Neuromodulation of Epilepsy Networks

Nathaniel D. Sisterson, MD[a], Vasileios Kokkinos, PhD[b,*]

KEYWORDS

• Neuromodulation • Seizure network • Closed-loop • Open-loop • Epilepsy

KEY POINTS

- Open-loop devices demonstrate nondestructive efficacy in reducing seizure frequency and severity.
- Closed-loop devices have shown improved outcomes, with evidence of therapeutic benefit through neuromodulation.
- Patient neurophysiology dictates custom programming of detection and stimulation parameters.

HISTORY OF NEUROMODULATION

The first uses of electrical stimulation applied to the human brain were documented in the late nineteenth and early twentieth century by neurosurgical pioneers including Victor Horsley and Harvey Cushing.[1,2] The human motor cortex was mapped during this time, and stimulation was used primarily for the purposes of diagnostics and localization.[3] The modern era of neuromodulation for epilepsy finds its roots with the experiments of Penfield and Jasper[4] during the 1950s. Penfield had observed inhibitory and modulatory effects in the recorded intracranial electroencephalogram (iEEG) as a result of electrical stimulation on neural tissue during his surgical procedures. Jasper and coworkers[5] further observed that low-frequency stimulation of the anterior nucleus (AN) of the thalamus enhanced synchronization in iEEG activity, whereas high-frequency stimulation had the opposite effect.

The first clinical applications of neural stimulation in the 1960s, however, focused on the use of deep brain stimulation (DBS) for chronic pain.[6,7] In the subsequent decades, neural stimulation for epilepsy gained popularity in the scientific community, because it was found to have significant inhibitory effects on interictal iEEG activity in epilepsy patients.[8–12] The experimental devices used for neurostimulation demonstrated promising efficacy, but the technology remained cumbersome and impractical. The first Food and Drug Administration (FDA)-approved device for epilepsy did not appear until 1997, when vagal nerve stimulation was approved for use in patients with refractory partial-onset seizures.[13]

NEUROMODULATION DEVICES

Treatment with antiepileptic drugs (AEDs) achieves 5-year seizure freedom in only 54% to 70% of patients.[14–16] Furthermore, the side effect profile for many AEDs has a considerable impact on quality of life, resulting in treatment failure in up to 40% of patients. Up to 88% of patients experience at least one AED-related adverse event.[17,18] Surgery is an attractive option for select patients, with 43% to 56% achieving seizure freedom at 5 years, and up to 74% experience a reduction of at least 50% in seizure frequency.[19,20] However, it is estimated that 50% to 90% of patients with drug-refractory epilepsy (DRE) may not be candidates for resective surgery.[21] For example, surgery may not be offered because of the proximity

[a] Department of Neurological Surgery, University of Pittsburgh, 3550 Terrace Street, Pittsburgh, PA 15261, USA; [b] Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, 429A Thier, Boston, MA 02114, USA
* Corresponding author.
E-mail address: vasileios.kokkinos@mgh.harvard.edu

Neurosurg Clin N Am 31 (2020) 459–470
https://doi.org/10.1016/j.nec.2020.03.009

of the primary seizure focus to eloquent cortex or the inability of investigations to identify a circumscribed epileptogenic zone (EZ).

Over the past several decades, the FDA has approved neurostimulation devices to address the existent therapeutic shortcomings of AEDs and surgery-refractory or inoperable epilepsy patients. The two primary categories of neuromodulation devices with FDA approval for use in patients with drug-resistant epilepsy are open-loop and closed-loop devices (Fig. 1). Open-loop, or nonresponsive devices, are so named because stimulation is preprogrammed and therefore independent of the brain-state. Conversely, closed-loop, or responsive devices, have a detection and stimulation component, and stimulation depends on detection of a specific brain-state (ie, the onset of an ictal event in epilepsy patients).

Open-Loop Neuromodulation

Vagus nerve stimulation

Open-loop stimulation of the left vagus nerve was approved for patients with partial-onset DRE in 1997. The device is comprised of a pulse generator implanted in the left chest and lead with helical attachments that wrap around the left vagus nerve. It has programmable parameters for output current, signal frequency, pulse width, signal on time, and signal off time (Table 1). It was designed to provide episodic and diffuse electrical stimulation to the brain, with the intention of nonspecifically inhibiting epileptogenesis.[22,23] Outcome studies have presented highly variable results, ranging from 24.5% to 73.4% of patients responding with a postimplantation seizure reduction around 50%.[24,25] However, fewer than 5% of patients achieve seizure freedom (Table 2).[26] More recently in 2017, vagus nerve stimulation (VNS) received approval for pediatric patients 4 years old, following the success of the postapproval study in Japan.[27] In 2001, evidence emerged that seizure control improved by nearly 50% when patients or their caretakers used a magnet to manually initiate stimulation in response to a seizure event.[28,29] This supported the idea that neural stimulation could be more effective when targeted to specific brain states. The most recent VNS device is capable of closed-loop control based on a hard-wired algorithm for detecting changes in heart rate that may indirectly indicate seizure onset.[30] However, these hard-wired algorithms do not have programmable features.

