

Clinical Efficacy and Electrophysiological Mechanisms of Closed-Loop Neuromodulation for the Treatment of Drug-Resistant Epilepsy

Zihao Wang

Second Hospital of Hebei Medical University

Tianqi Hu

Capital Medical University

Haipeng Xie

Second Hospital of Hebei Medical University

Di Zhang

Second Hospital of Hebei Medical University

Yaning Sun

Second Hospital of Hebei Medical University

Jingwen Zhang

Second Hospital of Hebei Medical University

Xuehua Cui

Second Hospital of Hebei Medical University

Jie Zheng

Second Hospital of Hebei Medical University

Jiegang Yu

Second Hospital of Hebei Medical University

Shunyao Zhang

Second Hospital of Hebei Medical University

Xiaolei Song

Second Hospital of Hebei Medical University

Meng Wang

Second Hospital of Hebei Medical University

Xi Gao

Second Hospital of Hebei Medical University

Bangchao Li

Second Hospital of Hebei Medical University

Xianying Zhao

Second Hospital of Hebei Medical University

Zhengyang Zhang

Second Hospital of Hebei Medical University

Yuxiao Zhang

Second Hospital of Hebei Medical University

Wenbo Liu

Second Hospital of Hebei Medical University

Wenling Li

27104413@hebmh.edu.cn

Second Hospital of Hebei Medical University

Research Article

Keywords: drug-resistant epilepsy, closed-loop neuromodulation, parameter selection, intracranial EEG, scalp EEG, power spectrum, phase lag index

Posted Date: October 12th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11123004/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Clinical Efficacy and Electrophysiological Mechanisms of Closed-Loop Neuromodulation for the Treatment of Drug-Resistant Epilepsy

Zihao Wang^{1†}, Tianqi Hu^{2†}, Haipeng Xie¹, Di Zhang¹, Yaning Sun¹, Jingwen Zhang¹, Xuehua Cui¹, Jie Zheng¹, Jiegang Yu¹, Shunyao Zhang¹, Xiaolei Song¹, Meng Wang¹, Xi Gao¹, Bangchao Li¹, Xianying Zhao¹, Zhengyang Zhang¹, Yuxiao Zhang¹, Wenbo Liu¹, Wenling Li^{1*}

1 Department of Neurosurgery, The Second Hospital of Hebei Medical University, Shijiazhuang, China

2 Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

† Zihao Wang and Tianqi Hu contributed equally to this work and should be considered co-first authors.

* Correspondence: Wenling Li, E-mail: 27104413@hebmu.edu.cn, Department of Neurosurgery, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China.

Abstract

Objective: To evaluate the clinical efficacy of closed-loop neuromodulation for drug-resistant epilepsy and to characterize its electrophysiological mechanisms by combining intracranial and scalp EEG, thereby providing experimental evidence for optimizing treatment protocols and identifying multidimensional efficacy biomarkers.

Methods: Eight patients with drug-resistant epilepsy who underwent closed-loop neuromodulation implantation were enrolled and followed for 12–24 months. Clinical efficacy was evaluated using the seizure reduction rate and the responder rate. Linear mixed-effects models and within-subject Spearman rank correlation analyses were used to systematically characterize the population-level associations and inter-individual heterogeneity between stimulation parameters and clinical efficacy. Interictal intracranial EEG (recorded before stimulation onset and at 12 months postoperatively) and scalp EEG (international 10–20 system) were collected, and power spectral density and the phase lag index were used to quantify frequency-band-specific EEG activity and brain functional connectivity, with correction for multiple comparisons.

Results: At 12 months postoperatively, the overall seizure reduction rate was 56.3% ($P < 0.05$), with a responder rate of 75.0%. At 24 months, the reduction rate increased to 75.0% ($P < 0.05$) and the responder rate reached 85.7%, indicating a progressive, cumulative improvement in efficacy with treatment duration. At the population level, no significant independent associations were found between stimulation amplitude, frequency, pulse width, or target changes and the seizure reduction rate, and the parameter–efficacy relationship

exhibited marked inter-individual heterogeneity. Intracranial EEG revealed significantly increased gamma and high-gamma band power after treatment (Cohen's $d > 0.8$, large effect sizes), with no significant changes in the low-frequency bands. The high-gamma band exhibited a heterogeneous network reorganization pattern characterized by significantly enhanced functional connectivity within the epileptogenic zone and suppressed long-range propagation pathways. Scalp EEG showed diffuse changes, with significantly increased whole-brain delta power and significantly decreased beta power, whereas inter-electrode phase synchrony showed no statistically significant differences across frequency bands. Gamma-band power changed in opposite directions between intracranial and scalp EEG.

Conclusion: Closed-loop neuromodulation is a safe and effective treatment for drug-resistant epilepsy. Its efficacy accumulates over time and is patient-specific, with no universally optimal programming parameters. The electrophysiological mechanism is closely related to the plastic reorganization of epileptic networks induced by chronic targeted stimulation: the increased intracranial gamma/high-gamma power suggests functional restoration of local parvalbumin (PV)-positive inhibitory interneuron microcircuits in the epileptogenic zone, with the excitation–inhibition balance re-established toward a physiological steady state; the heterogeneous changes in high-gamma connectivity may limit the transregional propagation of epileptiform discharges. The scalp EEG pattern of enhanced slow-wave and attenuated fast-wave activity reflects an overall downregulation of whole-brain cortical excitability. The opposite changes in intracranial and scalp gamma-band power may provide key experimental evidence for a deeper understanding of the mechanisms of closed-loop neuromodulation and for establishing a multidimensional electrophysiological biomarker system for efficacy evaluation.

Keywords: drug-resistant epilepsy; closed-loop neuromodulation; parameter selection; intracranial EEG; scalp EEG; power spectrum; phase lag index

Introduction

Epilepsy is one of the most common chronic neurological diseases worldwide, with approximately 9.6 million patients in China; the disease imposes a heavy public health burden on patients, their families, and society [1]. Although antiseizure medications (ASMs) constitute the first-line clinical treatment, approximately one-third of patients continue to experience seizures after medical treatment with two or more ASMs, which defines drug-resistant epilepsy (DRE) [2]. For DRE, surgical resection of the epileptogenic zone is

currently recognized as an effective approach to achieving long-term seizure control [3]. However, patients whose epileptogenic zones are multifocal or located in eloquent areas such as the language and motor cortices cannot tolerate resective surgery, and these patients have an urgent clinical need for safe and effective alternative treatments.

With the rapid development of neuromodulation technology, closed-loop neuromodulation has become an important alternative treatment: it continuously monitors brain electrical activity through implanted intracranial electrodes, identifies abnormal electrical signals before or during seizures in real time, and automatically triggers targeted electrical stimulation to abort seizures, combining precision with minimal invasiveness [4]. In 2013, the responsive neurostimulator (RNS) was approved by the U.S. Food and Drug Administration (FDA) as an adjunctive therapy for DRE, and multiple long-term follow-up studies have confirmed that seizure frequency was reduced by 53% within the first 2 years after implantation and by 72% within 6 years, indicating reliable long-term efficacy [5, 6].

Although the long-term efficacy of closed-loop neuromodulation has been well established, treatment responses vary considerably across individuals, and stimulation parameter settings are the core controllable factor affecting treatment outcomes. The most common stimulation settings are a frequency of 100–200 Hz, a current of 1.5–3 mA, a pulse width of 160 μ s, and a pulse train duration of 100–200 ms [7, 8]. However, there is no consensus on the timing and strategy of parameter optimization, and clinical parameter adjustments rely mainly on physician experience without objective evidence-based guidance. Therefore, clarifying the relationship between stimulation parameters and clinical efficacy is key to improving treatment outcomes [5].

In addition to parameter optimization, the unclear mechanism of action is another major bottleneck restricting the improvement of closed-loop neuromodulation efficacy [9]. Closed-loop neuromodulation is thought to exert its effects mainly by modulating the excitation–inhibition balance in the brain and inducing plastic reorganization of epileptic circuits, and its effects can be subdivided into direct and chronic effects: the former comprising acute postsynaptic inhibition and frequency modulation, and the latter comprising spontaneous seizure attenuation, spectral reshaping, discharge fragmentation, and modulation of seizure duration. It is now widely accepted that the therapeutic effect of closed-loop neuromodulation is related to chronic reorganization [10, 11]; however, the specific electrophysiological mechanisms have not been fully elucidated [12]. Power spectrum and functional connectivity analyses are important tools for exploring brain network activity [13–16], reflecting spectral

power and synchrony, respectively [17, 18]. These methods facilitate the quantification and comparison of EEG signals within specific frequency bands. EEG signals in different frequency bands correspond to different physiological activities [19]. Among these spectral components, gamma oscillations have attracted particular attention because of their prominent association with higher-order brain functions [20]. Fast oscillations in the gamma band of neural networks are jointly regulated by negative and delayed feedback, both of which are necessary for maintaining network homeostasis and can drive the formation of characteristic power peaks in the gamma and high-gamma bands [21, 22].

Most existing studies have focused on EEG feature analyses at a single time point, and relatively few studies have analyzed long-term EEG changes after neuromodulation; moreover, simultaneous analyses of scalp and intracranial EEG are scarce. Although RNS has been widely used internationally, closed-loop neuromodulation in China remains in its infancy, and reports of its efficacy in Chinese populations are limited [23–25]. Currently, closed-loop neuromodulation in China includes the Ruishen'an implantable closed-loop deep brain neurostimulator system (CNS) and the Jialiang Medical responsive neurostimulation device (RNS), both of which are in the clinical trial stage. Although the efficacy and safety of closed-loop neuromodulation have been preliminarily validated, no generally accepted stimulation parameters are currently available for closed-loop stimulators, and patients with epilepsy show highly individualized characteristics, with potential racial and regional differences in epilepsy.

Based on the above clinical needs and research gaps, the present study retrospectively analyzed the clinical data and electrophysiological indicators of patients with DRE who received closed-loop neuromodulation at the Epilepsy Center of the Second Hospital of Hebei Medical University between 2023 and 2025, aiming to investigate the efficacy of closed-loop neuromodulation in patients with multifocal DRE, the patterns of individualized parameter selection, and the treatment-related electrophysiological mechanisms, thereby providing a basis for the optimization of closed-loop neuromodulation protocols and the elucidation of its mechanisms.

