disrupt seizure propagation. Assuming our observed trend of a 12% gain in response rate with sEEG compared to the whole cohort represents a true effect, we calculate a cohort size of 100 (50 with prior sEEG, 50 without) would be necessary to demonstrate statistical significance ($\alpha = 0.05$, $\beta = 0.1$). Statistical calculations were made using G*Power 3 software (7).

Prior epilepsy surgery correlated with a poorer response rate in our study. This may indicate that continued disabling seizures after epilepsy surgery is a marker of refractory disease or kindling epilepsy networks beyond the identified and implanted ictal origin (8). Refractoriness may also be partially attributable to increasing years with epilepsy in this population, with an average of 24.1 (SD 7.6, range 10–34) years with epilepsy as compared to 20.5 years for the cohort as a whole. Inclusion of patients with low seizure frequency at baseline in this group may also contribute to poorer response rates. Notably, the majority of patients still experienced a reduction in seizure frequency. Further research is needed as to whether sEEG use may improve response rate.

Mesial temporal sclerosis may represent a slightly more refractory group; however this trend did not reach significance, nor did use of sEEG significantly affect response rate. History of prior VNS also has a trend towards lower response, suggesting this may also be a marker of more-refractory epilepsy. However, this trend did not reach significance, and presence of VNS is less likely to impact decisions regarding sEEG implantation.

5.2. Limitations

This is a small sample size limiting the ability to perform rigorous statistical analysis. Specifically, there is a risk to type I error with regards to poorer outcomes seen in the prior epilepsy surgery subpopulation analysis, and type II statistical error in the sEEG subpopulation analysis, as described above. We were unable to evaluate the confounding effects of continuous variables such as age and years with epilepsy on response rates in our subpopulation analysis, nor were we able to perform analysis of covariance. Our cohort was reasonably representative with respect to age, sex, and epilepsy localization but did not include any patients over the age of 55 nor patients with epilepsy duration <7 years, both of which factors might affect response rates. Our cohort also did not include specific epileptogenic lesions other than MTS and one patient with cortical dysplasia. Additionally, this as a single-center study may not be generalizable to all populations and centers.

Seizure frequency is tabulated by patient self-report, which may be unreliable especially in focal-unaware seizures. As a result, it is possible that some outliers reporting increased seizure frequency following implantation had a higher frequency at baseline which was inadequately captured without strict seizure-diary and RNS correlation. In patients with previous epilepsy surgery and/or VNS, data regarding preoperative seizure frequency and postoperative outcome are inconsistently available, as many patients were previously seen and treated by other centers. Finally, longitudinal data is less robust after 3 years post-implantation.

5.3. Conclusion

The present analysis of a single-center cohort supports the use of RNS in medically refractory epilepsy, with response rates matching or surpassing the original pivotal trial data and subsequent real-world study. Although the present study is limited by small study size, subpopulation analyses are encouraging for reasonable response rates in patients with previous sEEG vs. no sEEG and in mesial temporal vs. extratemporal pathology. It is possible that similar analysis with a larger sample size would reveal statistically significant differences in these groups that could influence management decisions. However, until larger studies are completed to confirm or refute the present findings, this study may be beneficial for other centers of similar volume in reconsidering the necessity of sEEG before RNS placement. Our study suggests additional research is needed to better evaluate the efficacy or limitations of RNS in patients with previous epilepsy surgery, and the relative utility of sEEG in this population. Finally, our study emphasizes the importance of internal review of surgical outcomes in order to better understand treatment failures and to identify trends that may inform future care in this complex population.

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 approval was not required for the studies involving humans because it is a retrospective, observational study without identifiable subject information. The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements because retrospective, observational studies without identifiable subject information fall under exemption 45 CFR 46.104(d)(4) for human subject research regarding informed consent.

Author contributions

MO contributed to analysis and interpretation of data and drafting the manuscript. MS contributed to the acquisition of data for the work, revising the draft critically for important intellectual content, and provided approval for publication of the content. TF contributed to conception and design of the study, completed the

initial data acquisition, analysis, and interpretation, revised the draft critically for important intellectual content, provided final approval for publication of the content, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

Conflict of interest

TF is on the speaker's bureau for NeuroPace, Inc.

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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1240380/full#supplementary-material

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Rehabilitation of cognition and psychosocial well-being – a better life with epilepsy (ReCaP-ABLE): a protocol for a randomized waitlist-controlled trial

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Despite advances in the understanding of cognitive dysfunction among people with epilepsy (PWE), evidence for cognitive rehabilitation in epilepsy (CoRE) remains scarce. We present the protocol of a randomized waitlist-controlled trial (ClinicalTrials.gov ID NCT05934786) of a psychological-behavioral intervention aiming to ameliorate quality of life as well as cognitive functioning in a mixed PWE sample. The study is set at Vilnius University Hospital Santaros Klinikos and will offer adult PWE six individual and two group sessions led by a certified psychologist and directed toward improving memory, attention, self-regulation, mood and quality of life. The trial is expected to address major gaps in the literature by providing novel evidence on the effectiveness of CoRE in patients with genetic generalized epilepsies, the importance of epilepsy-specific factors for the response to CoRE, the impact of CoRE on long-term memory as well as its maintenance effects.

KEYWORDS

epilepsy, neuropsychology, memory, cognitive functions, quality of life, mental health, rehabilitation

1. Introduction

Epilepsy is a multifaceted chronic neurologic disorder that occurs in every hundred individuals and directly affects patients' cognition, quality of life as well as professional and societal activities (1). Because of premature mortality, mental health and socioeconomic implications of this disorder, it is now also recognized as a global public health priority by the World Health Organization (2). Cognitive dysfunction is a major burden for people with epilepsy (PWE) as epilepsy limits their ability to remember, learn, focus, and think. It has been shown that a third of newly diagnosed PWE have subjective cognitive complaints, and up to one half perform worse than controls during objective neuropsychological evaluation (3). Epilepsy can affect various cognitive domains, such as memory or attention, with a possible increase in the level of impairment over time (4). While the problem of prevalent cognitive dysfunction is well-known and may have significant impact on quality of life and social functioning in epilepsy, studies investigating the feasibility and efficacy of cognitive rehabilitation in epilepsy (CoRE)

are rare: just nine group studies were identified in the most recent systematic review (5). Importantly, most were of only moderate quality. The lack of new studies of CoRE is seen as a significant shortcoming of modern epileptology: this neglect is thought to stem from a lack in resources and a historical focus on seizure control rather than cognitive outcomes in the clinical setting (6).

We aim to conduct a novel randomized waitlist-controlled cross-over trial of an original CoRE program, assess its overall efficacity and determine factors associated with a better response to this intervention. The main hypothesis of the trial is that a combined individual and group CoRE program is effective in improving quality of life and verbal as well as visual memory in PWE.

2. Methods and analysis

The study protocol is reported according to the "Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)" recommendations (7, 8). The SPIRIT checklist is provided as Supplementary Table S1.

2.1. Trial registration

The trial was registered at ClinicalTrials.gov as study No. NCT05934786 July 7, 2023. Items of the World Health Organization Trial Registration Data Set are presented in Table 1.

2.2. Study setting

The study will be set a tertiary epilepsy clinic of Vilnius University Hospital Santaros Klinikos (Vilnius, Lithuania) where patient recruitment and neuropsychological evaluation will take place. Patients will undergo CoRE at the Counseling and Training Center of the Faculty of Philosophy of Vilnius University.

2.3. Eligibility criteria

Patient enrolment and clinical evaluation will be done by a certified neurologist and include the following inclusion and exclusion criteria:

Inclusion criteria:

- Active epilepsy (medication for epilepsy and/or had at least one seizure in the past year).
- Adults (≥18 years).
- Lithuanian speakers.
- No intellectual disability.

Exclusion criteria:

- Sensory or motor deficit preventing task completion.
- Epilepsy surgery planned during the project.
- Active non-paroxysmal comorbid disorder of the central nervous system (e.g., neurodegeneration, multiple sclerosis).
- Active psychiatric disorder during the past year.
- Psychoactive substance use (except social alcohol, tobacco and caffeine use).

Patients with temporal lobe epilepsy as well as genetic generalized epilepsy will be enrolled.

2.4. Intervention

The intervention will consist of an eight-week-long psychological-behavioral program with six weekly individual sessions of 60 min followed by two group sessions. The group sessions are also planned to last 60 min and include five to seven PWE. The intervention will include all parts of the Strategies-Outsourcing-Social support toolbox (6) and involve psychoeducation, lifestyle issues, coping strategies, and homework (Box 1). The sessions will be led by certified psychologists, all of them will be trained by one leading specialist to ensure standardization. Patients will participate in group sessions led by the same specialist who provided individual sessions. There are no expected changes or modifications to the structure of the intervention upon its roll-out.