Deep brain stimulation

DBS targeting the ventral intermediate nucleus of the thalamus was first approved for essential tremor and Parkinson disease in 1997, and later in 2002 targeted to the subthalamic nucleus and internal globus pallidus. DBS targeting the anterior thalamus was approved for adults with DRE in 2017, following the success of the SANTÉ trial (see Table 2).[31,32] In this trial, DBS demonstrated a 69% reduction in seizure frequency at 5 years,

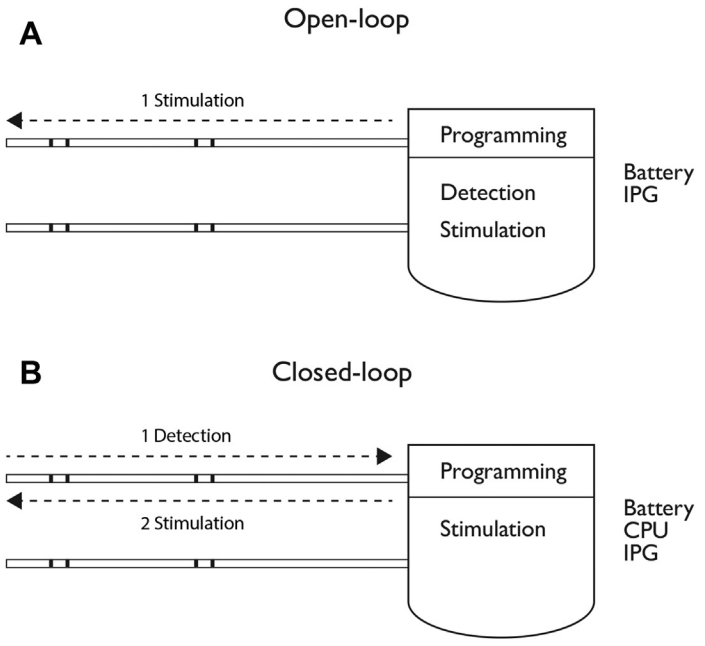

Fig. 1. Open-loop versus closed-loop neuromodulation. (*A*) Open-loop stimulation does not require detection, and stimulation is delivered independently of brain-state. (*B*) Closed-loop stimulation requires detection, and whether stimulation is delivered, where it is delivered, and the specific type of stimulation are dependent on brain-state at the time of detection. The process of detection followed by stimulation forms a "closed-loop."

Table 1
Default stimulation setting configurations for FDA-approved neuromodulatory devices

	Default Stimulation Settings				
Device	**Output**	**Frequency (Hz)**	**Pulse Width (μs)**	**On Time (s)**	**Off Time (min)**
VNS	1.0 mA	30	500	30	5
DBS	5.0 V	145	90	60	5
TNS	<10.0 mA	120	<250	—	—
RNS	1.0 mA	200	160	—	—

Abbreviations: RNS, responsive neurostimulation; TNS, trigeminal nerve stimulation; VNS, vagus nerve stimulation.
Data from Refs.[31,35,36,59,69,70]

with 16% of subjects experiencing seizure freedom lasting at least 6 months. Furthermore, recent evidence in which patients initially implanted with unilateral mesial temporal lobe (MTL) DBS received additional benefit from subsequent bilateral MTL DBS suggests the latter's superior efficacy in unilateral MTL epilepsy.[33] The device is comprised of a pulse generator implanted in the chest with two leads implanted in the brain parenchyma through an oblique trajectory targeting the thalamus. It has programmable parameters for amplitude, pulse width, rate, cycling on interval, and cycling off interval (see Table 1).

Trigeminal nerve stimulation

In 2013, the external trigeminal nerve stimulation (eTNS) for epilepsy clinical trial demonstrated a reduction of 34.8% in seizure frequency and a 50% responder rate of 36.8% at 12 months (see Table 2).[34,35] eTNS received Humanitarian Use Device designation from the FDA for Lennox-Gastaut syndrome in 2015. More recently, it received FDA approval for pediatric attention-deficit/hyperactivity disorder in 2019. However, eTNS has been approved for use in patients with DRE since 2012 in Europe. The eTNS is uniquely comprised of an external pulse generator with disposable bipolar transcutaneous electrodes. The electrodes are designed to provide electrical stimulation to the supraorbital branches of the trigeminal nerves (see Table 1).[36]

Closed-Loop Neuromodulation

Responsive neurostimulation

Closed-loop stimulation for epilepsy was formally introduced in 2004 with the external responsive neurostimulation (RNS) safety trial and subsequent FDA approval in 2012.[10] The RNS is comprised of an implantable neurostimulator indicated for patients with medically intractable partial-onset seizures arising from up to two foci. The RNS system is comprised of two bidirectional leads with a total of four channels connected to a programmable processor. Up to two channels may be configured for detection using up to four different patterns programmed from hardware designed line length, bandpass, or area under the curve detectors. A stimulation montage is configured to deliver up to five sequential stimulation therapies comprised of up to two bursts each. Each of the five therapies is contingent on redetection. The net total number of combinations of different programmable options is near infinite, which represents a significant challenge in working with closed-loop devices.[37]

CLINICAL UTILITY OF CLOSED-LOOP NEUROMODULATION

The remainder of this article focuses on closed-loop neuromodulation. Closed-loop stimulation is the only neuromodulatory therapy for which strong electrophysiologic evidence of network modulation exists.[38] Subanalyses of patient populations have been reported, which further describe the potential benefits of closed-loop therapy. The results of the randomized multicenter double-blinded controlled RNS pivotal trial were initially published in 2014 and contained 2 years of data for 191 subjects. The trial showed a median seizure reduction of 44% at 1 year and 53% at 2 years.[39]

Neocortical-Onset Epilepsy

Neocortical foci may be more challenging to localize than those arising from the MTL. These patients may additionally benefit from nondestructive neuromodulation therapy. Patients with primary seizure foci identified within inoperable neocortical structures, such as motor, sensory, and language areas, receive good benefit from closed-loop stimulation. Six-year follow-up data for 126 patients with neocortical epilepsy show a median seizure reduction of 77% and a 50% responder rate of 55%.[40]

Table 2
Clinical outcomes for neuromodulatory devices with FDA approval for drug-resistant epilepsy

	Approval	Indication	Clinical Trial Outcomes
Open-loop			
VNS	1997	Adults and adolescents older than 12 y of age with partial-onset seizures that are refractory to antiepileptic medications	E01, E02, E03, E04, E05 454 participants 35% reduction at 1 y 37% responder rate at 1 y 44% reduction at 2 y 43% responder rate at 2 y
	2017	Extended to use in patients 4 y of age and older	E3, E4, E5, E6, postapproval study (Japan) 117 participants 24.7% reduction at 1 y 35% responder rate at 1 y
DBS	2017	Adults with partial-onset seizures that are refractory to antiepileptic medications	SANTÉ 157 participants 41% reduction at 1 y 43% responder rate at 1 y 69% reduction at 5 y 68% responder rate at 5 y
TNS	2015[a]	Adults with partial-onset seizures that are refractory to antiepileptic medications	eTNS for DRE 50 participants 16.1% reduction at 18 wk 40.5% responder rate at 18 wk
Closed-loop			
RNS	2012	Adults with medically intractable partial-onset seizures arising from up to 2 foci	RNS pivotal trial 191 participants 41% reduction at 1 y 44% responder rate at 1 y 53% reduction at 2 y 55% responder rate at 2 y

Abbreviation: eTNS, external trigeminal nerve stimulation.
[a] Received Humanitarian Use Device designation from the FDA for Lennox-Gastaut syndrome but has been approved in Europe since 2012.

