Neuromodulation of Epilepsy Networks

Nathaniel D. Sisterson, MD, Vasileios Kokkinos, PhD,

**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 Jasper4 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 coworkers5 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

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* Corresponding author.
E-mail address: vasileios.kokkinos@mgh.harvard.edu

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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,

![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.”](image-url)
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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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%.\textsuperscript{40}

### Table 1

Default stimulation setting configurations for FDA-approved neuromodulatory devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Output (mA)</th>
<th>Frequency (Hz)</th>
<th>Pulse Width (μs)</th>
<th>On Time (s)</th>
<th>Off Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS</td>
<td>1.0</td>
<td>30</td>
<td>500</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>DBS</td>
<td>5.0</td>
<td>145</td>
<td>90</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>TNS</td>
<td>&lt;10.0</td>
<td>120</td>
<td>&lt;250</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RNS</td>
<td>1.0</td>
<td>200</td>
<td>160</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: RNS, responsive neurostimulation; TNS, trigeminal nerve stimulation; VNS, vagus nerve stimulation. Data from Refs.\textsuperscript{11,35,36,59,69,70}
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. 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%. 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. 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). 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

Table 2

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

<table>
<thead>
<tr>
<th>Approval</th>
<th>Indication</th>
<th>Clinical Trial Outcomes</th>
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<tbody>
<tr>
<td>Open-loop</td>
<td></td>
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<tr>
<td>VNS 1997</td>
<td>Adults and adolescents older than 12 y of age with partial-onset seizures that are refractory to antiepileptic medications</td>
<td>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</td>
</tr>
<tr>
<td>2017</td>
<td>Extended to use in patients 4 y of age and older</td>
<td>E3, E4, E5, E6, postapproval study (Japan) 117 participants 24.7% reduction at 1 y 35% responder rate at 1 y</td>
</tr>
<tr>
<td>DBS 2017</td>
<td>Adults with partial-onset seizures that are refractory to antiepileptic medications</td>
<td>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</td>
</tr>
<tr>
<td>TNS 2015</td>
<td>Adults with partial-onset seizures that are refractory to antiepileptic medications</td>
<td>eTNS for DRE 50 participants 16.1% reduction at 18 wk 40.5% responder rate at 18 wk</td>
</tr>
<tr>
<td>Closed-loop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNS 2012</td>
<td>Adults with medically intractable partial-onset seizures arising from up to 2 foci</td>
<td>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</td>
</tr>
</tbody>
</table>

Abbreviation: eTNS, external trigeminal nerve stimulation.

* Received Humanitarian Use Device designation from the FDA for Lennox-Gastaut syndrome but has been approved in Europe since 2012.
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).\(^\text{10,47,48}\) One explanation for the mechanism of this disruption is 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.\(^\text{49}\) 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).\(^\text{36}\) 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.\(^\text{50–52}\) Furthermore, this normalization also correlates with improved seizure control.\(^\text{53–55}\) However, more recent evidence suggests that these direct modulatory effects may have no appreciable association with outcome.\(^\text{38}\)

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 events 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. 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.

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.
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. A progressive failure of excitatory neuronal populations to achieve sufficiently high levels of synchronization could account for the observed spontaneous seizure attenuation effect. 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.
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. 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. 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. 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). 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. 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

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**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.

**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.
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. 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. 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. 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. 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.

**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. However, case reports have demonstrated promising results in the pediatric population. 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
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.

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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.