2.5. Outcomes

The primary outcome of the intervention will be measured by its effects (1) on quality of life and (2) memory function.

Changes in quality of life among PWE enrolled in the study will be estimated by comparing scores of the Quality of Life in Epilepsy 31-item inventory (patient weighted version, QOLIE-31-P) that has been validated in Lithuania and is among the most frequently used standardized quality of life assessment tools in PWE (9, 10). By selecting quality of life as the primary endpoint, we intend to detect broader effects of the intervention (i.e., beyond objective cognitive performance) representing direct benefits to participating PWE.

Verbal memory will be assessed by using the Lithuanian equivalent of the Rey Auditory Verbal Learning Test (RAVLT) that consists of five learning trials of a 15-word list A, one learning trial of a word list B and measuring the delayed recall of the word list after 30 min (11). Visual recall at 30 min will be measured by using the Medical College of Georgia (MCG) Complex Figure test for repeated testing (12).

Secondary outcomes will include symptoms of depression (Neurological Disorders Depression Inventory in Epilepsy, NDDI-E) (13, 14), anxiety (General Anxiety Disorder-7, GAD-7) (15) and suicidality (Columbia Suicide Severity Rating Scale, C-SSRS) (16), metacognition (Metacognition Questionnaire-30, MCQ-30) (17, 18), Jacoby's 3-item Stigma Scale (19), antiseizure drug adverse effects (Liverpool Adverse Events Profile, LAEP) (20, 21), health-related quality of life [the Short Form (36) Health Survey] (22) and subjective evaluation of cognitive functions (*ad hoc* Likert scales 0 to 10). Secondary cognitive outcomes will include reaction speed (Trail Making Tests A and B, Maze Task), working memory (Digit Span Test), verbal fluency (categorical and phonemic naming in 60 s), autobiographical memory (naming of recent personal autobiographical events), delayed verbal story recall as well as 1-week verbal recall to test for accelerated long-term forgetting. An

TABLE 1 Items of the World Health Organization Trial Registration Data Set.

Data category	Information
Primary registry and trial identifying number:	ClinicalTrials.gov ID NCT05934786
Date of registration in primary registry	2023-07-07
Secondary identifying numbers	P-MIP-23-333
Source(s) of monetary or material support	Research Council of Lithuania, agreement No P-MIP-23-333
Primary sponsor	Vilnius University (Principal Investigator – Rūta Mameniškienė)
Secondary sponsor(s)	Not applicable
Contact for public queries	Kristijonas Puteikis, kristijonas.puteikis@santa.lt
Contact for scientific queries	Rūta Mameniškienė, ruta.mameniskiene@santa.lt
Public title	Rehabilitation of Cognition and Psychosocial Well-being in Epilepsy
Scientific title	Rehabilitation of Cognition and Psychosocial Well-being – A Better Life with Epilepsy (ReCaP-ABLE): a randomized waitlist-controlled trial
Country of recruitment	Lithuania
Health condition studied	Epilepsy
Intervention	Behavioral: Cognitive rehabilitation Six individual one-hour therapy sessions with certified psychologists followed by two group sessions (a total of two months per patient). The intervention will consist of all parts of the Strategies-Outsourcing-Social support toolbox and include psychoeducation, lifestyle issues, coping strategies and homework.
Key inclusion and exclusion criteria	Inclusion criteria: • Active epilepsy (medication for epilepsy and/or had at least one seizure in the past year). • Adults (≥18 years). • Lithuanian speakers. • No intellectual disability. Exclusion criteria: • Sensory or motor deficit preventing task completion. • Epilepsy surgery planned during the project. • Active non-paroxysmal comorbid disorder of the central nervous system (e.g., neurodegeneration, multiple sclerosis). • Active psychiatric disorder during the past year. • Psychoactive substance use (except social alcohol, tobacco and caffeine use).
Study type	Interventional randomized waitlist-controlled trial
Date of first enrollment	2024-01-01 (Estimated)
Sample size	70
Recruitment status	Not yet recruiting
Primary outcomes	Quality of life (Quality of Life in Epilepsy 31-item patient weighted version, QOLIE-31-P) 4 weeks post-intervention. Delayed verbal recall (Rey Auditory Verbal Learning Test, RAVLT) 4 weeks post-intervention. Delayed visual recall (Medical College of Georgia (MCG) Complex Figure test) 4 weeks post-intervention.
Key secondary outcomes	Symptoms of depression (Neurological Disorders Depression Inventory in Epilepsy, NDDI-E), anxiety (General Anxiety Disorder-7, GAD-7), stigma (Jacoby's 3-item Stigma Scale).
Ethics review	Awaiting approval, Vilnius Regional Biomedical Research Ethics Committee
Completion date	2026-03-31 (estimated)
Summary results	Not applicable
Individual clinical trial participant-level data (IPD) sharing statement	No plan to share IPD

experimental task set to test learning and recall of a hypothetical weekly schedule will also be used (Figure 1). This task was created by the authors and will be explored for applicability in testing for real-world event data, such as memory of where (e.g., in conference room 62B of the office), when (e.g., Monday at 15:30) and for what purpose (e.g., to be present in a business meeting) the participant is hypothetically planning to participate. The task will also include an item about preparatory actions before each activity (e.g., familiarize with material of the meeting in the latter example) and will be scored for each item recalled (maximum of 20 points). Given the exploratory

BOX 1 Outline of the content of the CoRE intervention.

CoRE intervention plan (8 weeks)

1. Individual session.
   - Familiarization.
   - Goal setting. Discussion of the plan.
   - Presentation of the Mind-Emotion-Body connection.
   - Homework.
2. Individual session.
   - Discussion of homework.
   - Thought exercises.
   - Thinking training. Visual memory.
   - Homework.
3. Individual session.
   - Discussion of homework.
   - Body senses. Attention training.
   - Physiology training.
   - Homework.
4. Individual session.
   - Discussion of homework.
   - Working with emotions. Influence of emotions on quality of life and memory.
   - Emotion regulation.
   - Memory training.
   - Homework.
5. Individual session.
   - Discussion of homework.
   - Attention management.
   - Metacognition training.
   - Self-regulation.
   - Homework.
6. Individual session.
   - Discussion of homework.
   - Positive psychology.
   - Strengths and resources.
   - Memory training.
   - Homework.
7. Group session.
   - Discussion of homework.
   - The importance of social support.
   - Creating a circle of support.
   - Attention training.
   - Homework.
8. Group session.
   - Discussion of homework.
   - Compassion for self and others.
   - Memory and quality of life.
   - Homework. Summing up.

General plan of a 60-min session:

- 10 min: presentation of the topic and discussion of homework.
- 20 min: teaching of the topic.
- 20 min: skill building.
- 10 min: reflection. Questions. Homework.

nature of the task, it has not been previously validated and will rely on comparison between early and late intervention groups.

The possible learning effects at post-interventional follow-ups will be mitigated by using three different versions of the same memory tests as well as by comparing memory function in late vs. early intervention groups rather than improved performance in comparison to baseline scores in each subgroup.

Demographic (sex, age, educational and professional status, personal relationship status, socioeconomic status) and clinical (seizure type, epilepsy type, epilepsy etiology, epilepsy duration, seizure frequency, antiseizure medications used, seizure and electroencephalography laterality, localization of seizure focus (if present), handedness, somatic comorbidities) data of each participant will be collected to predefined case report forms.

2.6. Participant recruitment, allocation, and timeline

Study participants will be invited to participate in the trial during routine outpatient visits at the epilepsy clinic. They will have either temporal lobe or genetic generalized epilepsy as confirmed by the epileptologist, according to previously collected clinical (e.g., seizure semiology, patient history), instrumental (e.g., electroencephalography, video-electroencephalography), genetic and imaging (e.g., 3T magnetic resonance imaging) data required to substantiate the diagnosis according to guidelines by the International League Against Epilepsy. After acceptance, each new participant will be randomly assigned to either the early intervention group (EIG) or the late intervention group (LIG) at the time of enrolment by using open-source software for minimization (WinPepi) based on sex, epilepsy type and seizure control. The randomization will be done, and participants assigned to one of the groups by the principal investigator. Outcome assessors and data analysts will be blinded to participant status by using concealed patient coding and instructing patients not to discuss their status during examination. The principal investigator, psychologists performing the intervention and participants themselves will not be blinded.