Mesial Temporal–Onset Epilepsy

Although temporal lobectomy is the most effective treatment of many DREs arising from the MTL, 25% to 35% of patients do not achieve sustained seizure freedom.[41,42] Furthermore, patients with bilateral MTL foci cannot receive definitive surgical treatment. Six-year follow-up data for 111 patients with MTL show a median seizure reduction of 70% and a 50% responder rate of 66%.[43] Responsive MTL stimulation was equally effective in subjects with bilateral or unilateral seizure onsets.

MECHANISMS OF ACTION IN CLOSED-LOOP NEUROMODULATION

Abortive Intervention

The original premise of closed-loop stimulation for epilepsy was to develop a responsive pacemaker for the brain.[44,45] The rationale stems from the nature of epileptic seizures resulting from the abnormal synchronized firing of neuronal populations, and the hypothesis that intervening stimulation should interrupt epileptic synchronization and return neuronal activity to its normal baseline (**Fig. 2**).[12,46] Although this direct mechanism was observed in the RNS pilot study, it was not found to be associated with acute therapeutic benefit.[10,38]

Substrate Modulation

Although the RNS closed-loop device is indeed capable of detecting ictal evolution and delivering stimulation capable of directly terminating the electrographic activity and presumable subsequent clinical sequelae, the most in-depth analysis of electrophysiologic data in RNS patients to date did not find evidence that this intervention was responsible for the therapeutic effects of the patients who demonstrated a therapeutic response.[38]

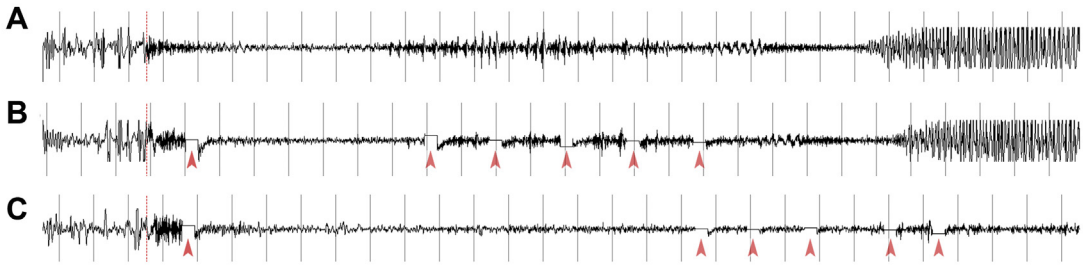

Fig. 2. Direct effects of neuromodulation: ictal inhibition. (*A*) Typical ictal pattern during the baseline period of recording, where only detection is active while stimulation is off. (*B*) The same typical ictal pattern after activation of stimulation. Note that although accurate detection occurs early, consecutive stimulations fail to abort the evolution of the seizure. (*C*) The first stimulation pulse aborts the evolution of the seizure and temporarily returns the iEEG to its interictal background. Note that it might take more than one stimulation pulse to avert the seizure completely and return the iEEG background to its interictal levels (5 seconds after the end of the page, not shown). *Red arrows* denote stimulation intervals during which the recording amplifier is off-line.

Direct effects

The direct effects of closed-loop stimulation occur via the application of an electrical pulse close in time and space to the origin of the ictal activity. One way this stimulation affects seizures is by disrupting ictal evolution and returning the seizure network to its baseline interictal state (see Fig. 2).[10,47,48] One explanation for the mechanism of this disruption in that transient stimulation-induced activation of local postsynaptic potentials creates extracellular fields that oppose those created by the excitatory epileptogenic postsynaptic potentials. In doing so, stimulation reduces the excitability of underlying epileptogenic neuronal populations.[49] Another potential mechanism is a temporary change in ictal-onset frequency of oscillation that occurs exclusively during and around the stimulation pulse interval (Fig. 3).[36] This phenomenon is explained as the result of a temporary desynchronization of the neuronal populations recruited by the epileptogenic source. Previous reports show that acute and subacute chronic stimulation correlates with background normalization on iEEG recordings over time.[50–52] Furthermore, this normalization also correlates with improved seizure control.[53–55] However, more recent evidence suggests that these direct modulatory effects may have no appreciable association with outcome.[38]

Indirect effects

Indirect modulatory effects are those that do not appear during the stimulation period and are not generated by individual stimulation events; instead of directly disrupting ictal synchrony to restore baseline brain-state, these effects modulate the epileptogenic network over time. Five categories of indirect modulation effects have been identified: (1) spontaneous attenuation, where electrographic seizure patterns were interrupted long after the applied stimulation pulses (Fig. 4); (2) frequency modulation, where the