Methods

2.1 Inclusion and exclusion criteria

Patients with DRE who received closed-loop neuromodulation at the Epilepsy Center of the Second Hospital of Hebei Medical University between 2023 and 2025 were enrolled in

this study. The study was conducted in accordance with the Declaration of Helsinki, and all procedures involving human participants were approved by the Ethics Committee of the Second Hospital of Hebei Medical University (approval numbers: 2022EC11-06-1 and 2022EC04-01-1). All patients or their legal guardians provided written informed consent to participate in the study prior to enrollment.

Patients who underwent closed-loop neuromodulation implantation met the following inclusion criteria. The exclusion criteria were as follows:

Inclusion criteria: (1) age between 10 and 70 years, inclusive, regardless of sex; (2) a diagnosis of drug-resistant epilepsy with focal-onset seizures; (3) surgical resection not recommended or not desired; (4) an average of ≥ 3 seizures per month during the 3 months before surgery; (5) the ability to independently complete, or complete with family assistance, a seizure diary; (6) good compliance and the ability to cooperate with the entire clinical trial; and (7) the patient or their family members could fully understand the treatment, adhere to the required follow-up, and voluntarily sign the informed consent form.

Exclusion criteria: (1) coexisting progressive neurological disease; (2) contraindications to neurosurgery; (3) a diagnosis of coexisting psychogenic nonepileptic seizures; (4) a diagnosis of generalized-onset seizures; (5) breastfeeding or pregnant women; (6) participation in other clinical trials; (7) skull conditions judged by the investigators to be unsuitable for device implantation; (8) surgical resection of an epileptogenic lesion within 6 months before implantation; (9) the presence of other implanted electrical stimulation devices that could not be discontinued during the study period; and (10) other conditions judged by the investigators and medical staff to be unsuitable for enrollment.

Ultimately, nine patients underwent closed-loop neuromodulation implantation: four received RNS and five received CNS. Of these, one patient implanted with the RNS was excluded because one of the intracranial electrodes fractured after a seizure-related fall that caused a head injury. The patient enrollment process is shown in Figure 1.

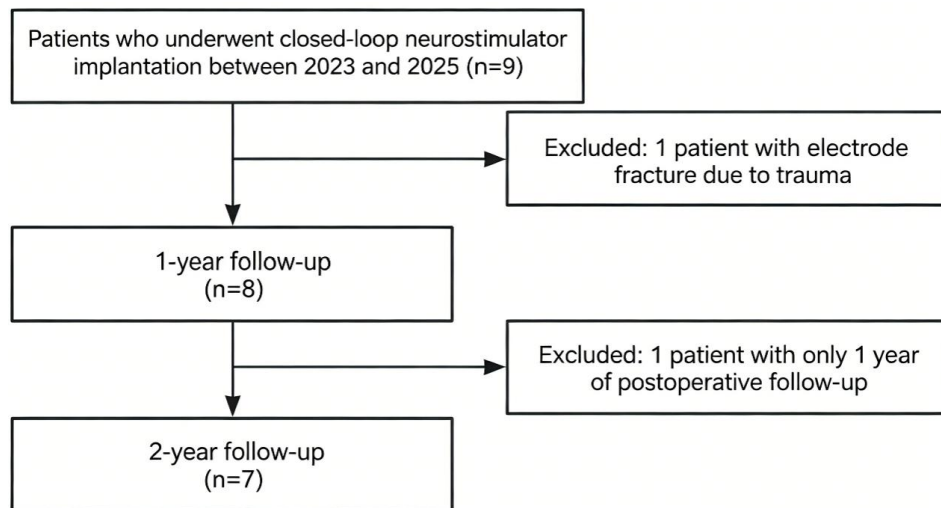


Figure 1. Flowchart of patient enrollment.

2.2 Preoperative evaluation and initial stimulation parameters

Preoperatively, all patients underwent long-term video-EEG (VEEG) monitoring to capture seizures, thin-slice cranial MRI, PET, neuropsychological assessment, and other routine preoperative evaluations for epilepsy surgery, to confirm multifocal seizure onset. All subjects were followed for at least 3 months before surgery to establish the baseline seizure frequency. After fusing the head MRI and PET images and integrating the seizure semiology, medical history, and VEEG results, a multidisciplinary discussion was conducted involving epilepsy surgeons, EEG physicians, and radiologists. After the treatment team reached a consensus on the treatment plan, the multifocal seizure onset zones were identified and the surgical plan was developed.

The Epilcure™ system (RNS) is equipped with two implantable brain neurostimulation electrode lead sets (cortical or depth electrodes can be selected). The neurostimulator continuously senses and monitors intracranial EEG (iEEG) signals from the two depth/cortical electrodes (each channel contains four contacts) at a sampling rate of 200 Hz. The initial parameters were a stimulation frequency of 200 Hz, a current of 1 mA, and a pulse width of 160 μ s. The mean values of the total amplitude, frequency, pulse width, pulse train duration, and charge density were 2.4 ± 1.0 mA, 150.2 ± 76.8 Hz, 183.3 ± 52.7 μ s, 150 ± 208.1 ms, and 11.4 ± 2.8 μ C/cm², respectively [24]. The implantable closed-loop deep brain neurostimulator system (CNS) has four implantable brain stimulation electrodes with 4–16 contacts (needle-type or strip electrodes can be selected). The neurostimulator continuously senses and monitors iEEG signals from the four needle-type or strip electrodes at a sampling rate of 250 Hz. When abnormal patterns of intracranial EEG activity are detected, the

neurostimulator automatically generates electrical stimulation. The initial stimulation parameters were a frequency of 130 Hz, a current of 0.5 mA, and a pulse width of 60 μ s. Figure 2 shows the schematic diagrams of intracranial EEG acquisition and recording modes for the two closed-loop neuromodulation systems.

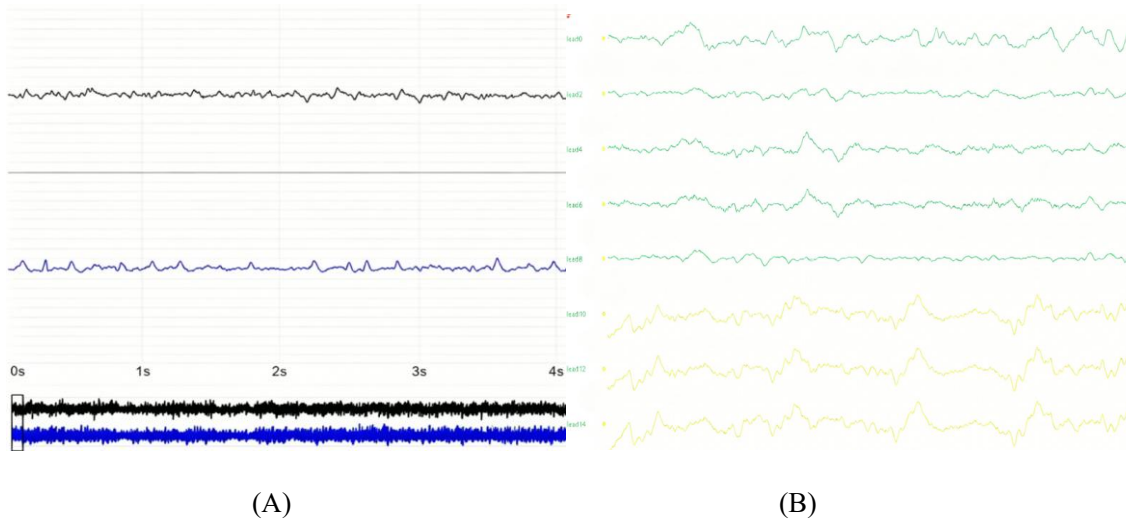


Figure 2. Schematic of intracranial EEG acquisition. (A) Intracranial EEG recorded and stored by the RNS. (B) Intracranial EEG recorded and stored by the CNS.

2.3 Seizure assessment

Seizure records were obtained by trained legal guardians based on direct observation of the patients' seizure events. Baseline and postoperative assessments were collected by specially trained evaluators to ensure the accuracy and reliability of the seizure diaries. The primary efficacy outcome was defined as the seizure reduction rate (SFR). Patients were followed for at least 3 months before surgery to establish the baseline seizure frequency, and the monthly seizure frequency reduction rate was calculated as $(\text{baseline} - \text{median postoperative monthly seizure frequency}) / \text{baseline} \times 100\%$. According to the degree of reduction, patients were further divided into two groups: responders (reduction $\geq 50\%$) and non-responders (reduction $< 50\%$). The responder rate was defined as the proportion of patients whose seizure frequency decreased by $\geq 50\%$ relative to baseline after treatment, with the effect maintained for at least 3 consecutive months. A seizure reduction $\geq 90\%$ was defined as a complete response, a reduction of 50%–89% as a partial response, and a reduction $< 50\%$ or an increase as non-response [26]. Any surgery-related adverse events (AEs) occurring during follow-up were also recorded. Continuous variables are presented as mean $\pm$ standard deviation (SD), and categorical variables as frequencies and percentages. Seizure frequency is presented as the median and interquartile range (IQR). Depending on the

data distribution, the Wilcoxon signed-rank test was used to compare continuous variables between baseline and follow-up, and the chi-square test was used for categorical variables. Statistical analyses were performed using R version 4.4.1, with the significance level set at $P < 0.05$. Statistical figures were generated using R and MATLAB.