Both the EIG and the LIG will undergo neuropsychological assessment at three time points (Figure 2). The EIG will be tested at baseline, with two follow-ups four and sixteen weeks after the intervention which itself lasts for eight weeks. The LIG will be tested at the same time points while on waitlist. Participants assigned to the LIG will be offered the intervention after the second follow-up. Both groups will receive otherwise routine clinical care (i.e., according to individual needs and best medical practice) at the tertiary epilepsy clinic. Given the non-invasive nature of the CoRE intervention, no adverse effects are expected. Therefore, discontinuation of the intervention is expected to occur only in the case of participant dropout. Patient attrition will be minimized by thoroughly discussing the aims and procedures of the trial before enrolment as well as by accommodating to the patients' availability and daily schedule for the weekly sessions.

Encoded pseudonymized patient data will be collected by assessors in paper questionnaires and standardized assessment forms to be transferred to Microsoft Excel and saved in a National Open Access Scientific Data Archive Information System ("MIDAS")[1] designed to collect and keep different research data as well as to secure

1 https://www.midas.lt/public-app.html#/apie/about?lang=en

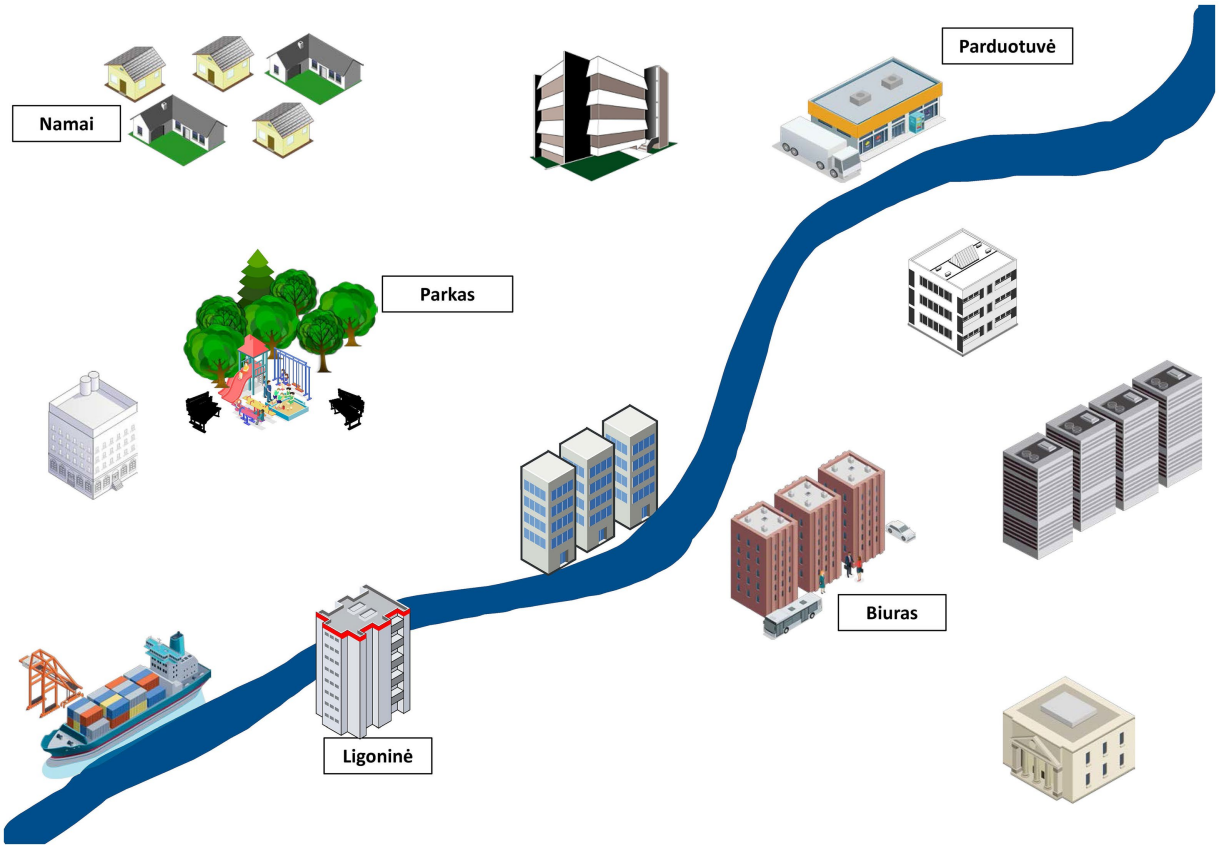

FIGURE 1
An example of a figure used in the experimental memory task. The figure will serve as a learning aid to memorize items of one week's schedule, including place, time, and activity, as they are being read by the investigator. Participants will be asked to recall the same data after 30 min.

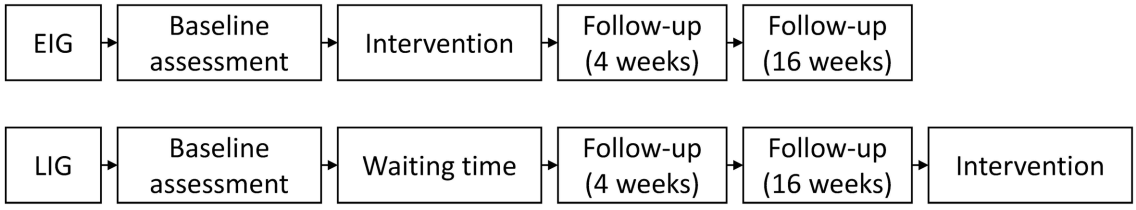

FIGURE 2
Timeline of the neuropsychological assessments and intervention. EIG, early intervention group; LIG, late intervention group.

accessibility of data and information in a digital environment. Data quality will be preserved by checking all data fields for missing values or errors upon completion of assessment. This task will be done by the investigators of the trial without the need for an external data monitoring committee because of the relatively small study sample.

The study is expected to last from January 2024 (start of patient recruitment) to late March 2026 (end of the intervention for the LIG). No interim analyses are planned.

2.7. Sample size and statistical analysis

The target sample size of the study was calculated for a between-group interaction of a two-way repeated measures analysis of variance (ANOVA) with $f = 0.40$, $\alpha = 0.05$, $\beta = 0.95$, two groups (early and late intervention), three measurement points, and 0.5 correlation between repeated measures. The resulting sample size of $n = 58$ (G*Power 3.1.9.7) was increased by 20% to $n = 70$ to account for dropouts (including the possibility of patient referral to presurgical evaluation if needed according to principles of best medical practice) and corresponded well to the mean sample size and attrition rates in previous trials (5). This sample size is deemed achievable as the trial will be conducted in a large university hospital covering tertiary epilepsy care services for approximately 1.4 million of inhabitants and include a group of PWE composed of patients with both TLE and GGE.

The efficacy of the intervention will be defined as statistically significant improvement on one of the primary outcomes (quality of

life or delayed memory), tested with a repeated-measures between-factors analysis of variance (ANOVA) in the EIG as compared to the LIG. For secondary analyses, dynamic changes of other outcome measures will be tested, respectively, by using ANOVA or ANCOVA. The association between demographic and clinical variables with study endpoints will be conducted by means of linear and ordinal regression modeling. Subgroup analyses are planned to be conducted based on sex, education status, professional status, epilepsy type, laterality and lesionality. In case of missing data, multiple imputation will be used in sensitivity analysis.

3. Discussion

This protocol describes a planned randomized waitlist-control trial of CoRE in epilepsy. The study was designed to address major research gaps identified through recent systematic literature reviews in this field, as discussed below (5, 6, 23).

First, the study will include patients with genetic generalized epilepsy (GGE). Most trials examined CoRE by including patients with temporal lobe epilepsy (TLE), often in the context of presurgical evaluation (5, 24–26). As epilepsy surgery is not indicated in GGE, these patients are less frequently tested for neuropsychological deficits and have long been thought to have nearly normal cognitive functions. However, recent studies show frequent cognitive dysfunction in GGE as well (27). Their inclusion is expected to help define the efficacy of CoRE when there is no indication that seizure onset is focal (as is expected in both lesional or non-lesional TLE). While the inclusion of patients with GGE makes the study sample more heterogeneous than if only patients with TLE were enrolled, we believe there will remain opportunities to detect the effects of CoRE on different types of epilepsy through subgroup analysis in case of a large effect size.