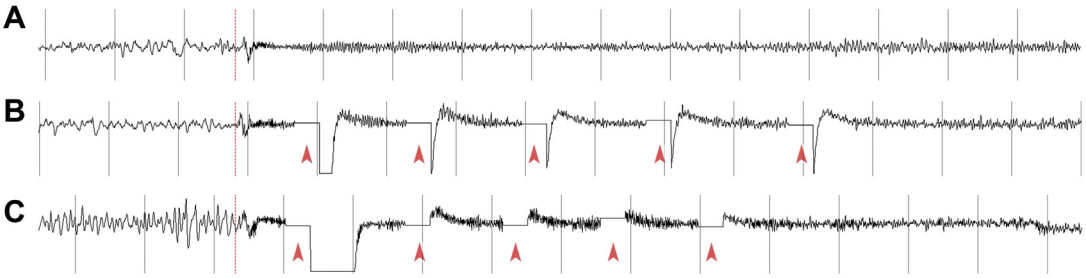

Fig. 3. Direct effects of neuromodulation: frequency modulation. (*A*) Typical ictal pattern during the baseline period. (*B*) Typical ictal pattern after activation of stimulation. (*C*) After several weeks of stimulation, a transient change in the ictal frequency of oscillation at the onset was observed. Otherwise, seizures remained the same in terms of evolution profile, spectral content, and mean duration. Red arrows as in Fig. 2.

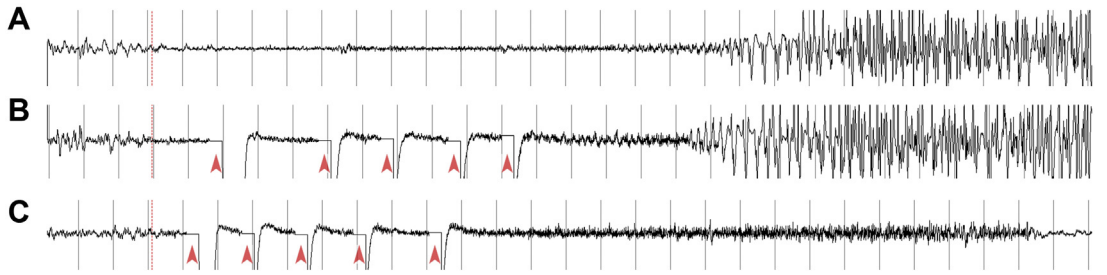

Fig. 4. Indirect effects of neuromodulation: spontaneous ictal attenuation. (*A*) Typical ictal pattern during the baseline period. (*B*) Typical ictal pattern after activation of stimulation. (*C*) After a few weeks of stimulation, among seizures following the typical pattern, seizures that initially evolved but failed to reach an adequate synchronization level were observed. Note that stimulations occur too early in the seizure onset to be related to the seizure resolution and the background normalization that followed. Red arrows as in Fig. 2.

spectral signature/pattern showed remarkable changes in frequency content (Fig. 5); (3) coarse fragmentation, where the discharge continuity was intermittently spontaneously interrupted by brief background intervals that were not a result of direct stimulation (Fig. 6); (4) fine fragmentation, where the refractory period between consecutive ictal spikes was markedly increased (Fig. 7); and (5) modulation of the electrographic seizure pattern duration, where the mean interval between the onset and the offset of the electrographic seizure patterns underwent remarkable changes (reductions and increases) that cannot be attributed to direct inhibition of the electrographic seizure patterns. One explanation regarding the mechanisms underlying indirect modulatory effects is that stimulation establishes over time extracellular electrical field barriers between functionally interconnected epileptogenic populations, thereby isolating excitatory neuronal pools. As a result, the seizure network progressively becomes fragmented, desynchronized, and thus less epileptogenic.[56,57] A progressive failure of excitatory neuronal populations to achieve sufficiently high levels of synchronization could account for the observed spontaneous seizure attenuation affect. Similarly, fine and coarse fragmented modulatory effects demonstrate consecutive and terminal failures of the modulated epileptogenic network to generate sufficient synchronization to precipitate a clinical seizure. Frequency modulatory effects indicate that stimulation can drive neuronal populations of the underlying epileptogenic network to synchronize and oscillate at multiple, alternative frequencies, thereby acting as a desynchronizer.

CHALLENGES IN CLOSED-LOOP NEUROSTIMULATION

Several major challenges must be overcome to direct the future of neuromodulation therapy (Fig. 8). First, the mechanisms of neuromodulation must be elucidated. Second, the impact of lead location on seizure detection and network stimulation must be evaluated. Third, evidence must be found for precisely what neurophysiologic signals of interest must be targeted for intervention.

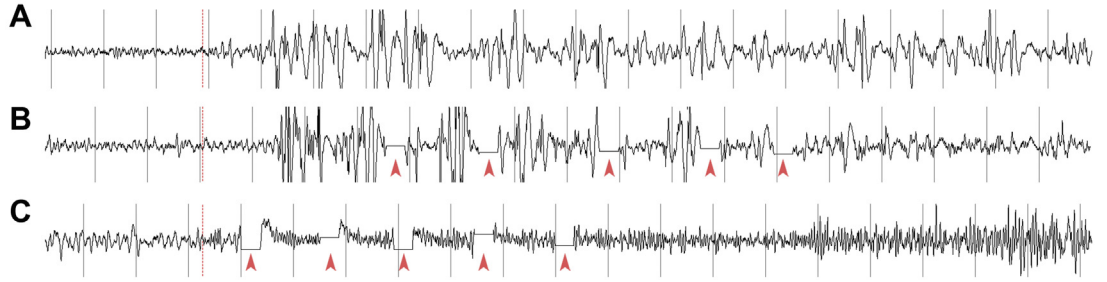

Fig. 5. Indirect effects of neuromodulation: frequency modulation. (*A*) Typical ictal pattern during the baseline period. (*B*) Typical ictal pattern after activation of stimulation. (*C*) After several weeks of stimulation, among the seizures with the typical pattern, seizures with a higher frequency spectral content were identified. Red arrows as in Fig. 2.