2.4 Association between clinical efficacy and programming parameters

Longitudinal follow-up data from 1 to 24 months after surgery were collected for each patient. The monthly seizure reduction rate was used as the clinical efficacy indicator, and stimulation amplitude, stimulation frequency, stimulation pulse width, and target changes were used as neuromodulation programming-related observational parameters, with follow-up time included as a temporal confounding factor. A linear mixed-effects model was constructed with the seizure reduction rate as the dependent variable; stimulation amplitude, stimulation frequency, stimulation pulse width, target changes, and follow-up time were included as fixed effects, and a random intercept was set for each patient to correct for the autocorrelation of repeated measurements and between-patient differences in baseline efficacy. The model was fitted using restricted maximum likelihood (REML), and the Satterthwaite approximation was used to adjust the degrees of freedom of the t tests. Continuous programming parameters were standardized to eliminate dimensional interference. On this basis, within-subject Spearman rank correlation analyses were performed to examine, within each patient's own longitudinal time series, the associations between each of the four programming parameters and the seizure reduction rate. Individuals in whom the programming parameters or the seizure reduction rate showed no temporal variation were not subjected to correlation testing. $P < 0.05$ was considered statistically significant in all analyses.

2.5 Intracranial field potential (iEEG) signal processing

Intracranial EEG signals were recorded in awake, quiet, eyes-closed patients with no obvious emotional fluctuation or body movement before stimulation onset (after intracranial electrode implantation) and at the 12-month follow-up after stimulation. Both recordings were obtained within a time window of ≥ 72 h after the most recent clinical seizure and ≥ 4 weeks after the most recent stimulation parameter adjustment, to exclude post-ictal effects and acute electrophysiological interference from parameter adjustment. One 60-s segment of interictal EEG without obvious movement artifacts or poor electrode contact artifacts was selected from each patient for subsequent analysis, and all data were resampled to 200 Hz.

All data were preprocessed using the EEGLAB v2024.0 toolbox on the MATLAB R2025a platform. Downsampling with built-in anti-aliasing filtering was performed using the `pop_resample` function; zero-phase finite impulse response (FIR) filtering was applied for 1–99 Hz band-pass filtering, and a 49–51 Hz notch filter was used to remove 50 Hz power-line interference. Digital re-referencing was performed using the common average reference. Pre- and postoperative data were preprocessed with identical parameters.

Power spectral density (PSD) was calculated using Welch's periodogram method with a Hanning window of 1 s (250 data points) and 50% window overlap, and the FFT length was automatically matched to the smallest power of two greater than the window length. The PSD was converted to logarithmic decibel units as $10 \times \log_{10}(\text{PSD})$. According to the six standard frequency bands δ (1–4 Hz), θ (4–8 Hz), α (8–13 Hz), β (13–30 Hz), γ (30–50 Hz), and high- γ (50–99 Hz), the mean power across all channels before and after surgery was calculated for each patient. Paired-sample *t* tests were used to compare pre- and postoperative power differences in each band, with Bonferroni correction for multiple comparisons (corrected significance level $\alpha = 0.0083$). Cohen's *d* was calculated as the effect size to quantify the magnitude of the differences ($d < 0.2$, negligible effect; $0.2 \leq d < 0.5$, small effect; $0.5 \leq d < 0.8$, medium effect; $d \geq 0.8$, large effect). All statistical analyses were performed in MATLAB R2025a, with uncorrected $P < 0.05$ considered statistically significant.

The phase lag index (PLI) was used to quantify the functional connectivity strength between the brain regions corresponding to each electrode pair. Specifically, the instantaneous phase of each band-pass filtered signal was extracted using the Hilbert transform, the phase difference between the two channel signals was calculated, and the PLI was obtained by taking the sign of the sine of the phase difference and computing the absolute value of its mean. The rate of change of the PLI at 1 year postoperatively relative to that before stimulation onset was also calculated to reflect the effect of neuromodulation. The high-gamma band, which is closely related to the synchronized discharge of neuronal clusters, was analyzed. To exclude the mathematical amplification artifact caused by extremely low baseline synchrony, only valid pairs with a pre-stimulation $\text{PLI} \geq 0.005$ were retained for analysis. According to the anatomical and functional characteristics of the electrode pairs, the valid pairs were divided into three groups: (1) core epileptogenic circuits, i.e., connections between the epileptogenic zone and key hubs of the epileptic network, such as the anterior nucleus of the thalamus (ANT) and the anterior cingulate cortex; (2) long-range propagation pathways, i.e., cross-hemispheric or cross-lobar pathways for the spread of

epileptiform discharges; and (3) local internal connections, i.e., connections between adjacent regions within the same hemisphere and lobe, or within the same bilateral nucleus or structure. The Wilcoxon signed-rank test was used for paired comparisons of the PLI between pre-stimulation and 1-year postoperative recordings, with $P < 0.05$ considered statistically significant, and Cohen's d was used to assess the effect size (0.2, small effect; 0.5, medium effect; 0.8, large effect). All calculations were implemented in MATLAB R2025a with the EEGLAB toolbox.

2.6 Scalp EEG signal processing

Resting-state EEG data were recorded using 19 scalp electrodes arranged according to the international 10–20 system (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2, Fz, Cz, Pz) at baseline and 1 year after closed-loop neuromodulation. During recording, patients lay comfortably in bed, with no seizures for at least 2 h, and 10 min of EEG data were collected with eyes open. All raw data were saved in the standard EEGLAB .set format. The entire preprocessing was performed in MATLAB with the EEGLAB toolbox, including precise electrode coordinate localization and standardized re-referencing. The signal sampling rate was 500 Hz; the raw signals were band-pass filtered at 0.1–100 Hz to remove low-frequency drift and high-frequency noise, and a 50 Hz notch filter was applied to eliminate power-line interference. Independent component analysis (ICA) was used to separate and remove physiological artifacts such as ocular and cardiac artifacts, maximizing signal purity. The EEG signals were then converted to double-precision values, the DC offset was removed from each channel, and the continuous EEG was segmented using a unified 2-s non-overlapping window, ensuring identical temporal resolution and analysis baseline between pre- and postoperative data, thereby providing standardized, high-purity raw data for subsequent spectral and phase synchrony analyses.

The preprocessed standardized EEG data were further subjected to spectral analysis and brain functional connectivity analysis. The power spectral density of each channel was calculated using the native MATLAB pwelch algorithm with a 2-s analysis window, no signal overlap, and 1 Hz frequency resolution. The absolute and relative power of the five classical EEG bands, delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–100 Hz), were extracted; relative power was defined as the percentage of the power in a given band relative to the total power across the full 1–100 Hz range, and the whole-brain mean power was calculated by averaging across the 19 channels. Interregional

phase synchrony was quantified using the phase lag index (PLI). After fourth-order Butterworth band-pass filtering of each band, the instantaneous phase of each channel was extracted using the Hilbert transform, and the PLI of all electrode pairs was calculated based on the absolute mean of the sign of the inter-channel phase differences, reflecting the strength of phase synchrony in the brain network. Paired-sample t tests were used to compare the relative power of each band at each channel and the PLI of all electrode pairs between pre- and postoperative recordings, and the Benjamini–Hochberg false discovery rate (FDR) method was used for multiple comparison correction, with corrected $P < 0.05$ considered statistically significant.

Results

3.1 Patient characteristics

Seven patients (87.5%) completed the 2-year follow-up, and one patient (12.5%) completed the 1-year follow-up. The number of patients evaluated, the attrition, and the corresponding reasons are summarized in Figure 1. The demographic characteristics of the patients are summarized in Table 1. The mean age at surgery was 24 ± 9.1 years, and seven patients (87.5%) were male. The mean disease duration was 11.9 ± 8.4 years, and the mean baseline seizure frequency was 8.0 seizures/month, with a median of 8.0 seizures/month (IQR 5.8–8.8). The seizure semiology varied across patients, predominantly focal to bilateral tonic–clonic seizures (FBTCS; $n = 3$, 37.5%) and focal impaired awareness seizures (FIAS; $n = 4$, 50.0%), with generalized seizures in one patient (12.5%). Temporal lobe epilepsy (TLE) was found in four patients (50.0%), frontal lobe epilepsy (FLE) in one patient (12.5%), parietal epileptogenic zones in two patients (25%), and an occipital epileptogenic zone in one patient (12.5%). Regarding antiseizure medications (ASMs), three patients (37.5%) were taking two ASMs and five patients (62.5%) were taking three. Detailed characteristics are shown in Table 1.

Table 1. Baseline characteristics of the enrolled patients.

No.	Device	Sex	Age (years)	Age at onset (years)	Disease duration (years)	Oral medications	Previous surgery	Baseline seizure frequency	Electrode location	Semiology	MRI	PET	EEG	Surgical complications
1	RNS	M	20	13	7	CZB, VPA, LTG	Resection of right frontal epileptogenic zone	8/month	Right frontal piriform cortex, left frontal lobe	Automatism, behavioral arrest	Bilateral hippocampal atrophy	Slightly reduced metabolism in the bilateral inferior frontal gyri and temporal lobes, most prominent in the anteromedial temporal region	Numerous spike-and-slow waves in the left frontotemporal region; few spike-and-slow waves in the right temporal region	Suspected intracranial infection
2	RNS	M	29	13	16	LEV, LCM	Craniocerebral injury	6/month	Right temporal lobe, right insula	GTCS, head discomfort, behavioral arrest	Large patchy encephalomalacia in the right parieto-occipital lobe; encephalomalacia in the left frontal lobe	Encephalomalacia with metabolic defect in the right temporo-parieto-occipital lobe, with markedly reduced metabolism in the surrounding right temporo-parieto-occipital region and the precentral gyrus; encephalomalacia with metabolic defect in the left frontal pole	Persistent irregular slow-wave activity in the right region; fast waves in the right region and the mid-temporal area	None
3	RNS	M	24	9	15	LEV, LCM	SEEG	11/month	Bilateral medial occipital surfaces	GTCS, behavioral arrest	Right occipital encephalomalacia	Decreased metabolism in the right occipital region compared with the contralateral side	Few spike-and-slow waves in the bilateral posterior head and the right temporal region	None
4	CNS	F	17	6	11	CBZ, LEV, NZP	None	14/month	Bilateral ANT, bilateral hippocampus	GTCS, staring-like seizures, drop attacks	Increased bilateral hippocampal signal	Decreased FDG metabolism in the bilateral temporal lobes, more prominent on the right; decreased FDG metabolism in the left anterior cingulate	Nearly continuous slow waves in the bilateral temporal regions; multifocal onset (right temporal, left temporal, and	None