Second, we are planning to investigate epilepsy-associated factors in response to cognitive rehabilitation beyond seizure laterality. Only two of the previous trials examined the impact of background patient epilepsy-related variables (e.g., seizure frequency, polytherapy, epilepsy onset time) on the efficacy of CoRE (5, 26, 28). This information will be gathered through standardized patient forms and included in secondary analyses.

Our project also includes novel measures of cognitive assessment. Baseline and follow-up assessments will consist of both traditional and experimental neuropsychological tools. While traditional instruments will ensure the comparability of the results with previous studies, novel tools will be essential to address the need to train and test ecologically valid everyday cognitive functions. We selected to test memory of a week's schedule of daily activities – the task is expected to depend on attention, short-term visual and verbal memory as well as associative learning and transfer effects. Furthermore, we envision evaluating patients for accelerated long-term forgetting – to the best of our knowledge, the effects of CoRE on long-term memory deficits have not been investigated in earlier studies (29).

Moreover, the assessment we suggest includes testing for mental health status, metacognition and quality of life in addition to objective cognitive performance. The psychosocial status of the patient will be evaluated to adjust for subclinical levels of anxiety and depression as well as to see whether CoRE may improve patient mental health. Moreover, we will also investigate suicidality – this part of the evaluation is rarely done in the clinical setting and is especially important in Lithuania, which has extremely high suicide rates (14). Patients will also complete a metacognition questionnaire – a relatively novel tool in PWE set to assess coping and thinking mechanisms that underlie self-regulation in psychopathology and may help to explain better response to CoRE (17, 18). Finally, patient-oriented outcome measures (i.e., quality of life) will be essential to define the overall impact of the CoRE program (30, 31).

To increase the likelihood of the efficacy of the tested intervention, it will be done by following the S.O.S. toolbox: Strategies (internal and external), Outsourcing (use of physical and digital media) and Social support (education and co-operation) (6, 32). The intervention includes elements of psychoeducation mindfulness, positive psychology and acquires intensity from weekly homework that makes the program a continuous process that is not limited to the sessions themselves. The intervention will combine compensatory and restitution techniques alongside focus on general mental well-being and self-regulation. Because of such a varied inventory within the CoRE program, we expect it to have transfer effects for domains that will not be trained directly (e.g., long-term memory) (28).

Finally, our trial includes a longer follow-up period: while most previous studies had a limited follow-up period of 12 weeks, our timeline will include a follow-up of 16 weeks and provide a better estimate of the maintenance effects of CoRE (5).

4. Limitations

Despite the advantages of the planned study mentioned above, some of its limitations should be considered as well. First, the study will be of a single-country and single-center design, imposing boundaries on the sample size, generalizability of the study findings as well as the application of the intervention in different socioeconomic and cultural backgrounds. Second, the PWE group is expected to be heterogeneous in epilepsy type. This limitation will be addressed through subgroup and adjusted analyses. Third, the intervention will be focused on improving cognitive strategies rather than directly training selected cognitive domains. This may decrease the perceived effectiveness of the CoRE program on objective cognitive functioning as the effects of near transfer in such rehabilitation remain unknown. Finally, despite a longer follow-up than in other studies, the understanding of any emerging maintenance effects will remain limited to a relatively short period of 4 months.

5. Dissemination

Open access publishing of the study results will be given priority. The raw anonymized dataset is planned to be made available after publishing the results of the study upon reasonable request by third parties. The key to decode pseudonymized data will be available only to the principal investigator in physical format. Study results will also be disseminated through meetings with policy makers as well as in plain language articles in patient community websites and public press.

6. Conclusion

In this protocol we outlined a plan to conduct a randomized waitlist-controlled trial exploring the effects of a

psychological-behavioral cognitive rehabilitation program on the quality of life and memory function in adults with epilepsy. This trial is an attempt to demonstrate feasibility and test the effectiveness of CoRE in a mixed PWE sample as well as to provide additional evidence about the target population for CoRE and the determinants of its effects. We believe that such an initiative will help further translate the experience that has emerged from neuropsychological evaluation in epilepsy to non-invasive add-on rehabilitation programs addressing burdensome cognitive issues among PWE.

Ethics statement

Ethical review and approval for the study is sought from the Vilnius Regional Bioethics Committee that is overseeing all biomedical studies conducted in the Vilnius region. The Committee is responsible for the independent supervision of research conduct. The trial may also be subject to internal auditing by the administration of Vilnius University Hospital Santaros Klinikos. The study will be conducted with respect to the principles of the World Medical Association Declaration of Helsinki and each participant will provide written informed consent upon enrolment.

Author contributions

KP: Conceptualization, Methodology, Visualization, Writing – original draft, Data curation, Formal analysis, Validation. AsJ: Methodology, Writing – review & editing. ArJ: Conceptualization, Methodology, Writing – review & editing. PW: Supervision, Writing – review & editing. RM: Conceptualization, Methodology, Visualization, Writing – original draft, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The 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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Supplementary material

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Ultrasonic therapies for seizures and drug-resistant epilepsy

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Ultrasonic therapy is an increasingly promising approach for the treatment of seizures and drug-resistant epilepsy (DRE). Therapeutic focused ultrasound (FUS) uses thermal or nonthermal energy to either ablate neural tissue or modulate neural activity through high- or low-intensity FUS (HIFU, LIFU), respectively. Both HIFU and LIFU approaches have been investigated for reducing seizure activity in DRE, and additional FUS applications include disrupting the blood–brain barrier in the presence of microbubbles for targeted-drug delivery to the seizure foci. Here, we review the preclinical and clinical studies that have used FUS to treat seizures. Additionally, we review effective FUS parameters and consider limitations and future directions of FUS with respect to the treatment of DRE. While detailed studies to optimize FUS applications are ongoing, FUS has established itself as a potential noninvasive alternative for the treatment of DRE and other neurological disorders.

KEYWORDS

focused ultrasound, drug-resistant epilepsy, seizures, therapeutic ultrasound, animal models of epilepsy, clinical epilepsy research, high-intensity focused ultrasound, low-intensity focused ultrasound

1 Introduction

Epilepsy is a common and costly neurological disorder. Epilepsy is characterized by recurrent spontaneous seizures and affects one out of 26 people worldwide (1). While this is a worldwide disorder, using the Unites States as an example, there are approximately 150,000 new cases of epilepsy per year in the United States, and epilepsy has been estimated to directly and indirectly cost $54 billion a year in the United States if one assumes that 3.4 million people in the US have epilepsy (2–5). Patients with drug-resistant epilepsy (DRE) make up 80% of this cost (2, 6). Therefore, other less invasive therapies for DRE are a critical unmet medical need.

Approximately 30–40% of people with DRE could respond to a more invasive treatment intervention, such as tissue resection surgery or deep brain stimulation, to achieve meaningful reductions in seizures (7–9). Invasive tissue resection surgery to remove the seizure-generating focus is often a successful line of therapy for people with DRE, with at least 50% of people undergoing surgical treatment reaching seizure freedom (10, 11). However, less than 1.5% of people with DRE currently receive this therapy (8, 12). Various barriers prevent or discourage people from undergoing invasive surgery for epilepsy, such as the distribution of information to healthcare providers about the therapy, patient hesitancy, time of recovery, and fear of invasive surgery (3, 11, 13–15). Thus, we need additional, less invasive interventions for people with DRE. The different therapeutic focused ultrasound (FUS) modalities discussed in this review

may be that promising intervention. More specifically, high-intensity focused ultrasound (HIFU), discussed in more detail below, can be a direct replacement for tissue resection surgery that eliminates some of the barriers listed previously.

FUS is advantageous over other techniques. Surgical techniques, such as radiofrequency thermocoagulation and laser interstitial thermotherapy involve passing a probe through normal brain parenchyma through a burr hole drilled in the skull and are not truly noninvasive whereas, FUS, is completely noninvasive in humans (13). Additionally, deep brain stimulation and transcranial magnetic stimulation are comparable modalities to LIFU but are either invasive or are not spatially specific and do not target subcortical structures, respectively (16). Therefore, this suggests that FUS may be a leading alternative for noninvasive surgery and neuromodulation therapy, especially when there is a need for focal and subcortical targets.

FUS is a noninvasive brain stimulation approach that uses energy in the form of acoustic waves above the range of human hearing to target a focal area in the brain (15). FUS therapies are discussed in terms of the type of energy or general intensity (power delivered over the tissue area) delivered at the target (17). Currently, the two main modalities of FUS in experimental use are HIFU and low-intensity focused ultrasound (LIFU) (18). HIFU uses thermal energy with high intensity (>200 W/cm^2), and LIFU uses nonthermal energy with low intensity (<100 W/cm^2) to affect brain tissue and activity (19).