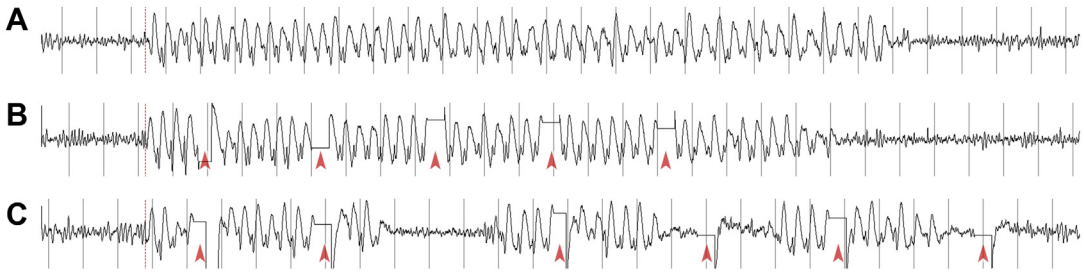

Fig. 6. Indirect effects of neuromodulation: coarse fragmentation. (*A*) Typical ictal pattern during the baseline period. (*B*) Typical ictal pattern after activation of stimulation. (*C*) After several weeks of stimulation, pronounced and systematic discontinuities appeared in the ictal evolution pattern, during which the iEEG signal returned to background levels. Red arrows as in Fig. 2.

Fourth, algorithms for determining correct stimulation parameters must be systematically deduced. Barriers to overcoming these problems include limited insight into what is actually occurring during closed-loop stimulation. Heterogeneity of patient population further complicates this challenge.

Heterogeneity in Device Activity

Device behavior in closed-loop stimulation is not transparent, largely because of practical constraints on storage space.[58] Detailed data come from iEEG recordings, and only the four most recent recordings before device interrogation are saved. Approximately 97% of the recordings are overwritten on a daily basis.[58] This results in a significant temporal bias in the iEEG recordings physicians observe. Summary data provide total detection and stimulation counts at a resolution of hours and days. However, the hourly and daily counters are also subject to space constraints, with approximately 15% and 13% of the data being truncated, respectively.[58] Counters without timestamps tally detection and stimulation counts between downloads from the device to a laptop and are designed in a way that prevents data truncation. Unpredictable variability exists in detector accuracy between patients, ranging from 45% to 100% (**Fig. 9**).[58] There is significant variability in the cumulative (total) amount of stimulation therapy delivered between patients, with some patients receiving greater than 10 times the amount, or dosage, as others. For patients with a bilateral lead configuration, cumulative therapy delivered to the left and right hemispheres is also unpredictably asymmetric.

Lead Placement

The official recommendation of the RNS device manufacturer is to implant the leads within the estimated EZ, if the patient had not had previous intracranial monitoring, or at the seizure-onset zone (SOZ), if the patient underwent previous intracranial monitoring.[59] Identification of the EZ and the SOZ is currently determined by consensus of multidisciplinary epilepsy conference panels. Evidence involves a combination of imaging and invasive and noninvasive diagnostic modalities. One rationale for lead placement in the SOZ is that detection at the site of origin, before propagation, provides the greatest lead time for intervention before the evolution of an ictal event. However, strong evidence that the SOZ should be targeted

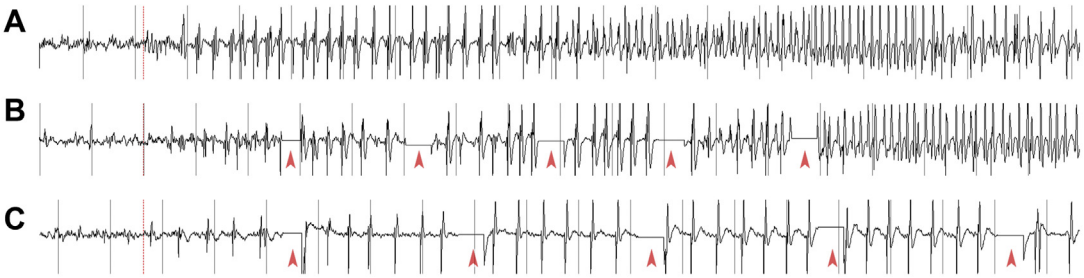

Fig. 7. Indirect effects of neuromodulation: fine fragmentation. (*A*) Typical ictal pattern during the baseline period. (*B*) Typical ictal pattern after activation of stimulation. (*C*) After several weeks of stimulation and changes in stimulation settings, the refractory period between consecutive ictal spikes markedly increased. Red arrows as in Fig. 2.

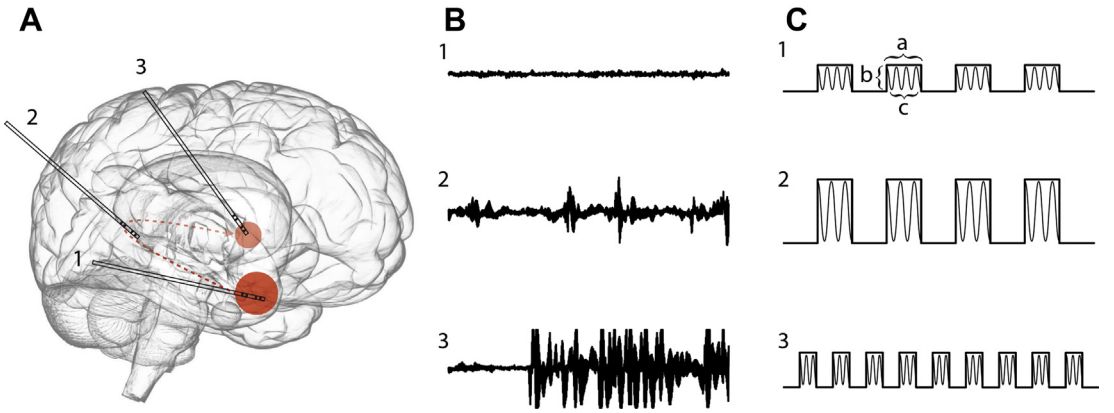

Fig. 8. Critical questions in closed-loop stimulation for seizure networks. (*A*) There is no evidence demonstrating whether leads implanted within the primary seizure focus (1), along the path of the network (2), or within a secondary focus (3) are optimal for either detection or stimulation. Furthermore, leads may be configured such that individual electrodes are either both within a focus (1) or partially within a focus (2). (*B*) There is no evidence demonstrating that optimal network modulation is achieved by stimulating particular neurophysiologic events, such as background activity (1), interictal bursts (2), or ictal activity (3). (*C*) There is no evidence demonstrating that particular stimulation parameters work better than others to achieve network modulation, including pulse width (a), amplitude (b), and frequency (c). Simple examples of different stimulation paradigms within a given time (eg, 1 second) are shown: (1) four medium-width pulses with high-frequency, low-amplitude (current/voltage) stimulation; (2) four medium-width pulses with low-frequency, high-amplitude stimulation; and (3) nine short-width pulses with low-frequency, low-amplitude stimulation.