No.	Device	Sex	Age (years)	Age at onset (years)	Disease duration (years)	Oral medications	Previous surgery	Baseline seizure frequency	Electrode location	Semiology	MRI	PET	EEG	Surgical complications
5	CNS	M	10	8	1.5	OXC, VPA, LCM	None	4/month	Bilateral parieto-occipital sulci, intraparietal sulci	Tonic seizures with loss of consciousness	Narrow gyri in the bilateral parietal lobes	cortex compared with the contralateral side Hypometabolism in the bilateral posterior head	right posterior temporal regions) Numerous spike-and-slow waves in the bilateral posterior head	None
6	CNS	M	36	33	3	VPA, LCM, TPM	None	5/month	Bilateral ANT, bilateral hippocampus	GTCS with head turning to the right, staring-like seizures	No abnormality	Slightly decreased FDG metabolism in the bilateral medial and anterior temporal regions and the bilateral hippocampal regions, more prominent on the right	Numerous spikes, spike-and-slow waves, and sharp-and-slow waves in the bilateral frontotemporal regions	None
7	CNS	M	18	6	12	OXC, LEV	None	8/month	Bilateral hippocampus, bilateral parietal encephalomalacia	GTCS, behavioral arrest	Signal changes in the deep white matter of the bilateral parietal lobes	Diffuse decreased FDG metabolism in the bilateral parietal and temporal lobes, more prominent in the right parietal and right temporal lobes	Numerous spikes, sharp waves, and sharp-and-slow waves in the bilateral temporo-parietal regions	None
8	CNS	M	38	8	30	VPA, CZB, PER	None	8/month	Bilateral ANT, bilateral anterior cingulate cortex	Clonic seizures, GTCS	Small punctate hyperintense T1 signals in the bilateral hippocampus	Decreased metabolism in the right frontal and right parietal lobes	Widespread spike rhythm; numerous spike-and-slow waves and sharp-and-slow waves in the bilateral frontotemporal and posterior head regions	None

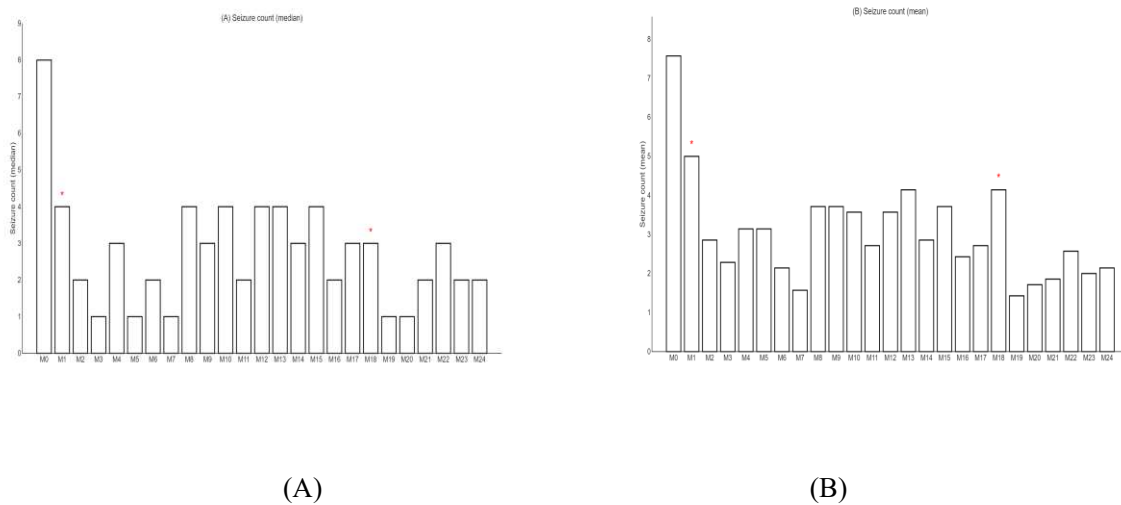
3.2 Efficacy evaluation

At the 12-month follow-up, the seizure reduction rates of the eight patients were 12.5%, 50.0%, 81.8%, 71.4%, 100%, 60.0%, 50.0%, and 37.5%, respectively. The overall mean reduction in monthly seizure frequency was $57.9\% \pm 27.1\%$. The median monthly seizure frequency (SF) decreased from 8.0 (IQR 5.5–9.5) to 3.5 (2.0–4.5), a reduction of 56.3% ($P < 0.05$).

Patient 3 had not yet reached the 24-month postoperative time point. After excluding this patient, the mean reduction in monthly seizure frequency in the remaining seven patients at the 12-month follow-up was $51.4\% \pm 25.8\%$. The median monthly seizure frequency decreased from 8.0 (5.0–8.0) to 4.0 (2.0–5.0), a reduction of 51.6% ($P < 0.05$).

At the 24-month follow-up, the seizure reduction rates were 62.5%, 66.7%, 78.6%, 100%, 40.0%, 75.0%, and 75.0%, respectively. The mean reduction in seizure frequency was $71.1\% \pm 18.2\%$. The median monthly seizure frequency decreased to 2.0 (2.0–3.0), representing a 75.0% reduction relative to baseline ($P < 0.05$) and a 50.0% reduction relative to the 12-month postoperative value ($P > 0.05$). The mean monthly seizure counts of all patients are shown in Figure 3.

At the 3-, 6-, and 12-month follow-ups, the responder rate of the eight patients was 75.0% at each time point. After excluding patient 3, the group responder rates of the seven patients at the 3-, 6-, 12-, and 24-month follow-ups were 71.4%, 71.4%, 71.4%, and 85.7%, respectively.



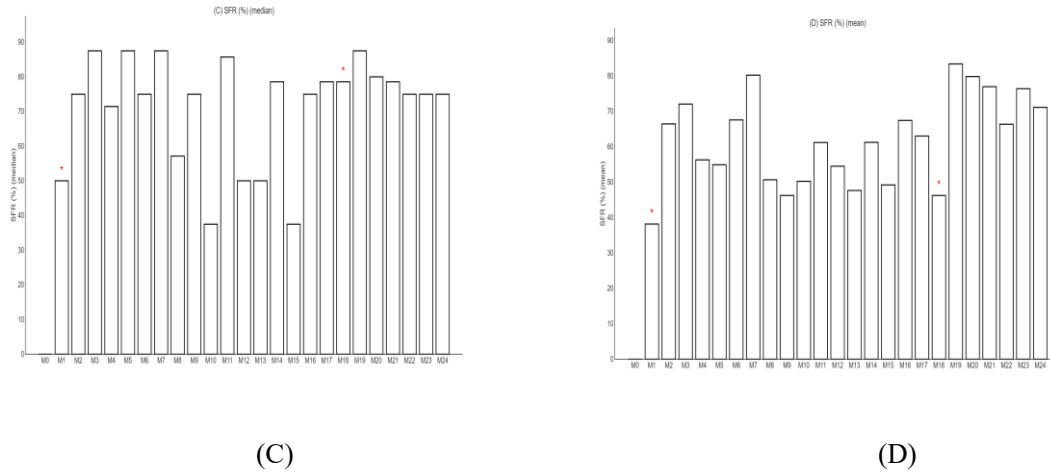


Figure 3. Median (A) and mean (B) monthly seizure counts across months; median (C) and mean (D) of the monthly seizure frequency reduction rate (SFR, %) across months. M0 represents the baseline seizure frequency, and M1–M24 represent the device activation and long-term follow-up parameter adjustment period. Red asterisks (*) indicate statistically significant differences from baseline by the paired Wilcoxon signed-rank test. Owing to the relatively small sample size and the marked inter-individual heterogeneity of treatment response, the clinically evident reduction in seizures at some time points did not reach statistical significance. SFR: seizure frequency reduction rate.

3.3 Stimulation parameter analysis

The first postoperative year was mainly a parameter optimization period, during which the stimulation amplitude was primarily adjusted to explore each patient's optimal treatment parameters (Figure 4). The optimal stimulation parameters for each patient are shown in Table 2.

Table 2. Parameter selection at the time of best efficacy in the eight patients

Patient No.	Stimulation frequency	Pulse width	Current amplitude
1	200 Hz	160 μ s	3 mA
2	200 Hz	160 μ s	1 mA
3	200 Hz	160 μ s	1 mA
4	130 Hz	60 μ s	2 mA
5	130 Hz	60 μ s	0.5 mA
6	130 Hz	60 μ s	1.5 mA
7	130 Hz	60 μ s	1.5 mA
8	130 Hz	60 μ s	0.5 mA

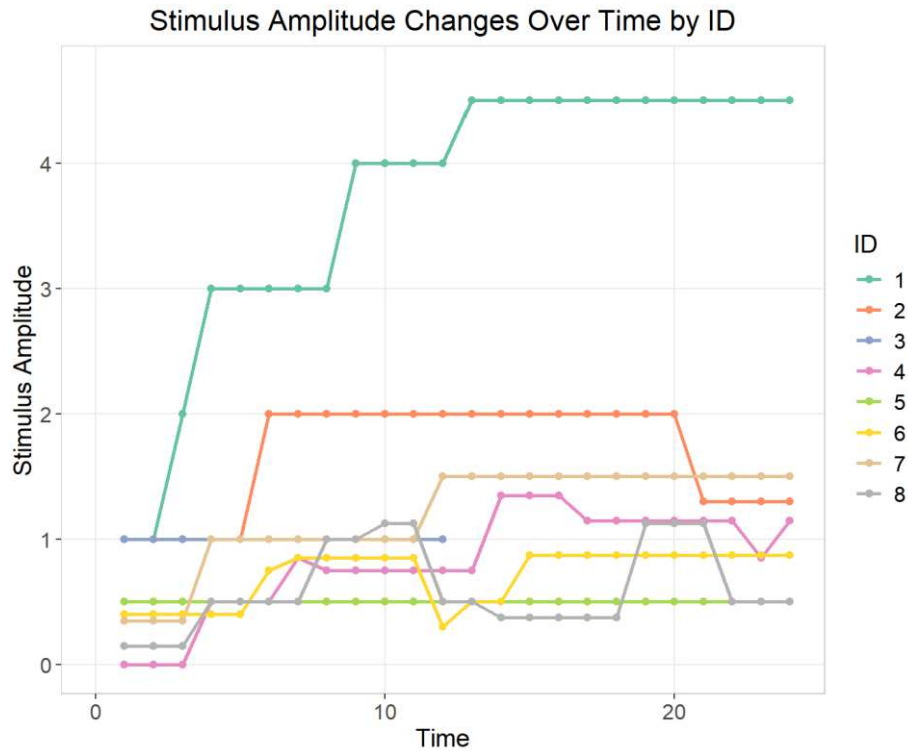


Figure 4. Adjustment process of the stimulation amplitude in the eight patients. The horizontal axis indicates the programming follow-up time (months), and the vertical axis indicates the neuromodulation stimulation amplitude (mA).