HIFU holds tremendous potential for people with DRE over invasive surgical options, such as laser interstitial thermal therapy, as it does not involve opening the skull (13). LIFU is advantageous over other noninvasive neurological treatments, such as transcranial magnetic stimulation, because of its greater spatial resolution at depth and can stimulate deep brain areas such as the amygdala and hippocampus (15, 19, 20). Therefore, HIFU and LIFU have increased advantages over other technologies when targeting small and deep brain structures.

2 Current studies of HIFU and LIFU demonstrate seizure suppression

2.1 HIFU has shown promise for seizure modulation in human studies

HIFU has shown promise for decades in seizure suppression. In the 1960s, researchers used ultrasound lesioning on cats ($n = 12$) induced with seizures by alumina crema to target either the middle suprasylvian gyrus or anterior sigmoid gyrus (21). Ultrasound lesioning resulted in 82% of the animals reaching seizure freedom 12 weeks post-HIFU (21). Today, magnetic resonance imaging (MRI)-guided FUS (MRgFUS) is a HIFU-approved approach by the United States Food and Drug Administration (FDA) for treating essential tremor and Parkinson's disease (19). The procedure intentionally delivers enough ultrasound to thermally ablate the target region in the thalamus (22). Magnetic resonance guidance (MR-guidance) is used to accurately visualize brain regions while also monitoring the temperature, in real-time, for ablation of the targeted brain region (22). The advantages of MR-guidance make MRgFUS a great noninvasive surgical alternative for patients with DRE. Originally, MRgFUS studies have included studies from non-epileptic human skull with tissue-gel phantoms to demonstrate the possibility of MRgFUS treatment on humans, as limitations of MRgFUS procedures may include increased skull heating (22, 23). Monteith et al. showed that by using the ExAblate Neuro® phased-array system from Insightec, a 30-seconds sonication duration rather than a 10-s sonication duration achieved irreversible lesions in patients with temporal lobe epilepsy (TLE) (23). However, the longer sonication duration of 30 s also generated skull heating (23). Abe et al. were one of the first groups to investigate the treatment for people with DRE with mesial TLE using MRgFUS in humans (24). This group targeted the hippocampus with 12 sonications of 10–12 s duration in one subject to determine safety and efficacy (24). While the procedure did not produce an observable lesion, the patient remained relatively seizure-free for 12 months following the MRgFUS procedure (24). While the patient did report dizziness and headaches during the actual HIFU procedure, no other adverse events were demonstrated (24). However, this study had other limitations, such as a short follow-up period, sub-ablation temperatures below the minimum of 50°C, lack of a discernible lesion, limited sample size, and lack of a control group (24). Another case report of MRgFUS in DRE was recently described for a patient with a hypothalamic hamartoma (25). While this patient was seizure-free one-year post-MRgFUS removal of the hamartoma, the study's main limitation was that it was a case report with a single patient (25).

The main benefit of MRgFUS for people with DRE, especially TLE, is that now smaller and deeper brain areas, such as the fornix, can be targets, especially when comparing against the current standard of resective surgical treatment, which is a temporal lobectomy (26). MRgFUS has recently been used for DRE to ablate the anterior nucleus of the thalamus in a Phase-1 open-label study in two people with DRE (27). While the primary outcome was safety, a secondary outcome was seizure frequency (27). Safety was based on neuropsychological assessments evaluating language, memory, executive functioning, motor skills, emotional functioning, and quality of life (27). The study had two patients who experienced verbal and attention/working memory issues at the three points of the 12-month follow-up following the procedure; therefore, safety is inconclusive in this study as it could also relate to the lesion's size or site (27). One of the patients was seizure-free for at least a year, while the other benefitted from a dramatic decrease in seizures from an average of 90–100 seizures per month to around 3–6 seizures per month (27). While open-label studies with small patient numbers have limitations, these preliminary results are encouraging and support the need for additional studies. There are three ongoing clinical trials with MRgFUS for patients with DRE, specifically focal epilepsy. There is one study targeting the epilepsy foci (NCT02804230) in people with DRE that is currently recruiting. There are two studies targeting the anterior nucleus of the thalamus. One of those studies is recruiting (NCT03417297). The second of those studies (NCT05032105) is not yet recruiting but only offers the trial to people with DRE who are comorbid with anxiety. It is exciting that MRgFUS trials are underway for a much-needed patient group, and it will certainly be interesting to see the effects of MRgFUS on varying targets and disease states. These three clinical trials evaluating the effect of HIFU ablation for people with DRE are summarized in Supplementary Table S1, whereas Supplementary Table S2 includes published work on HIFU lesioning in people with DRE.

2.2 LIFU has shown promise for seizure modulation in animal studies

LIFU has been used in animal and human studies to affect neural activity and has been shown to suppress electrographic seizure activity (28–37). However, as seen in Supplementary Table S2, which describes the studies in terms of FUS parameters, animal models used, and stimulation targets, most animal studies were conducted in evoked seizure models and not in a chronic disease model of epilepsy (28–32, 34–37). Conducting these studies in an evoked seizure model is the main limiting factor to these studies. There continues to be a need for more studies in animal models of epilepsy to understand the FUS parameters that affect the disease state. In a recent study from 2020, LIFU suppressed seizures in a penicillin-induced nonhuman primate seizure model through stimulation of the prefrontal motor cortex with numerous FUS stimulation parameters (37). The FUS parameters that reduced the number, duration, and frequency of seizures and increased the inter-seizure interval duration for 7 h post-FUS were an ultrasound frequency of 800 kHz, a pulse repetition frequency (PRF) of 500 Hz, a duty cycle of 36%, an intensity of 1 MPa, and a stimulation duration of 15 min (37). These effects were not seen when using a 750 kHz frequency with 5-, 30-, or 60-min FUS duration (37). Limitations in this study included a small sample size of two and using an induced seizure model rather than a chronic disease model of epilepsy (37). Additionally, the lack of sufficient information regarding their sham protocol to understand if the auditory artifact (discussed in the "*Limitations of focused ultrasound for the treatment of epilepsy*" section below), which occurs as a consequence of activating the auditory network via vibrations across the skull from LIFU stimulation, was controlled for properly was another limitation (37). Another recent study using a penicillin-induced nonhuman primate seizure model used a single-element transducer, an ultrasound frequency of 750 kHz, a PRF of 1 kHz, a duty cycle of 30%, an intensity of 0.35 MPa, and a stimulation duration of 30 min (38). A histological study was performed on one nonhuman primate 30 min post-FUS stimulation, and the tissue was found to be intact; therefore, LIFU was deemed to be a safe treatment (38). Additionally, a significant reduction in seizure count and seizure frequency per hour was seen 8 h post-FUS (38). However, this study lacked both a control that rules out the auditory artifact as the potential reason for the effect seen and the use of a chronic disease model (38). Nevertheless, these nonhuman primate studies were important in showing the safety and efficacy of using LIFU for seizure suppression, even though they did not use a chronic disease model of epilepsy.