for stimulation has not been demonstrated. Additionally, the statistical properties of time-series detection algorithms, such as the least unique information hypothesis, do not necessarily dictate that placement within the SOZ is optimal.[60] For instance, it is possible that detection could be accomplished with the greatest sensitivity and specificity at a site adjacent to the SOZ within the seizure network (see Fig. 8A).

Detection and Stimulation

The average detector accuracy achieved across patients is approximately 85% for ictal events.[58] Accuracy, however, is contingent on appropriate programming and continual refinement. Stimulation occurs during normal physiologic activity, interictal bursts, and ictal events. Stimulation is limited by a preprogrammed cap to the number of stimulation therapies delivered in a 24-hour period. At this time, evidence has not conclusively demonstrated that quantity of stimulation, either in amount of current or number of stimulations, correlates with better outcomes.

OFF-LABEL USAGE OF CLOSED-LOOP NEUROMODULATION

Generalized Epilepsy

DBS of the centromedian region of the thalamus has been shown to reduce the frequency and severity of generalized seizures.[53,61] However, current DBS devices cannot record intracranial data and lack the ability to modulate stimulation parameters necessary for optimization according to a patient's unique neurophysiology. Closed-loop stimulation is an attractive alternative because of its customizable detection and stimulation features, and its significant efficiency.[40,43] Recent data suggest that patients with idiopathic generalized epilepsy may benefit from a closed-loop, network modulation approach to therapy targeted to the AN or centromedian region of thalamus.[62–64]

Pediatric Epilepsy

Although VNS has been approved for use in the pediatric population, programmable closed-loop stimulation has not. However, many children are not candidates for surgery because of seizure foci in eloquent brain structures. Additionally, seizure foci often remain unclear despite appropriate work-up, making destructive therapy less attractive for the pediatric brain. Although closed-loop stimulation has been proposed as a treatment option for pediatric epilepsy, FDA approval is not yet in place.[65,66] However, case reports have demonstrated promising results in the pediatric population.[67] Notably, a 14-year-old patient with medically and surgically refractory type I cortical dysplasia was implanted with bilateral lateral temporal strip electrodes, and experienced an 80% to 90% reduction frequency at 19 months. A 9-year-old patient with a seizure focus in

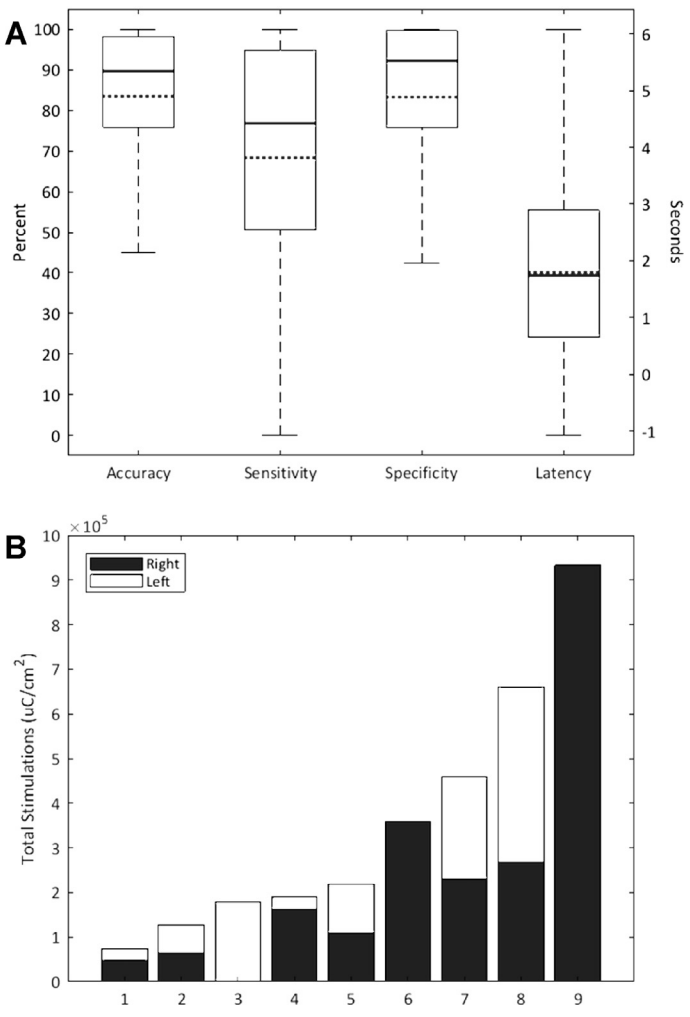

Fig. 9. Heterogeneity of device programming and behavior. (*A*) Wide interquartile ranges, with disagreement between the mean (*dashed lines*) and median (*solid lines*), revealing heterogeneous and widely distributed differences in device behavior between patients. (*B*) Total stimulation per patient at 8.5 months postimplant shows significant variability in the rate at which stimulation therapy is delivered between patients. For patients with a bilateral lead configuration, the rate at which stimulation therapy is delivered to the left and right hemispheres may be uneven.