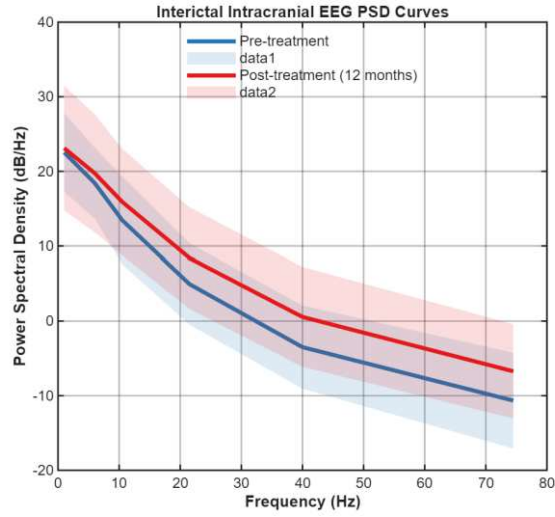
The linear mixed-effects model analysis included 180 valid longitudinal observations. The random-effects analysis revealed marked heterogeneity in the baseline seizure reduction rates among patients, with an individual random intercept variance of 0.141 and a residual variance of 0.082, indicating inherent inter-individual differences in initial treatment efficacy; after correcting for individual differences, the random fluctuation of efficacy across time points was relatively controllable. The fixed-effects analysis showed that stimulation amplitude (estimate = 0.022, $P = 0.746$), stimulation frequency (estimate = -0.033 , $P = 0.486$), stimulation pulse width (estimate = 0.113, $P = 0.444$), target changes (estimate = 0.123, $P = 0.179$), and follow-up time (estimate = 0.003, $P = 0.445$) were not significantly independently associated with the seizure reduction rate at the population level; only the model intercept was statistically significant (estimate = 0.561, $P = 0.007$), indicating a mean baseline seizure reduction rate of 56.05% for the patient population after correcting for confounders.

The within-subject Spearman rank correlation analysis further revealed marked inter-individual heterogeneity in the associations between programming parameters and efficacy. In patient 4, stimulation amplitude, stimulation frequency, and stimulation pulse width were

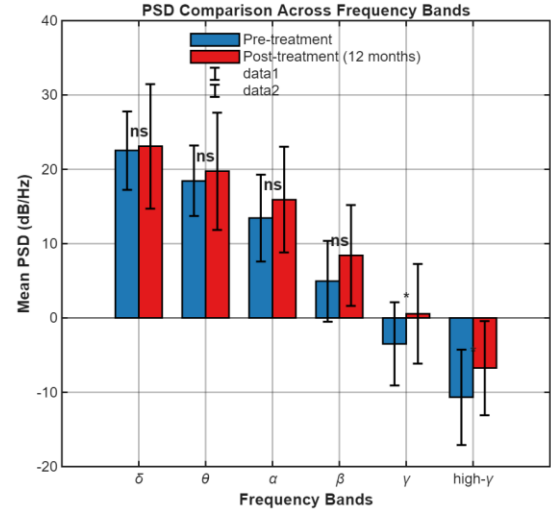
all significantly positively correlated with the seizure reduction rate. In patient 1, stimulation frequency was significantly negatively correlated with the seizure reduction rate, whereas stimulation amplitude showed a positive trend that did not reach statistical significance. In patient 6, only target changes were significantly positively correlated with the seizure reduction rate, whereas in patient 8, only target changes were significantly negatively correlated with the seizure reduction rate. In the remaining patients, the programming parameters were either fixed for a long period without temporal variation or showed no significant correlation with the seizure reduction rate. Overall, these findings confirm that there is no unified population-level pattern in the relationship between neuromodulation programming parameters and efficacy, with marked patient-specific heterogeneity in the associations.

3.4 Intracranial EEG analysis

Interictal intracranial EEG signals were recorded before neuromodulation onset and at 12 months after surgery, and power spectral density (PSD) analysis was performed. The overall comparison of PSD across all frequency bands before and after treatment is visualized in Figure 5. Paired-sample *t* tests were used to compare the mean power of the six standard frequency bands: δ (1–4 Hz), θ (4–8 Hz), α (8–13 Hz), β (13–30 Hz), γ (30–50 Hz), and high- γ (50–99 Hz). No statistically significant differences were found between pre- and postoperative mean power in the low-frequency δ , θ , α , and β bands (all $P > 0.05$): δ band, 22.54 ± 5.27 vs. 23.11 ± 8.37 dB/Hz ($t = -0.246$, $P = 0.8127$); θ band, 18.43 ± 4.74 vs. 19.75 ± 7.90 dB/Hz ($t = -0.620$, $P = 0.5552$); α band, 13.45 ± 5.85 vs. 15.91 ± 7.12 dB/Hz ($t = -1.076$, $P = 0.3178$); β band, 4.96 ± 5.43 vs. 8.42 ± 6.78 dB/Hz ($t = -1.758$, $P = 0.1222$), suggesting that focal neuromodulation had no significant effect on the low-frequency background activity of interictal EEG in patients with epilepsy. The γ and high- γ bands showed a postoperative power increase: γ band, from -3.49 ± 5.57 to 0.56 ± 6.68 dB/Hz ($t = -2.623$, $P = 0.0342$); high- γ band, from -10.66 ± 6.42 to -6.73 ± 6.33 dB/Hz ($t = -2.527$, $P = 0.0394$). Uncorrected, both differences were statistically significant (both $P < 0.05$); after Bonferroni correction for multiple comparisons (corrected significance level $\alpha = 0.0083$), neither difference reached statistical significance (both $P > 0.0083$). Effect size analysis yielded Cohen's $d = 0.93$ for the γ band and Cohen's $d = 0.89$ for the high- γ band, both representing large effect sizes.



(A)



(B)

Figure 5. (A) Changes in interictal intracranial EEG power spectral density (PSD) before and 12 months after neuromodulation. (B) Comparison of PSD across EEG frequency bands (δ , θ , α , β , γ , and high- γ) before and after treatment. * Uncorrected $P < 0.05$; ns: $P > 0.05$.

Using each patient's preoperative multi-electrode intracranial EEG power as the individual baseline, the standardized Z values of the postoperative relative power changes in each band were calculated. The overall mean Z values of the δ and θ low-frequency bands were close to zero (-0.18 ± 1.63 and 0.54 ± 1.49 , respectively). The Z values of the α and β bands were 1.08 ± 2.40 and 1.35 ± 2.02 , respectively; although the means showed a slight positive shift, the inter-individual dispersion was large, with high standard deviations, indicating marked inter-individual heterogeneity.

The Z values of the γ and high- γ bands showed a marked overall positive shift, with means of 1.64 ± 1.99 and 1.93 ± 2.21 , respectively, characterized predominantly by a postoperative power increase.

The changes in high-gamma (50–99 Hz) PLI were analyzed in 33 intracranial electrode pairs ($1 \times 3 + 5 \times 6$); after screening, 21 valid pairs entered the statistical analysis. The grouped statistical results are shown in Table 3. One year after surgery, the high-gamma PLI of local internal connections within the epileptogenic zone was significantly increased ($P = 0.039$, Cohen's $d = 0.88$), suggesting that long-term RNS/CNS stimulation induced enhanced local synchrony in the epileptic network. The PLI changes of the long-range connections of the epileptogenic zone showed no statistically significant difference, but five of the six pairs showed a decreasing trend, with a decrease of 10.7%–90.0% and a median change of -0.0054 , suggesting a tendency of neuromodulation to suppress the long-range spread of epileptiform discharges. The PLI changes of the core epileptogenic circuits showed no statistically significant difference; however, clear modulatory effects were observed at the individual level: the PLI of the right anterior cingulate cortex–right ANT pathway decreased

by 93.6% in patient 8, and the PLI of the hippocampus–parietal encephalomalacia pathway decreased by 90.0% in patient 7.

Table 3. Grouped statistics of high-gamma (50–99 Hz) phase lag index (PLI) changes after 1 year of treatment

Group	Valid pairs	Preoperative PLI (mean $\pm$ SD)	Postoperative PLI (mean $\pm$ SD)	Median change	P value*	Cohen's d effect size
Core epileptogenic circuits (epileptogenic zone $\leftrightarrow$ ANT/anterior cingulate cortex)	7	0.0228 $\pm$ 0.0133	0.0583 $\pm$ 0.0612	0.0194	0.156	0.57
Long-range propagation pathways (cross-hemispheric/cross-lobar)	6	0.0143 $\pm$ 0.0059	0.0154 $\pm$ 0.0179	−0.0054	0.438	0.05
Local internal connections (within the same hemisphere and lobe/bilateral same structure)	8	0.0156 $\pm$ 0.0045	0.0266 $\pm$ 0.0145	0.0105	0.039	0.88

* Wilcoxon signed-rank test.