There has been more research in rodent models of seizures or epilepsy with LIFU than in nonhuman primates. One of the first studies of LIFU stimulation in rodents was in 2011 (32). This study noted a suppression in the number of epileptic bursts and theta band peaks in a rat pentylenetetrazol (PTZ) model of seizures (32). This study used a single-element transducer, a frequency of 690 kHz, a PRF of 100 kHz, and a stimulation duration of 36 min (32). They did not use a control for a potential auditory artifact, and their results cannot be interpreted as only being attributed to a targeted neuromodulation effect (32). Additionally, they did not use a chronic disease model (32). A group in 2015 was one of the first to study LIFU in a chronic mouse model of epilepsy (29). They studied the effects of LIFU on seizures induced by hippocampal infusion of KA and later saw a reduction in spontaneous recurrent seizure activity and improved behavioral measures in the animals that received LIFU (29). This group used a single-element transducer, a frequency of 200 kHz, a PRF of 0.5 kHz, a duty cycle of 50%, and a stimulation duration of 30 s per seizure (29). They noted a decrease in seizures and improved performance in behavioral tasks during the chronic period of epilepsy (29). While this 2015 study used a chronic disease model, they did not use a control for the auditory artifact, and thus, the auditory artifact cannot be ruled out as the reason for the LIFU's effects (29). A major study in the area of LIFU for DRE using rodents was from a 2020 study, which investigated six different FUS stimulation parameters on seizure suppression (28). This study used a single-element transducer, a frequency of 500 kHz, a PRF of 0.1 kHz, a duty cycle of 0, 3, or 0.8%, and stimulation durations of 0 s, 600 s, or 100 s (28). The higher duty cycle and longer stimulation durations saw a correlation between the safety parameter, Mechanical Index (discussed in the *FUS parameters used and FDA safety guidelines* section below), and spike suppression (28). Additionally, FUS stimulation parameters showed a decreased activation of the mTOR pathway (28). Again, this study did not use a chronic disease model and did not control for the auditory artifact (28). A group recently studied the effect of LIFU on brain connectivity in a kainic acid (KA) intraperitoneal (i.p.) injection rat model (36). Using a single-element transducer, a frequency of 500 kHz, a PRF of 1.5 kHz, and a duty cycle of 50%, the group showed that the brain network connection strength was significantly decreased using measurements of the path length and local and global efficiency among their indicators (36). They also observed that FUS stimulation caused the power in the delta and theta bands to decrease (36). While these are important findings of LIFU on brain connectivity and activity, the study did not include the use of multiple FUS parameters and their findings were in an acute seizure-induced model (36). Additionally, when looking at the characterizations of the pressure field and the intended target, the hippocampus, the ultrasound targeted more than just the hippocampus (36). When studies use rodents, the stimulation areas tend to be larger than the intended target, and this can be hard to discern the impact on just the targeted area. In another study, this group investigated the use of both pulsed and continuous LIFU modes using a single-element transducer, a frequency of 500 kHz, a PRF of 1.5 kHz, and a stimulation duration of 40 min (39). Using an i.p. injection of kainic acid (KA) to induce seizures in rats, this group found that the power in the delta, theta, and alpha bands decreased significantly because of LIFU (39). However, while this decrease was seen after stimulation, there was no significance between the two different pulsing modes, and they did not control for the auditory artifact (39). Power in the delta, theta, and alpha bands decreased during FUS in a model of epilepsy is an interesting finding to begin to discern the direct effect of FUS on brain activity. However, this study was deficient in testing additional FUS parameters and studying the effects in a chronic disease model. More recently, in 2022, research in the intrahippocampal kainate mouse model of TLE, targeting LIFU to the hippocampus that was contralateral to KA injection showed a short-lasting decrease in the occurrence of spikes (40). This decrease in hippocampal spikes suggests that there could be the potential to suppress seizures using a custom fiber photometry coupled focused ultrasound system (40). Besides some clear limitations of controlling for the auditory artifact, stimulating more than the target, studying effects in a seizure model, and needing a stimulation parameter study on a chronic disease model, these studies show clear effects of LIFU stimulation on seizure suppression in rodents.

Aside from rodent studies, human studies have been performed with LIFU stimulation. However, there are very few human studies that have been done with LIFU stimulation in DRE. One of the first studies in 2021 assessed FUS for TLE for safety (33). This team used the BX Pulsar transducer with a frequency of 650 kHz, a PRF of 0.25 or 0.1 kHz, a duty cycle of 50% or 5%, a stimulation duration of 8 × 0.5 s or 2 × 30 s on eight patients (33). Using histological testing, the tissue post-FUS, which was removed post-resection surgery, was not destroyed and, thus, deemed safe for stimulation in humans (33). As this was a study performed on patients receiving tissue resection surgery for the treatment of DRE, there was no long-term follow-up and future work investigating the long-term impact of LIFU on the treatment of seizures is warranted (33). A clinical study, (NCT03860298) published in 2022, assessed the safety of a LIFU device and the effect of FUS on seizures (41). They used the NaviFus™ multi-phased array system to stimulate six patients at the seizure onset zone, with a duty cycle of 30% and a stimulation duration of 30 min, showing various effects on seizures and the frequency of EEG waves (41). In one-third of the patients, a decrease in seizures and a greater decline in power of the theta, alpha, and beta bands over multiple sessions were seen (41). However, one-sixth of the patients saw an increase in seizures, whereas one-third saw an increase in interictal spikes (41). The study was not without its limitations, as the follow-up period was brief, just 72 h, and adverse events included scalp heating and transient naming and memory problems (41). However, these adverse events resolved after a few weeks (41). Following this safety study, this team is performing another clinical trial (NCT04999046) using the NaviFUS™ system, which allows for an in-office treatment with a neuronavigational system (41). They are studying the effects of FUS stimulation on people with DRE over a two-month follow-up period, with outcomes including seizure frequency, anxiety, and depression effects measured by self-report metrics. The limitations here involve using self-report metrics as the main measured outcome in the study. However, nonetheless, this is an important step forward in understanding a potential treatment for DRE. Aside from using a commercial device, another research group has developed their own experimental LIFU setup for stimulating people with DRE (42). In a clinical study (NCT03868293), they used a single-element transducer, a frequency of 548 kHz, a PRF of 0.5 kHz, a duty cycle between 36 and 50%, and a stimulation duration of 140 s per target (42). They have targeted the hippocampus in one patient with TLE and have not experienced adverse events (e.g., scalp heating) (42). The effects on seizure modulation are still being studied and have not yet been published. Skull shape and size can affect targeting and skull heating during FUS and having a small sample size like this study limits the understanding of these potential effects from the setup on a general patient group. This study shows the promise of using non-commercial setups, which can be costly, in a research setting. Additional clinical trials are summarized in Supplementary Table S1 of LIFU for DRE.

As shown, there is a general trend of more studies involving LIFU for DRE than any other FUS therapies for DRE, and there are various effects depending on the FUS stimulation parameters used. Therefore, further studies are needed to investigate the effects of FUS stimulation parameters in the chronic disease state. Clinical trials evaluating the effect of LIFU for DRE are summarized in Supplementary Table S1. Supplementary Table S2 summarizes the published work discussed here and additional works, beyond the scope of the present review, on LIFU stimulation for DRE. While both HIFU and LIFU show promising results in current studies for seizure suppression, much work is needed to determine which FUS parameters result in optimal seizure suppression.

3 Targeted-drug delivery with ultrasound as a potential therapy for DRE

HIFU and LIFU are not the only ultrasound therapies for DRE. Using ultrasound to target drug treatments to specific seizure-generating brain areas could limit systemic side effects of antiseizure medications (ASMs). Additionally, this ultrasound therapy can provide new drug therapy options for classes of pharmaceuticals that cannot cross the blood–brain barrier (BBB). Targeted-drug delivery is done primarily in two ways. The first approach disrupts the BBB in precise locations due to targeted LIFU with the use of microbubbles. This microbubble approach allows previously impermeable molecules to pass through the BBB at or near the seizure foci. The second approach uses FUS to target the uncaging of lipophilic agents (e.g., propofol) from nanoparticles without using intravenous microbubbles in precise anatomical locations (43, 44).

BBB opening through the pressure of ultrasound in the presence of microbubbles is currently being explored for clinical application and has shown to transiently open the BBB for 24–72 h (44, 45). Microbubbles, approved by the FDA for use as a contrast agent for diagnostic imaging ultrasound, are gas bubbles less than 5-micron diameter in size (44, 45). Microbubbles are now being investigated for therapeutic purposes by reversibly opening the blood–brain barrier through cavitation from the alternating pressure applied from ultrasound (44, 45). Microbubbles are injected intravenously, and once circulated, LIFU can stimulate the targeted area in the brain with peak pressures between 0.1 and 0.6 MPa, depending on the microbubble sizes, and with frequencies typically around 0.25 MHz (44, 45). Molecules unable to pass through the BBB previously can enter the brain where the BBB is transiently opened at the area where cavitation occurred in the membrane from microbubbles and LIFU stimulation (44). Thus, this targeted-drug delivery approach provides therapy in a localized manner in specific brain regions (44). The research in FUS-mediated BBB opening with microbubbles has shown that it may be a potential application and adapted for humans with DRE as it has been safely used in patients with other neurological disorders targeting the hippocampus and prefrontal cortex (44, 45). However, as discussed thoroughly in the review by Konofagou et al. (44) ultrasound procedures and pressures need to be within the researched parameters that can knowingly avoid unwanted cavitation or damage to blood vessels.

As mentioned above, LIFU can also be paired with a drug carrier such as nanoparticles (43). Nanoparticles have a diameter on the scale of less than 100 nm and have shells made of perfluorocarbon with a gas or liquid core that can cage lipophilic drugs of choice (43, 46, 47). Nanoparticles can be intravenously delivered, and LIFU can transiently and locally target drug delivery directly to a specific brain area (43, 44). However, there are limitations to this method. When intravenously delivered, researchers have found that not all of the drug is delivered locally, and the encapsulations used to deliver the drug across the BBB may be toxic (44). Additionally, this is a costly technique to study (44).