eloquent cortex was implanted with cortical leads in the EZ and experienced an 83% reduction in seizure frequency. The authors observed that improvements and sustained therapeutic benefit over time suggest a strong neuromodulatory effect, which justifies the consideration of off-label closed-loop stimulation for children with DRE.[68]

SUMMARY

Neuromodulation is a valuable therapeutic option for patients with DRE who are not good candidates for surgical resection. First-generation open-loop devices were the first to demonstrate nondestructive efficacy in reducing seizure frequency and severity. Subsequently, closed-loop devices have shown improved outcomes, with evidence that therapeutic benefit is achieved through modulation of seizure networks. However, the precise therapy a patient receives is contingent on the relationship between the patient's own unique neurophysiology and the custom programming of detection and stimulation parameters. This heterogeneity poses significant challenges in the evaluation of closed-loop stimulation for DRE. Nevertheless, the improvement in outcomes achieved combined with its minimally invasive, nondestructive nature make closed-loop stimulation a promising therapy for additional indications, such as generalized and pediatric epilepsy.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Horsley V. Case of occipital encephalocele in which a correct diagnosis was obtained by means of the induced current. Brain 1884;7(2):228–43.

2. Cushing H. A note upon the faradic stimulation of the postcentral gyrus in conscious patients. 1. Brain 1909;32(1):44–53.
3. Bidwell LA. Focal epilepsy: trephining and removal of small haemorrhagic focus: no improvement; removal of part of leg centre after electrical stimulation: improvement. BMJ 1893;2(1714):988–9.
4. Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. Boston: Little Brown; 1954.
5. Jasper H, Naquet R, King EE. Thalamocortical recruiting responses in sensory receiving areas in the cat. Electroencephalogr Clin Neurophysiol 1955;7(1):99–114.
6. Gol A. Relief of pain by electrical stimulation of the septal area. J Neurol Sci 1967;5(1):115–20.
7. Heath RG. Psychiatry. Annu Rev Med 1954;5(1): 223–36.
8. Kinoshita M, Ikeda A, Matsumoto R, et al. Electric stimulation on human cortex suppresses fast cortical activity and epileptic spikes. Epilepsia 2004;45(7): 787–91.
9. Kinoshita M, Ikeda A, Matsuhashi M, et al. Electric cortical stimulation suppresses epileptic and background activities in neocortical epilepsy and mesial temporal lobe epilepsy. Clin Neurophysiol 2005; 116(6):1291–9.
10. Kossoff EH, Ritzl EK, Politsky JM, et al. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. Epilepsia 2004;45(12):1560–7.
11. Psatta DM. Control of chronic experimental focal epilepsy by feedback caudatum stimulations. Epilepsia 1983;24(4):444–54.
12. Chkhenkeli SA, Chkhenkeli IS. Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. Stereotact Funct Neurosurg 1997;69(1–4): 221–4.
13. Terry RS, Tarver WB, Zabara J. The implantable neurocybernetic prosthesis system. Pacing Clin Electrophysiol 1991;14(1):86–93.
14. Cockerell OC, Johnson AL, Sander JWAS, et al. Prognosis of epilepsy: a review and further analysis of the first nine years of the British national general practice study of epilepsy, a prospective population-based study. Epilepsia 1997;38(1): 31–46.
15. Lindsten H, Stenlund H, Forsgren L. Remission of seizures in a population-based adult cohort with a newly diagnosed unprovoked epileptic seizure. Epilepsia 2002;42(8):1025–30.
16. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. Epilepsia 1979;20(6):729–37.
17. Perucca E, Meador KJ. Adverse effects of antiepileptic drugs. Acta Neurol Scand 2005;112(s181):30–5.
18. Perucca P, Carter J, Vahle V, et al. Adverse antiepileptic drug effects: toward a clinically and neurobiologically relevant taxonomy. Neurology 2009;72(14): 1223–9.
19. Mohan M, Keller S, Nicolson A, et al. The long-term outcomes of epilepsy surgery. Biagini G, ed. PLoS One 2018;13(5):e0196274.
20. Engel J, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in Association with the American Epilepsy Society and the American Association of Neuro. Neurology 2003;60(4):538–47.
21. Engel J. The current place of epilepsy surgery. Curr Opin Neurol 2018;31(2):192–7.
22. The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures: The Vagus Nerve Stimulation Study Group. Neurology 1995;45(2):224–30.
23. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51(1):48–55.
24. Ben-Menachem E, Sander JW, Privitera M, et al. Measuring outcomes of treatment with antiepileptic drugs in clinical trials. Epilepsy Behav 2010;18(1–2):24–30.
25. Cersósimo RO, Bartuluchi M, Fortini S, et al. Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies. Epileptic Disord 2011;13(4):382–8.
26. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the therapeutics and technology assessment subcommittee and quality standards subcommittee of the American Academy of Neurology and the American Epile. Neurology 2004;62(8):1261–73.
27. Kawai K, Tanaka T, Baba H, et al. Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry. Epileptic Disord 2017;19(3):327–38.
28. Boon P, Vonck K, Van Walleghem P, et al. Programmed and magnet-induced vagus nerve stimulation for refractory epilepsy. J Clin Neurophysiol 2001;18(5):402–7.
29. Morris GL 3rd. A retrospective analysis of the effects of magnet-activated stimulation in conjunction with vagus nerve stimulation therapy. Epilepsy Behav 2003;4(6):740–5.
30. Hamilton P, Soryal I, Dhahri P, et al. Clinical outcomes of VNS therapy with AspireSR 1 (including cardiac-based seizure detection) at a large complex epilepsy and surgery centre. Seizure 2018;58: 120–6.

31. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5):899–908.
32. Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 2015;84(10):1017–25.
33. Vonck K, Sprengers M, Carrette E, et al. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Int J Neural Syst 2013;23(01):1250034.
34. Soss J, Heck C, Murray D, et al. A prospective long-term study of external trigeminal nerve stimulation for drug-resistant epilepsy. Epilepsy Behav 2015;42:44–7.
35. Slaght SJ, Nashef L. An audit of external trigeminal nerve stimulation (eTNS) in epilepsy. Seizure 2017;52:60–2.
36. DeGiorgio CM, Soss J, Cook IA, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. Neurology 2013;80(9):786–91.
37. Sisterson ND, Wozny TA, Kokkinos V, et al. Closed-loop brain stimulation for drug-resistant epilepsy: towards an evidence-based approach to personalized medicine. Neurotherapeutics 2018. https://doi.org/10.1007/s13311-018-00682-4.
38. Kokkinos V, Sisterson ND, Wozny TA, et al. Association of closed-loop brain stimulation neurophysiological features with seizure control among patients with focal epilepsy. JAMA Neurol 2019;76(7):800–8.
39. Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia 2014;55(3):432–41.
40. Jobst BC, Kapur R, Barkley GL, et al. Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. Epilepsia 2017;58(6):1005–14.
41. Engel J. Early surgical therapy for drug-resistant temporal lobe epilepsy. JAMA 2012;307(9):922.
42. Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345(5):311–8.
43. Geller EB, Skarpaas TL, Gross RE, et al. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. Epilepsia 2017;58(6):994–1004.
44. Pereira EAC, Green AL, Stacey RJ, et al. Refractory epilepsy and deep brain stimulation. J Clin Neurosci 2012;19(1):27–33.
45. Akamatsu N, Tsuji S. Deep brain stimulation for epilepsy. Brain Nerve 2011;63(4):365–9 [in Japanese] Available at: http://www.ncbi.nlm.nih.gov/pubmed/21441639.
46. Lesser RP, Kim SH, Beyderman L, et al. Brief bursts of pulse stimulation terminate after discharges caused by cortical stimulation. Neurology 1999;53(9):2073.
47. Skarpaas TL, Morrell MJ. Intracranial stimulation therapy for epilepsy. Neurotherapeutics 2009;6(2):238–43.
48. Morrell MJ, Halpern C. Responsive direct brain stimulation for epilepsy. Neurosurg Clin N Am 2016;27(1):111–21.
49. Durand D. Electrical stimulation can inhibit synchronized neuronal activity. Brain Res 1986;382(1):139–44.
50. Velasco AL, Velasco F, Velasco M, et al. Neuromodulation of epileptic foci in patients with non-lesional refractory motor epilepsy. Int J Neural Syst 2009;19(03):139–47.
51. Child ND, Stead M, Wirrell EC, et al. Chronic subthreshold subdural cortical stimulation for the treatment of focal epilepsy originating from eloquent cortex. Epilepsia 2014;55(3):e18–21.
52. Lundstrom BN, Van Gompel J, Britton J, et al. Chronic subthreshold cortical stimulation to treat focal epilepsy. JAMA Neurol 2016;73(11):1370.
53. Velasco M, Velasco F, Velasco a L, et al. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 2000;41(2):158–69.
54. Elisevich K, Jenrow K, Schuh L, et al. Long-term electrical stimulation–induced inhibition of partial epilepsy. J Neurosurg 2006;105(6):894–7.
55. Kerezoudis P, Grewal SS, Stead M, et al. Chronic subthreshold cortical stimulation for adult drug-resistant focal epilepsy: safety, feasibility, and technique. J Neurosurg 2018;129(2):533–43.
56. Bragin A, Wilson CL, Engel J. Chronic epileptogenesis requires development of a network of pathologically interconnected neuron clusters: a hypothesis. Epilepsia 2000;41(s6):S144–52.
57. Schevon CA, Ng SK, Cappell J, et al. Microphysiology of epileptiform activity in human neocortex. J Clin Neurophysiol 2008;25(6):321–30.
58. Sisterson ND, Wozny TA, Kokkinos V, et al. A rational approach to understanding and evaluating responsive neurostimulation. Neuroinformatics 2020. https://doi.org/10.1007/s12021-019-09446-7.
59. NeuroPace® RNS® Technical User's Manual. 2015.
60. Bertschinger N, Rauh J, Olbrich E, et al. Quantifying unique information. Entropy 2014;16(4):2161–83.
61. Valentín A, García Navarrete E, Chelvarajah R, et al. Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. Epilepsia 2013;54(10):1823–33.
62. Kokkinos V, Urban A, Sisterson ND, et al. Responsive neurostimulation of the thalamus improves

seizure control in idiopathic generalized epilepsy: a case report. Neurosurgery 2020. https://doi.org/10.1093/neuros/nyaa001. pii:nyaa001.

63. Martín-López D, Jiménez-Jiménez D, Cabañés-Martínez L, et al. The role of thalamus versus cortex in epilepsy: evidence from human ictal centromedian recordings in patients assessed for deep brain stimulation. Int J Neural Syst 2017;27(07):1750010.
64. Herlopian A, Cash SS, Eskandar EM, et al. Responsive neurostimulation targeting anterior thalamic nucleus in generalized epilepsy. Ann Clin Transl Neurol 2019;6(10):2104–9.
65. Karsy M, Guan J, Ducis K, et al. Emerging surgical therapies in the treatment of pediatric epilepsy. Transl Pediatr 2016;5(2):67–78.
66. Ravindra VM, Sweney MT, Bollo RJ. Recent developments in the surgical management of paediatric epilepsy. Arch Dis Child 2017;102(8):760–6.
67. Singhal NS, Numis AL, Lee MB, et al. Responsive neurostimulation for treatment of pediatric drug-resistant epilepsy. Epilepsy Behav Case Rep 2018;10:21–4.
68. Kokoszka MA, Panov F, La Vega-Talbott M, et al. Treatment of medically refractory seizures with responsive neurostimulation: 2 pediatric cases. J Neurosurg Pediatr 2018;21(4):421–7.
69. Berens P. CircStat: A *MATLAB* toolbox for circular statistics. J Stat Softw 2009;31(10). https://doi.org/10.18637/jss.v031.i10.
70. LivaNova. Technical User's VNS Therapy Programming Software. 2019;(June).