3.5 Scalp EEG analysis

Paired *t* tests of whole-brain relative power showed that, after closed-loop neuromodulation, delta relative power significantly increased from 64.29% $\pm$ 11.37% to 79.84% $\pm$ 8.08% (*P* = 0.015), and beta relative power significantly decreased from 6.41% $\pm$ 2.21% to 3.37% $\pm$ 1.56% (*P* = 0.010); both differences were statistically significant. Alpha relative power decreased from 8.95% $\pm$ 8.04% to 4.51% $\pm$ 2.80% (*P* = 0.078), showing a marginal decreasing trend. Theta and gamma relative power both decreased postoperatively but did not reach statistical significance (*P* > 0.05) (Figure 6). At the single-electrode level, paired *t* tests were performed for the five bands of the 19 scalp electrodes, with Benjamini–Hochberg FDR correction for multiple comparisons (95 tests in total). After correction, the *q* values for all electrodes and all bands were > 0.05, indicating that no statistically significant changes in electrode power were found postoperatively. The modulation of EEG power by closed-loop neuromodulation manifested as a diffuse whole-brain trend, without statistically significant effects in any localized brain region.

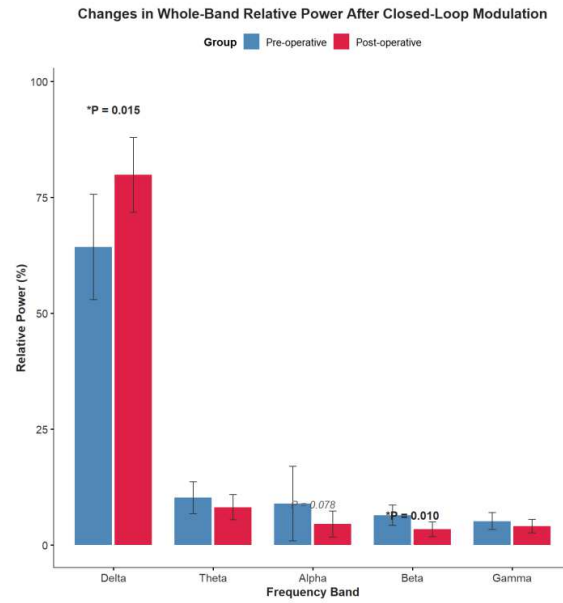
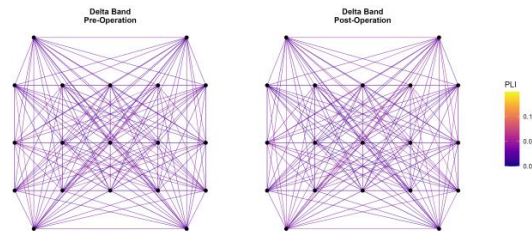
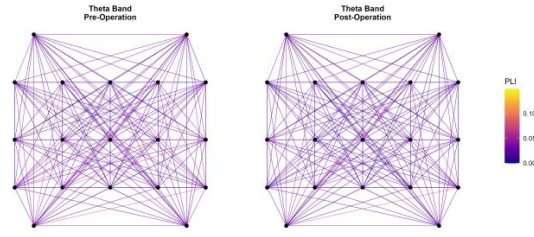


Figure 6. Comparison of scalp EEG relative power in each frequency band before and after closed-loop neuromodulation. The vertical axis indicates the relative power percentage (%), and the horizontal axis shows the five classical EEG frequency bands (Delta, Theta, Alpha, Beta, and Gamma). Blue bars represent the preoperative baseline level, red bars represent the 12-month postoperative follow-up level, and error bars indicate the standard deviation. The postoperative delta relative power was significantly increased relative to baseline (*P = 0.015), the postoperative beta relative power was significantly decreased relative to baseline (*P = 0.010), alpha showed a marginal decreasing trend (P = 0.078), and the differences in theta and gamma were not statistically significant.

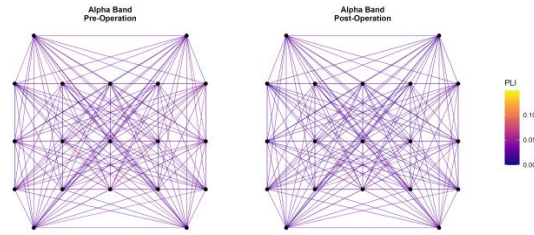
The phase lag index (PLI) was used to evaluate changes in brain functional connectivity. Paired t tests were performed on the 171 electrode pairs in each band, with Benjamini–Hochberg correction applied separately for multiple comparisons within each band. The results showed that the corrected q values of all electrode connections in the delta, theta, alpha, beta, and gamma bands were > 0.05 , and no statistically significant differences in EEG phase synchrony were found between pre- and postoperative recordings (Figure 7).



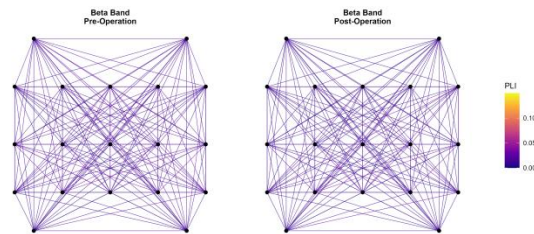
(A)



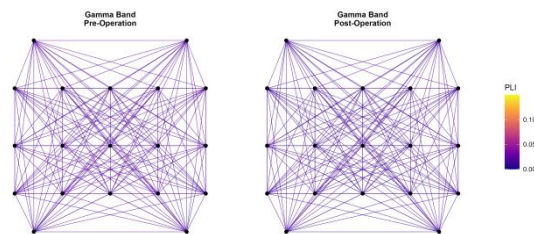
(B)



(C)



(D)



(E)

Figure 7. Comparison of scalp EEG phase lag index (PLI) functional connectivity across frequency bands before and after closed-loop neuromodulation. A–E correspond to the delta, theta, alpha, beta, and gamma bands, respectively. In each subplot, the left panel shows the preoperative baseline state and the right panel shows the 12-month postoperative follow-up state. The color scale on the right indicates the PLI values, reflecting the strength of phase synchrony between EEG electrodes. After paired t tests with Benjamini–Hochberg multiple comparison correction, no statistically significant differences in EEG phase synchrony were found between pre- and postoperative recordings in any frequency band (corrected $q > 0.05$).

Discussion

4.1 Efficacy and clinical value of closed-loop neuromodulation

The results of this cohort showed that the median seizure frequency decreased from the baseline of 8.0 seizures/month to 4.0 seizures/month at the 1-year follow-up, a reduction of 51.6%, and further decreased to 2.0 seizures/month at the 2-year follow-up. These results are generally consistent with international multicenter studies reporting a 53% seizure reduction at 2 years and a 72% reduction at 6 years after RNS treatment [5], confirming the efficacy of closed-loop neuromodulation in the Chinese population. Notably, marked inter-individual heterogeneity in treatment response was observed, with seizure reduction rates ranging widely from 12.5% to 100%; one patient achieved complete seizure freedom, and four patients achieved a seizure reduction of more than 50%.

With prolonged treatment, the efficacy of closed-loop neuromodulation showed a clear cumulative improvement [5, 27]. At 24 months postoperatively, the median monthly seizure frequency of the seven patients who completed follow-up further decreased to 2.0 seizures, representing a 75.0% reduction relative to baseline. Although the difference did not reach statistical significance compared with the 12-month postoperative value, this trend clearly reflects the chronic therapeutic effect of closed-loop neuromodulation: rather than acutely aborting individual seizures, the treatment induces progressive plastic reorganization of the epileptic network through long-term, repeated targeted stimulation, which is corroborated by the changes in brain network connectivity observed in the subsequent electrophysiological analyses of this study.

Regarding the temporal distribution of the responder rate, the responder rates at 3, 6, and 12 months postoperatively were stably maintained at 75.0%, suggesting that closed-loop neuromodulation has a relatively rapid onset of action and that most patients obtain clear clinical benefit early in treatment, enabling clinicians to judge treatment effectiveness at an early stage [28]. Meanwhile, the further increase in the responder rate at 24 months indicates that, for patients with a poor early response, allowing sufficient time for individualized parameter adjustment can also improve seizure control.

4.2 Individualized characteristics of stimulation parameters

Neuromodulation programming parameters such as stimulation amplitude, stimulation frequency, stimulation pulse width, and target changes showed no statistically significant associations with the seizure reduction rate at the population level, and no universal programming rule applicable to all patients with epilepsy was identified. In contrast, patients showed significant inter-individual differences in baseline efficacy, and some patients

exhibited specific temporal associations between programming parameters or target adjustments and seizure control, with marked inter-individual heterogeneity in both the strength and the direction of the associations. These findings suggest that the therapeutic benefit of neuromodulation for epilepsy does not depend on a unified parameter-setting pattern but is more likely an individual-specific response. This is consistent with previous studies: Skarpaas et al. pointed out that the epileptogenic zone location, electrophysiological characteristics, and neural circuit plasticity differ markedly among patients with epilepsy, such that identical stimulation parameters may produce different therapeutic effects. Chiang et al. considered that the same stimulation protocol can have different effects on the same patient under different seizure risk states [29]. Heck et al. considered that most patients can achieve efficacy improvement without high-amplitude stimulation [12]. In clinical practice, a standardized, unified programming parameter protocol is not recommended; instead, progressive, targeted, and differentiated adjustment of stimulation parameters and targets should be performed according to the individualized characteristics of long-term postoperative efficacy follow-up, which can provide objective statistical references for developing individualized neuromodulation strategies for epilepsy.

4.3 Spectral power and functional connectivity reorganization of intracranial EEG

To clarify the underlying electrophysiological mechanisms by which closed-loop neuromodulation improves epileptic seizures, this study leveraged the high spatial resolution of intracranial electrodes to perform focal analyses from the two dimensions of spectral power and network connectivity. The results showed that, after 12 months of treatment, the interictal EEG power of the γ (30–50 Hz) and high- γ (50–99 Hz) bands showed a significant increasing trend, whereas no significant changes were found in the δ , θ , α , and β low-frequency bands.

Physiological γ and high- γ oscillations are autonomously generated by local networks of parvalbumin (PV)-positive inhibitory interneurons [30]. Their generation depends on focal synaptic interconnection and microcircuit regulation and is closely related to the physiological synchronized discharge, information coding, and microcircuit integration of neuronal clusters [31]. The power of these oscillations directly reflects the integrity of local GABAergic inhibition and the homeostatic level of the excitation–inhibition (E-I) balance [22]. Under pathological conditions in the epileptogenic zone, PV-positive interneurons undergo degeneration and loss, and GABAergic synaptic transmission is impaired, directly

disrupting the generation of physiological γ oscillations [32] and manifesting as reduced baseline γ power, decreased rhythmic stability, and pathological hypersynchronous discharges of neuronal clusters due to the loss of precise inhibitory regulation [33]. The specific recovery of γ power after treatment thus indirectly reflects the functional restoration of the corresponding inhibitory microcircuits.