Nonetheless, targeted-drug delivery with FUS and nanoparticles is an important technique to mention as it could provide relief for people with DRE. This technique has been used to disrupt seizure activity in the PTZ-induced seizure rat model (43). This study disrupted seizure activity after delivering propofol-loaded nanoparticles for two 60-s sessions at a maximum peak amplitude of 1.5 MPa using MR-guided LIFU (43). With this same paradigm, mean broadband and theta power declined significantly (43). Furthermore, propofol concentrations showed no increase in the serum level when measured for 10 min post-FUS (43). Blood serum levels that show no increase in the drug concentration post-FUS indicate that with propofol encapsulations and LIFU stimulation, there may be a potential to overcome the method limitation mentioned in the previous paragraph that all of the drug may not be delivered locally (43). Interestingly, a group using a pilocarpine-induced model of epilepsy used LIFU to open the BBB with MR-guidance to deliver quinolinic acid to create lesions in the brain at the hippocampus (48). Even though this is a lesion approach, it is discussed here as they use the targeted-drug technique and LIFU stimulation (48). They reduced the frequency of seizures in mice ($n = 11$) by an average of 21.2%. However, the seizure frequency varied as a function of the areas of neuronal loss, which is summarized in Supplementary Table S2 (48). Key findings showed that bilateral damage to the septal hippocampus increased seizure frequency, while those without bilateral damage to the septal hippocampus and with damage only in the intermediate hippocampus decreased seizure frequency following a 30-day post-FUS period (48). Additionally, an animal which did not have a complete lesion (neuronal loss) showed increased seizure frequency (48). This group used a phased-array system, a 1.5 MHz frequency, a PRF of 0.001 kHz, a duty cycle of 2%, and a stimulation duration of 120 s with multiple sonications (48). The limitation of this study is that even with MR-guidance, there can be incomplete lesions. This same group repeated a similar experiment in the pilocarpine-induced rat model of epilepsy (49). The FUS parameters were similar, apart from using a 650 kHz frequency and a 90-s stimulation duration when targeting the hippocampus (49). Again, this group used quinolinic acid to induce lesions (49). They noticed a general decrease in the number of seizures in the FUS-treated groups, and one-third of these rats did not have convulsive seizures during the 30-day follow-up period (49). While targeted-drug delivery has shown promise in rodent models of epilepsy to modulate seizures, this methodology needs to be studied in humans with DRE, and further study of drugs to encage that could be delivered locally is needed. Targeted-drug delivery with ultrasound is a promising opportunity for people with DRE.

4 FUS parameters used and FDA safety guidelines

When designing experimental and clinical studies with FUS, it is important to consider the FUS parameters to be used and to follow safety guidelines to prevent unwanted tissue damage or side effects (50). Unwanted effects, such as cavitation and tissue heating, are supposed to be limited by using the FDA safety parameters; however, other effects, such as undesired behavioral changes, can still occur (51). Interestingly, current safety parameters for therapeutic FUS are based on the FDA guidelines for diagnostic imaging-based ultrasound and are not based on treatment/therapeutic applications for the brain (19, 50, 52). Additionally, diagnostic ultrasound is generally performed at a lower power than therapeutic ultrasound in the brain (53). Furthermore, diagnostic ultrasound involves pulsing sonication for a very brief duration with a frequency greater than or equal to 5 MHz, which varies from the transcranial sub-MHz frequency (53). Thus, optimal stimulation parameters for transcranial applications may be difficult to discern as FDA guidelines use diagnostic ultrasound criteria (19, 50, 52).

The four acoustic factors that are included in the FDA safety guidelines for diagnostic ultrasound are: (1) spatial-peak temporal-average intensity (I_{SPTA}); (2) spatial-peak pulse-average intensity (I_{SPPA}); (3) mechanical index (MI); and (4) thermal index (TI) (51). I_{SPTA} and I_{SPPA} are in units of W/cm^2 (19). The safety parameters detail the maximum allowed intensity delivered to the tissue (19). The upper limit set forth by the FDA for these sonication parameters, when applicable, is displayed in Table 1 (19). However, these maximum limits for the parameters are set for the ultrasound focus (the convergence of ultrasound beams at the brain target) (50, 53). These limits can be less than what is needed for neuromodulation FUS, even though it is stimulating at a higher power but at a lower frequency than diagnostic ultrasound (50, 53). These parameters are currently being researched for LIFU to determine efficacious treatment at the maximum intensity levels before unwanted side effects occur in LIFU stimulation (19, 52, 54).

In addition to safety (maximum intensity output) for therapeutic ultrasound, some other FUS parameters, mostly for LIFU, are a current focus of investigation for optimizing the neural effect desired (e.g., inhibitory neuronal response, excitatory neuronal response, transient response, permanent) at the target while minimizing the size of the ultrasound focus (50, 52, 55–57). The FUS field has various terms for some of the same parameters and there are no strict criteria for reporting parameters used in a study (50). Therefore, it is important to understand each stimulation parameter and the effect different stimulation parameters have had in the varying brain regions when designing protocols to achieve the desired purpose. A summary of the safety parameters, commonly used stimulation parameters, common terms for parameters, if applicable, the FDA limits, and the relevance to the type of therapeutic FUS is shown in Table 1 (50, 51).

When designing pulsing protocols for the FDA-approved application of HIFU, the most important parameter is the peak temperature to create a lesion in the tissue, which occurs around 55–60°C (22). Peak temperature cannot directly be controlled, but both sonication duration and power independent of each other have shown to increase peak temperature by increasing (58, 59). The size of the lesion is another important characteristic, which is routinely evaluated using magnetic resonance thermal imaging throughout and following the procedure, with the desired size of most lesions being in the range of a few millimeters (mm) (22). Additionally, the sonication duration can be adjusted to affect the lesion (22). FUS parameters, besides safety, play an important role in governing the desired outcome.

For LIFU pulsing protocols, most procedures are currently performed at low pressures (less than 0.6 MPa) at the ultrasound focus. However, some studies have used stimulation protocols above 1 MPa for seizure suppression (37). LIFU pulse durations are usually less than or equal to 300 milliseconds (53). The increase in temperature with these parameters is small - only an increase of less than or equal to 0.01°C has been recorded (53). LIFU generally has a pulsing protocol with longer durations during the stimulation session than

TABLE 1 Safety and common parameters of FUS.

Definitions	FUS parameter definitions	Commonly used terms	FDA limits	HIFU or LIFU
Spatial-peak temporal-average intensity (I_{SPTA})	Average intensity of the FUS waveform over sonication duration	Not applicable (NA)	720 mW/cm^2 (51)	LIFU
Mechanical index (MI)	Peak negative pressure at focus divided by the square root of the fundamental frequency	NA	1.9 (51)	LIFU
Thermal index	Acoustic power is divided by the acoustic power required to achieve a 1°C temperature increase for a given tissue	NA	6 (51)	LIFU
Spatial-peak pulse-average intensity (I_{SPPA})	Average intensity of the FUS waveform over pulse duration	NA	190 W/cm^2 (51)	LIFU
Fundamental frequency	Frequency of the ultrasound transducer	Frequency, FUS frequency, carrier frequency, transducer frequency	NA	Both
Pulse repetition frequency (PRF)	Number of FUS pulses that occur within 1 s of stimulation	Reciprocal of the pulse repetition interval (PRI)	NA	LIFU
Pulse duration (PD)	The time of a single pulse, generally in milliseconds	Pulse width	NA	LIFU
Duty cycle (DC)	Percentage showing how often during sonication duration the FUS signal is on	Can calculate using PD * PRF * 100%	NA	LIFU
Temperature at focus	The temperature at the focus is due to HIFU stimulation	Focal temperature, max temperature	NA	HIFU
Thermal dose	Temperature at focus over a defined period of time	NA	NA	HIFU
Session duration	How long the subject is stimulated with the given ultrasound parameters	Sonication duration, stimulation duration, experimental time	NA	Both

FDA limits are included for the safety parameters. Commonly used terms for the same parameter are displayed. Additionally, the usage of each parameter for the different therapeutic types of FUS is displayed.

HIFU, on the scale of minutes over seconds (53). Generally, an increase in the time of LIFU stimulation increases the behavior response seen (53). Individual pulse length and the stimulation duration for a session are important considerations when determining a pulsing protocol for the desired outcome.

