Neurostimulation Devices for the Treatment of Neurologic Disorders

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) identify common electrostimulation systems, indications, and technologies for neurologic disorders; (2) understand the historical progress of electrostimulation for neurologic disorders; and (3) describe new technologies being developed to optimize electrostimulation techniques and procedures.

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Abstract

Rapid advancements in neurostimulation technologies are providing relief to an unprecedented number of patients affected by debilitating neurologic and psychiatric disorders. Neurostimulation therapies include invasive and noninvasive approaches that involve the application of electrical stimulation to drive neural function within a circuit. This review focuses on established invasive electrical stimulation systems used clinically to induce therapeutic neuromodulation of dysfunctional neural circuitry. These implantable neurostimulation systems target specific deep subcortical, cortical, spinal, cranial, and peripheral nerve structures to modulate neuronal activity, providing therapeutic effects for a myriad of neuropsychiatric disorders. Recent advances in neurotechnologies and neuroimaging, along with an increased understanding of neurocircuitry, are factors contributing to the rapid rise in the use of neurostimulation therapies to treat an increasingly wide range of neurologic and psychiatric disorders. Electrical stimulation technologies are evolving after remaining fairly stagnant for the past 30 years, moving toward potential closed-loop therapeutic control systems with the ability to deliver stimulation with higher spatial resolution to provide continuous customized neuromodulation for optimal clinical outcomes. Even so, there is still much to be learned about disease pathogenesis of these neurodegenerative and psychiatric disorders

and the latent mechanisms of neurostimulation that provide therapeutic relief. This review provides an overview of the increasingly common stimulation systems, their clinical indications, and enabling technologies.

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Neurostimulation devices provide much needed therapeutic relief to an unprecedented number of people affected by debilitating neurologic and psychiatric disorders worldwide. The rise of modern-day neuromodulation therapies extends over half a century, which are rich with serendipitous discoveries and technological advances that have led to different types of neurostimulation strategies. Within the past 2 decades, innovation in medical device technology has begun to drive the evolution of these neurostimulation systems at a more accelerated pace.

Neurostimulation therapies include invasive and noninvasive approaches that apply electromagnetic energy to specific anatomical targets to induce neuromodulation of the corresponding neural circuitry. In particular, invasive neurostimulation therapies have emerged as an effective treatment for a growing number of medically resistant neurologic and neuropsychiatric disorders. As such, this review will focus on the following established invasive neurostimulation strategies used clinically to modulate disordered circuitry to restore functionality: deep brain stimulation (DBS), motor cortex stimulation (MCS), responsive neurostimulation (RNS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS) (Figure 1). All these implantable neurostimulation systems include 3 primary components: stimulating electrode(s), an internalized pulse generator (IPG) that serves as a battery pack, and electrode extender(s) to subcutaneously connect the electrode(s) to the pulse generator. The surgical placement of the components depends on the type of neurostimulation system device, the anatomical location of the targeted dysfunctional neuronal circuitry, and the patient's medical history.

DEEP BRAIN STIMULATION

Historical Perspective

The earliest history of what became neuromodulation therapy started with ablative procedures in stereotactic and functional neurosurgery in the mid-20th century to treat neuropsychiatric disorders. At that time, without pharmaceutical options for psychiatric disorders, desperate measures were taken to mitigate debilitating symptoms. The American neurophysiologist John Farquhar Fulton observed that modulation of regions of the cerebral cortex affected behavior in nonhuman primate studies.[1] These studies found that lesioning the prefrontal cortex reduced anxiousness and inspired the Portuguese neurologist Egas Moniz to develop a frontal lobotomy procedure for which he received a Nobel Prize in 1949. For over a decade, until the mid-1950s, tens of thousands of lobotomies were performed in the United States to treat severe psychiatric disorders such as schizophrenia; however, these procedures often led to severe adverse effects, including extreme personality changes. With the introduction of the first antipsychotic drug chlorpromazine in 1952, along with the devastating adverse effects of lobotomies, these controversial procedures were largely abandoned by the late 1960s. Meanwhile, the Spanish neuroscientist Jose Delgado observed that implantable stimulating intracranial electrodes could aid in diagnosis and possibly provide therapeutic effects for neurologic disorders such as schizophrenia and epilepsy.[2] Furthermore, Robert G. Heath conducted clinical studies that leveraged intracranial electrodes to modulate brain activity to understand and treat intractable psychiatric disorders.[3-5]