γ and high- γ activity in local field potentials has a high degree of spatial focality, and its effective signal sources are mainly confined to neuronal clusters within millimeters of the electrode [34]. This spatial property determines that the γ and high- γ power recorded by intracranial field potentials can accurately reflect the functional state of microcircuits around the stimulation target, with almost no confounding interference from activity in distant brain regions, and can serve as a valid indicator for evaluating focal circuit changes [20]. A previous long-term follow-up study of deep brain stimulation (DBS) for epilepsy showed that high-frequency oscillation power exhibited a persistent increasing trend after long-term electrical stimulation [35], and the increased intracranial γ and high- γ power may serve as an electrophysiological biomarker of improved seizure control [36–39]. This progressive power increase is not an acute transient effect of electrical stimulation but arises from synaptic plasticity changes induced by chronic repeated stimulation, including upregulation of the expression of the GABA-A receptor $\alpha 1$ subunit, increased density of inhibitory synaptic structures, and altered function of PV neuron calcium-binding proteins, among multiple cellular-level changes [40], ultimately achieving the physiological re-establishment of the local E-I balance [41]. Compared with the seizure-frequency counts used clinically, changes in γ and high- γ power can quantify the degree of functional restoration of the target circuit earlier and more objectively, are not affected by biases in patient seizure recording, and provide a reliable quantitative electrophysiological indicator for early postoperative efficacy evaluation and stimulation parameter optimization.

The PLI functional connectivity analysis provided direct evidence for the network reorganization hypothesis [42]. We observed a heterogeneous connectivity pattern in the high-gamma band, characterized by significantly increased connectivity within the epileptogenic zone and a tendency toward suppression of the long-range external connections of the epileptogenic zone, consistent with the RNS reorganization theory proposed in previous studies [11]. Scheid et al. found that patients with lower preictal high-gamma network synchronization capacity achieved better long-term outcomes with closed-loop neuromodulation, suggesting that the network synchronization and propagation

characteristics are factors influencing treatment benefit [43]. From the perspective of circuit mechanisms, the enhanced high-gamma connectivity within the epileptogenic zone corresponds to the recovery of synchrony in local inhibitory interneuron networks. Classical neuroscience theory has confirmed that synchronized γ oscillations in the cortex are generated by the interactions of PV-positive inhibitory interneurons through GABAergic synapses, and their synchrony strength directly reflects the functional integrity and information-processing capacity of local microcircuits [20], representing a direct manifestation of the normalization of microcircuit information processing. Meanwhile, the suppression of long-range pathway connectivity results from the sustained desynchronizing effect of chronic stimulation on aberrant excitatory projections within the epileptic network, weakening the structural basis for the transregional recruitment and spread of epileptiform discharges [44], consistent with the early finding of Sohal et al. that RNS can inhibit long-range γ phase synchrony [10].

The postoperative increases in intracranial field potential γ and high- γ power and local connectivity paralleled the significant reduction in seizure frequency, accompanied by suppression of long-range propagation pathway connectivity, suggesting that these changes are not pathological manifestations of enhanced epileptogenicity but more likely reflect restorative reorganization of local inhibitory microcircuit function [45]. The coordinated changes in the power spectrum and functional connectivity jointly indicate that the therapeutic effect of closed-loop neuromodulation does not arise from the acute direct blockade of individual seizures as traditionally conceived, but rather from the induction of progressive, adaptive plastic reorganization of the epileptic network through long-term, repeated targeted stimulation [46]. Khambhati et al. pointed out that these changes can be observed as early as 1 year postoperatively, providing the possibility of early prediction of therapeutic efficacy [11].

4.4 Electrophysiological changes in scalp EEG

Compared with the focal and precise monitoring of intracranial EEG, scalp EEG is noninvasive and covers the whole brain, allowing the overall effect of neuromodulation on whole-brain cortical excitability to be assessed at the macroscopic level. The scalp EEG effects of closed-loop neuromodulation were analyzed with respect to both spectral power and phase synchrony connectivity. One year after closed-loop neuromodulation, scalp EEG relative power showed an increase in the delta band and a decrease in the beta band, with a

decreasing trend in the alpha band; theta and gamma power also showed small decreases, suggesting that the intervention induced a diffuse whole-brain power change trend.

This diffuse whole-brain power change pattern has been partially corroborated by previous chronic follow-up studies of other neuromodulation modalities: intraoperative electrophysiological studies of centromedian nucleus stimulation showed that increased cortical delta power was significantly associated with postoperative seizure reduction and was considered a characteristic electrophysiological marker of inhibitory modulation of the thalamocortical circuit [47]; multiple neuromodulation studies for epilepsy, including vagus nerve stimulation (VNS) and deep brain stimulation of the thalamus, have observed decreased beta relative power in effective responders after long-term modulation [19, 48, 49], suggesting that the power spectral pattern of increased delta and decreased beta may be a common chronic electrophysiological change of antiseizure neuromodulation, reflecting the overall downregulation of cerebral cortical excitability.

The phase synchrony analysis showed no statistically significant differences in the phase synchrony levels of electrode pairs across all bands (delta, theta, alpha, beta, and gamma) before and after the intervention. This result is consistent with previous electrophysiological studies of long-term neuromodulation: existing studies have shown that, during chronic follow-up, only the gamma band of scalp EEG may show a mild desynchronization trend related to efficacy, whereas the whole-brain electrode-pair phase synchrony levels of the other bands usually show no statistically significant differences [50], suggesting that closed-loop neuromodulation mainly exerts its effects by modulating cortical spectral power rather than large-scale whole-brain phase synchrony.

4.5 Opposite changes in γ -band power between intracranial field potentials and scalp EEG

By combining intracranial and scalp EEG, this study found that γ -band power showed diametrically opposite changes between the two recording modalities: the γ and high- γ power in the intracranial epileptogenic zone significantly increased ($P < 0.05$), whereas the whole-brain γ power in scalp EEG showed a slight decreasing trend ($P > 0.05$). Previous studies have provided indirect support for this phenomenon from the intracranial and scalp recording perspectives, respectively. Local field potential studies have confirmed that activating PV-positive inhibitory interneuron circuits in target brain regions induces upregulation of local γ and high- γ oscillations, which is considered a local electrophysiological marker of

GABAergic inhibition restoration and normalization of epileptic network excitability [22, 30]. Volume conduction studies of scalp EEG have shown that gamma and high-gamma activity is heavily attenuated by the skull and soft tissues, with local cortical gamma signals attenuated by 10- to 100-fold in scalp recordings [20, 51]; therefore, focal gamma increases are difficult to capture in whole-brain scalp recordings, and responders to neuromodulation tend to show a reduction in overall scalp gamma power [19]. Most existing studies have analyzed intracranial and scalp signals separately, confirming the upregulation of intracranial high-frequency oscillatory activity and the suppression of scalp γ -band activity after closed-loop neuromodulation, respectively; however, no study has yet monitored intracranial and scalp electrical activity simultaneously in a paired manner and reported this opposite pattern of changes. This electrophysiological feature may provide a reference basis for future studies refining the mechanisms of neuromodulation.

Conclusion

Closed-loop neuromodulation can provide clear clinical benefit for patients with drug-resistant epilepsy, with efficacy showing progressive improvement over treatment duration and marked inter-individual heterogeneity. No universally optimal programming parameters applicable to all patients were identified in this cohort, suggesting that clinical practice should incorporate the patient's individualized follow-up efficacy to guide targeted adjustment of parameters and targets. The electrophysiological results support the chronic plastic reorganization hypothesis: the therapeutic effect of long-term closed-loop stimulation does not depend on the acute blockade of individual seizures but rather induces progressive functional reorganization of the epileptic network through repeated targeted intervention. In intracranial EEG, γ and high- γ power showed an increasing trend with significant effect sizes, suggesting functional restoration of inhibitory microcircuits in the stimulation target region, which may be an important electrophysiological feature of the re-establishment of the cerebral E-I balance toward a physiological steady state. High-gamma functional connectivity showed a heterogeneous pattern, with significantly enhanced local connections within the epileptogenic zone and a tendency toward suppression of long-range propagation pathways, reflecting both the normalization of the synchrony and information-processing capacity of local inhibitory neural networks and the possible weakening of the circuit basis for the transregional recruitment and spread of epileptiform discharges, providing intracranial-level experimental evidence for the network mechanisms of closed-loop neuromodulation. The

whole-brain increase in delta power and decrease in beta power observed in scalp EEG are consistent with the chronic electrophysiological effects of various antiseizure neuromodulation approaches, suggesting an overall downregulation of cerebral cortical excitability. By jointly monitoring intracranial and scalp EEG in a paired, simultaneous manner, this study observed, for the first time, opposite patterns of change in γ -band power between the two signal types, providing new experimental evidence for a deeper understanding of the mechanisms of closed-loop neuromodulation and for establishing a multidimensional electrophysiological biomarker system for efficacy evaluation.

Limitations

This study has several limitations. First, it is a single-center retrospective observational study with a limited sample size; future studies with larger samples and multicenter prospective designs are warranted to further validate the conclusions. Second, stimulation parameter adjustments in this study were based on individualized clinical practice rather than a prespecified standardized parameter gradient controlled trial; therefore, only the temporal associations between programming parameters and efficacy could be revealed, and it is difficult to directly establish causality between them or to determine universal optimal parameter thresholds. Future standardized parameter optimization trials could be designed to further explore individualized programming strategies for closed-loop neuromodulation.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This study was supported by the Key Research and Development Program of Hebei Province (Special Project for Biomedical Innovation, No. 23377709D), the Key Research and Development Program of Hebei Province (Special Project for Health Innovation, No. 23177732D), and the "14th Five-Year Plan" Clinical Medicine Innovation Research Team Project of the Department of Science and Technology of Hebei Province-Hebei Medical University (No. 2022LCTD-A6).