Fundamental frequency (transducer frequency) can determine the spatial length of the ultrasound focus and can impact the effectiveness of the FUS stimulation (53). Generally, the fundamental frequency is below the MHz range (53). For pulsing protocols and focal areas of several millimeters in humans, a typical frequency is between 250 and 500 kHz for LIFU (53). Having a shorter wavelength creates a sharper spatial focus with a higher frequency (53). Lower frequencies tend to penetrate through the skull more effectively than higher frequencies. FUS parameters are important in designing studies, ensuring the desired outcome, and translating findings to the clinic.

5 Limitations of focused ultrasound for the treatment of epilepsy

FUS holds tremendous promise for DRE. However, a few major limitations noted above and discussed here, mostly for LIFU, need to be considered before executing a FUS protocol. The benefit of FUS, both HIFU, and LIFU, is that the depth penetration allows the device to stimulate subcortical structures and has a small spatial resolution (~3 mm) when compared to other noninvasive devices, such as transcranial magnetic stimulation (52, 60, 61). However, the skull creates a barrier for the ultrasonic waves (60, 61). The impedance from the skull causes ultrasonic wave attenuation, refraction, and dispersion, which creates an unknown delivered dose of intensity at the focus (61). Investigators in the field of FUS are actively working to correct for the attenuation of intensity created by the skull through computational methods that correct for the intended dose at the target tissue and develop new devices that compensate for different skull thicknesses between subjects (62, 63).

LIFU has been shown to modulate neural activity; however, it has also been shown to stimulate the auditory network (40, 64, 65). Activating the cochlear pathway of the auditory network by vibrations across the skull that occur during LIFU stimulation is called an "auditory artifact" (64–67). Several approaches have been used to control for this artifact. The auditory artifact can be corrected following transection of the auditory nerves or removal of the cochlear fluid, utilizing an envelope for the

ultrasonic waveform pulse regime to minimize abrupt pulsing transition, and/or stimulation at an off-target brain area (40, 64, 66–68). Besides work by Murphy et al. (40), groups that have researched FUS application in evoked seizure or epilepsy preclinical models have either not or inadequately controlled for this artifact (28–30, 32, 34, 36, 38, 40, 69). Thus, there is a need for careful interpretation of the findings and properly controlled experiments before concluding that targeted LIFU is sufficient to modulate seizure activity.

6 Future directions for FUS therapy for DRE

While HIFU is FDA-approved to treat movement disorders, preclinical models of epilepsy could provide a new avenue of study for MRgFUS to understand treatment for DRE (70, 71). Animal studies provide the means to study phenotypes and syndromes that we cannot study in humans (70, 71). By using preclinical animal models, the field could determine the preferred brain targets for this line of therapy, the optimal FUS parameters (i.e., peak temperature, temperature rise, thermal dose, etc.) for correct lesion sizes, and long-term side effects of treating DRE with HIFU before clinical translation. Determining the effectiveness of HIFU for DRE could decrease barriers to surgery and side effects with deeper and smaller targets, such as the fornix, for ablative surgery with HIFU (3, 11, 13–15, 26).

Optimization of LIFU parameters to achieve the desired outcomes in epilepsy is still needed. LIFU has been shown to inhibit and excite brain circuits with different stimulation parameters across different brain areas and networks (i.e., excitation of the motor cortex, decreased seizures) (28–32, 34–37, 57, 72–74). LIFU has also been shown to act on various mechanosensitive and voltage-gated ion channels (56, 75–79). At the cellular level, there has been minimal work done to show the effects of LIFU stimulation on various neuronal cell types, and it has been suggested that LIFU can activate cell types beyond neurons (e.g., astrocytes) (80). These neuronal supporting cells are investigated in the search for new therapeutic targets for epilepsy (81). Therefore, optimizing FUS parameters to stimulate and alter the function of these cells with LIFU could be an interesting direction of study (80–82). Murphy et al. (40), created a device that allows imaging to be performed during LIFU stimulation, and a proof of concept was performed in the intrahippocampal kainate mouse model of epilepsy, showing brief suppression of neural activity in the hippocampus (40). Techniques such as coupling imaging with LIFU would provide the opportunity to research the mechanisms of LIFU stimulation in the epilepsy network (40). Understanding how specific LIFU parameters disrupt the epileptic network at the neuronal activity, cellular, and molecular levels may inform us of the appropriate stimulation paradigms for the ultimate treatment of epilepsy.

Ablation of epileptic foci with HIFU could potentially be a direct substitute for invasive or minimally invasive resection surgeries in people with DRE. Additionally, targeted therapy with LIFU could provide novel treatments for people with DRE, such as targeted-drug delivery to seizure-generating brain regions (43). These therapies are combinational therapies (stimulation + nanoparticle encapsulated drug or nonthermal lesioning) and may provide a localized effect rather than the systemic effects of current anti-seizure medications (ASMs) (43). Additionally, investigating the effects of ASMs when delivered locally to determine if there is a change in drug resistance, antiepileptic effects, and/or unwanted side effects may be of potential therapeutic benefit. Combinational therapy also opens the door for new experimental avenues. Targeted-drug delivery with nanoparticles can be used in brain mapping and could provide an important research tool for understanding the seizure-generating and/or comorbid neural networks (46). Combinational therapies show promise in numerous clinical and experimental applications.

The current future directions of HIFU and LIFU indicate the exciting potential applications for experimental and therapeutic techniques for DRE.

7 Conclusion

FUS is a completely noninvasive approach that can be used for both surgical and nonsurgical neuromodulation therapies using both thermal and nonthermal energy (19). Additionally, FUS can be used to reversibly and locally perturb the BBB to allow focused delivery of ASMs and investigational molecules to the seizure foci (43). While MRgFUS is the commonly used HIFU device and is FDA-approved for the surgical treatment of essential tremor and Parkinson's disease, it is in the early days of clinical epilepsy research, with one Phase-1 open-label trial using MRgFUS targeting the anterior nucleus of the thalamus and one report derived from a retrospective study that used a theoretical modeling study to demonstrate the potential benefits of ablating the fornix/fimbria connection for DRE (27, 83). However, numerous LIFU studies in rodents and nonhuman primate studies have shown seizure suppression, and clinical trials for LIFU intervention for people with DRE are currently planned (28–32, 37, 40, 45). Details of clinical trials and preclinical and case report studies relating to FUS effects on seizures and epilepsy have been summarized in Supplementary Tables S1, S2, respectively. Future studies elucidating the cellular mechanisms through which LIFU modulates neuronal activity will also drive innovation and improve safety and efficacy. Thus, future work is poised to determine which FUS applications may be beneficial in treating DRE.

Author contributions

CC: Conceptualization, Data curation, Funding acquisition, Writing – original draft, Writing – review & editing. EF: Data curation, Writing – review & editing. JR: Writing – review & editing. KW: Conceptualization, Writing – review & editing, Funding acquisition.

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Conflict of interest

The 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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Supplementary material

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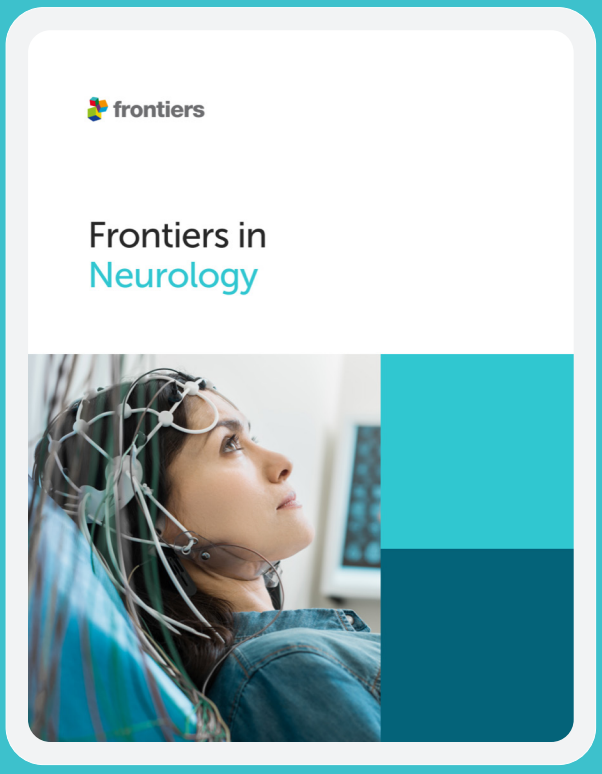

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