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Lin, Y., et al., Epilepsy centers in China: Current status and ways forward. *Epilepsia*, 2021. 62(11): p. 2640-2650.
2. Gonen, O.M., et al., The prognosis of refractory epilepsy patients rejected from epilepsy surgery. *Acta Neurol Scand*, 2015. 131(1): p. 58-62.
3. Ravat, S., et al., Clinical characteristics, surgical and neuropsychological outcomes in drug resistant tumoral temporal lobe epilepsy. *Int J Surg*, 2016. 36(Pt B): p. 436-442.
4. Eliashiv, D., et al., Postapproval Study for Brain-Responsive Neurostimulation for Drug-Resistant Focal Epilepsy: Three-Year Efficacy and Interim Safety Results. *Neurology*, 2026. 106(9): p. e214875.
5. Jobst, B.C., et al., Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. *Epilepsia*, 2017. 58(6): p. 1005-1014.
6. Lee, S.T., et al., Responsive neurostimulation in children, adolescents, and young Adults-Longitudinal effectiveness and safety. *Neurotherapeutics*, 2026. 23(2): p. e00865.
7. Inaji, M., et al., Responsive Neurostimulation as a Novel Palliative Option in Epilepsy Surgery. *Neurol Med Chir (Tokyo)*, 2021. 61(1): p. 1-11.
8. Skarpaas, T.L., B. Jarosiewicz, and M.J. Morrell, Brain-responsive neurostimulation for epilepsy (RNS((R)) System). *Epilepsy Res*, 2019. 153: p. 68-70.
9. Morrell, M.J. and C. Halpern, Responsive Direct Brain Stimulation for Epilepsy. *Neurosurg Clin N Am*, 2016. 27(1): p. 111-21.
10. Kokkinos, V., et al., Association of Closed-Loop Brain Stimulation Neurophysiological Features With Seizure Control Among Patients With Focal Epilepsy. *JAMA Neurol*, 2019. 76(7): p. 800-808.
11. Khambhati, A.N., et al., Long-term brain network reorganization predicts responsive neurostimulation outcomes for focal epilepsy. *Sci Transl Med*, 2021. 13(608).
12. Yan, H., et al., Interictal short-term high-frequency cortical stimulation modulates epileptogenic zone and distributed network. *Brain Commun*, 2025. 7(5): p. fcaf378.
13. Westin, K., et al., Neurophysiological effects of continuous cortical stimulation in epilepsy - Spike and spontaneous ECoG activity. *Clin Neurophysiol*, 2019. 130(1): p. 38-45.
14. Ronborg, S.N., et al., Acute effects of brain-responsive neurostimulation in drug-resistant partial onset epilepsy. *Clin Neurophysiol*, 2021. 132(6): p. 1209-1220.

15. Bodin, C., et al., Responders to vagus nerve stimulation (VNS) in refractory epilepsy have reduced interictal cortical synchronicity on scalp EEG. *Epilepsy Res*, 2015. 113: p. 98-103.
16. Ilyas, A., et al., Modulation of neural oscillations by vagus nerve stimulation in posttraumatic multifocal epilepsy: case report. *J Neurosurg*, 2019. 131(4): p. 1079-1085.
17. Sangare, A., et al., The Effectiveness of Vagus Nerve Stimulation in Drug-Resistant Epilepsy Correlates with Vagus Nerve Stimulation-Induced Electroencephalography Desynchronization. *Brain Connect*, 2020. 10(10): p. 566-577.
18. Pegg, E.J., J.R. Taylor, and R. Mohanraj, Spectral power of interictal EEG in the diagnosis and prognosis of idiopathic generalized epilepsies. *Epilepsy Behav*, 2020. 112: p. 107427.
19. Tong, X., et al., Analysis of power spectrum and phase lag index changes following deep brain stimulation of the anterior nucleus of the thalamus in patients with drug-resistant epilepsy: A retrospective study. *Seizure*, 2022. 96: p. 6-12.
20. Bartos, M., I. Vida, and P. Jonas, Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat Rev Neurosci*, 2007. 8(1): p. 45-56.
21. Heers, M., et al., Spectral bandwidth of interictal fast epileptic activity characterizes the seizure onset zone. *Neuroimage Clin*, 2018. 17: p. 865-872.
22. Sohal, V.S., et al., Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature*, 2009. 459(7247): p. 698-702.
23. Li, G., et al., A bimodal closed-loop neuromodulation implant integrated with ultraflexible probes to treat epilepsy. *Biosens Bioelectron*, 2025. 271: p. 117071.
24. Yang, Y., et al., Early assessment of responsive neurostimulation for drug-resistant epilepsy in China: A multicenter, self-controlled study. *Chin Med J (Engl)*, 2025. 138(4): p. 430-440.
25. Feng, C., et al., Dataset of chronic intracranial EEG of epilepsy patients via responsive neurostimulation system. *Front Neurosci*, 2026. 20: p. 1815732.
26. Morrell, M.J. and R.N.S.S.i.E.S. Group, Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*, 2011. 77(13): p. 1295-304.
27. Nair, D.R., et al., Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. *Neurology*, 2020. 95(9): p. e1244-e1256.
28. Vonck, K. and P. Boon, Epilepsy: closing the loop for patients with epilepsy. *Nat Rev Neurol*, 2015. 11(5): p. 252-4.
29. Chiang, S., et al., Evidence of state-dependence in the effectiveness of responsive neurostimulation for seizure modulation. *Brain Stimul*, 2021. 14(2): p. 366-375.
30. Buzsaki, G. and J.J. Chrobak, Temporal structure in spatially organized neuronal ensembles: a role for interneuronal networks. *Curr Opin Neurobiol*, 1995. 5(4): p. 504-10.
31. Huang, K., et al., EEG microstate-derived dynamic network biomarkers for lateralization and structural etiology in temporal lobe epilepsy. *Epilepsia*, 2026. 67(5): p. 2518-2532.
32. Leitch, B., The Impact of Glutamatergic Synapse Dysfunction in the Corticothalamocortical Network on Absence Seizure Generation. *Front Mol Neurosci*, 2022. 15: p. 836255.

33. Leitch, B., Parvalbumin Interneuron Dysfunction in Neurological Disorders: Focus on Epilepsy and Alzheimer's Disease. *Int J Mol Sci*, 2024. 25(10).
34. Einevoll, G.T., et al., Modelling and analysis of local field potentials for studying the function of cortical circuits. *Nat Rev Neurosci*, 2013. 14(11): p. 770-85.
35. Aiello, G., et al., Intracranial biomarkers for anterior thalamic deep brain stimulation in epilepsy: a long-term observational study. *Brain*, 2026.
36. Okoroafor, F., et al., Neurophysiologic Biomarkers of Invasive Neuromodulation Therapy for Epilepsy. *Neuromodulation*, 2026. 29(3): p. 360-375.
37. Sun, F.T., et al., Changes in the electrocorticogram after implantation of intracranial electrodes in humans: The implant effect. *Clin Neurophysiol*, 2018. 129(3): p. 676-686.
38. Arcot Desai, S., T.K. Tcheng, and M.J. Morrell, Quantitative electrocorticographic biomarkers of clinical outcomes in mesial temporal lobe epileptic patients treated with the RNS(R) system. *Clin Neurophysiol*, 2019. 130(8): p. 1364-1374.
39. Sanger, Z.T., et al., Anterior nucleus of thalamus deep brain stimulation for medication refractory epilepsy modulates theta and low-frequency gamma activity: a case study. *Ther Adv Neurol Disord*, 2025. 18: p. 17562864251323052.
40. Xu, K., et al., Influence of hippocampal low-frequency stimulation on GABA(A) R alpha1, ICER and BDNF expression level in brain tissues of amygdala-kindled drug-resistant temporal lobe epileptic rats. *Brain Res*, 2018. 1698: p. 195-203.
41. Ghafouri, S., et al., Deep brain stimulation restores the glutamatergic and GABAergic synaptic transmission and plasticity to normal levels in kindled rats. *PLoS One*, 2019. 14(11): p. e0224834.
42. Guo, K., et al., State-dependent alterations of network characteristics between seizure and non-seizure onset zones in drug-resistant epilepsy. *Cogn Neurodyn*, 2026. 20(1): p. 31.
43. Scheid, B.H., et al., Intracranial electroencephalographic biomarker predicts effective responsive neurostimulation for epilepsy prior to treatment. *Epilepsia*, 2022. 63(3): p. 652-662.
44. Fan, J.M., et al., Network connectivity predicts effectiveness of responsive neurostimulation in focal epilepsy. *Brain Commun*, 2022. 4(3): p. fcac104.
45. Rao, V.R. and J.D. Rolston, Unearthing the mechanisms of responsive neurostimulation for epilepsy. *Commun Med (Lond)*, 2023. 3(1): p. 166.
46. Ding, Y., et al., Brain functional connectivity and network characteristics changes after vagus nerve stimulation in patients with refractory epilepsy. *Transl Neurosci*, 2023. 14(1): p. 20220308.
47. Ho, J.C., et al., Refining centromedian nucleus stimulation for generalized epilepsy with targeting and mechanistic insights from intraoperative electrophysiology. *Nat Commun*, 2025. 16(1): p. 5272.
48. Ernst, L.D., et al., Electrocorticography Analysis in Patients With Dual Neurostimulators Supports Desynchronization as a Mechanism of Action for Acute Vagal Nerve Stimulator Stimulation. *J Clin Neurophysiol*, 2023. 40(1): p. 37-44.

49. Monto, S., et al., Epileptogenic neocortical networks are revealed by abnormal temporal dynamics in seizure-free subdural EEG. *Cereb Cortex*, 2007. 17(6): p. 1386-93.
50. Fraschini, M., et al., VNS induced desynchronization in gamma bands correlates with positive clinical outcome in temporal lobe pharmaco-resistant epilepsy. *Neurosci Lett*, 2013. 536: p. 14-8.
51. Petroff, O.A., et al., A comparison of the power spectral density of scalp EEG and subjacent electrocorticograms. *Clin Neurophysiol*, 2016. 127(2): p. 1108-1112.