During these clinical studies to modulate pathological behavior related to neuropsychiatric disorders, it was observed that stimulation of specific deep brain structures induced analgesia.[6] This serendipitous discovery ushered in decades of clinical studies to explore different neurostimulation targets to provide relief from intractable neuropathic and nociceptive pain.[7-9] Deep brain stimulation targets included the sensory nuclei of the thalamus, periaqueductal/periventricular gray, anterior cingulate cortex, internal capsule, posterior hypothalamus, and nucleus accumbens (NAc).[10] For decades to follow, rather than treating neurologic movement disorders, DBS

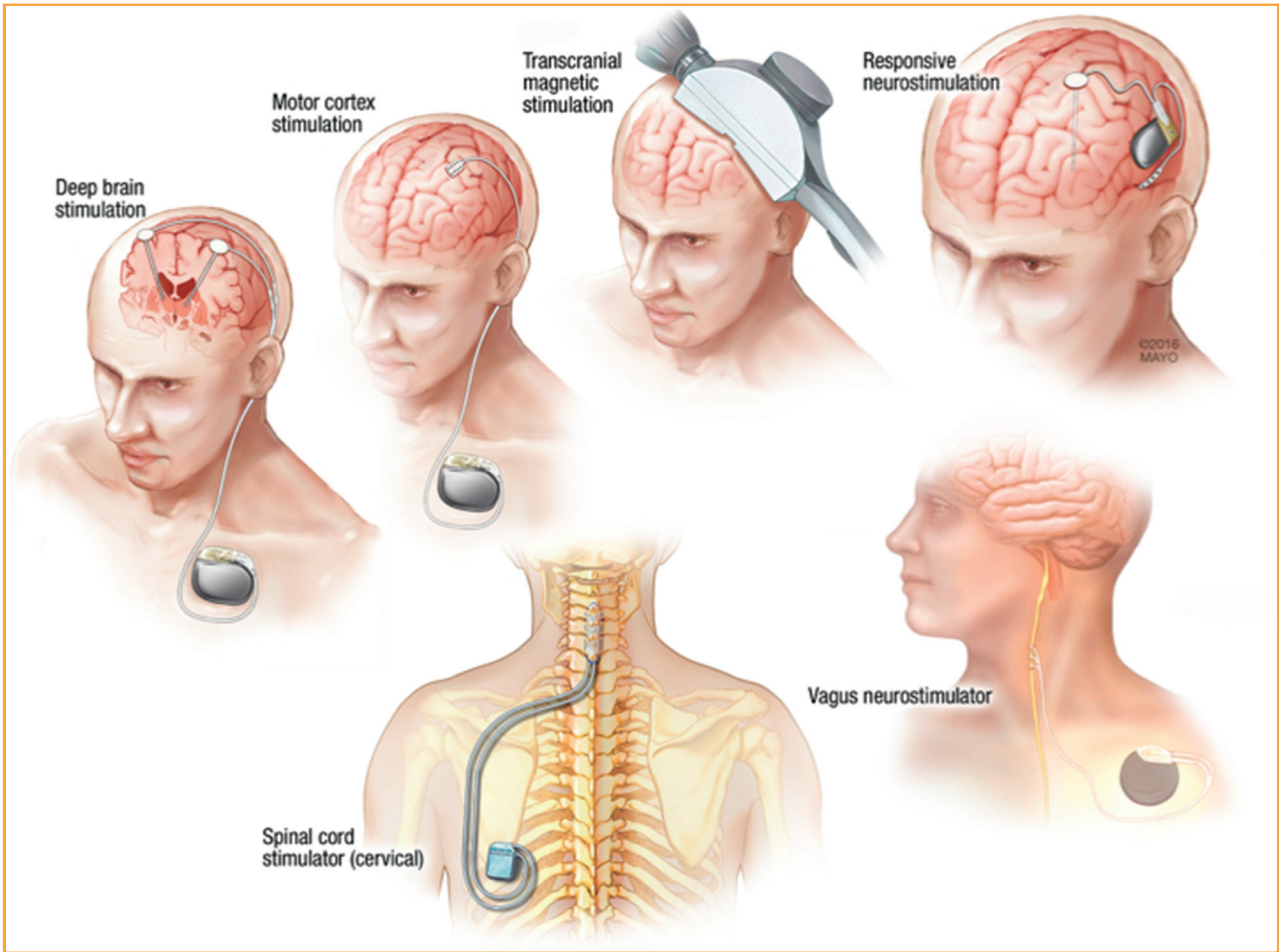

FIGURE 1. Neuromodulation devices for the treatment of neurologic disorders. Schematic summarizing common neuromodulation devices and stimulation targets in the central and peripheral nervous systems.

procedures were primarily used as a treatment for intractable chronic pain.[10]

Meanwhile, surgical interventions for neurologic movement disorders were underway. Early on, a cerebral pedunculotomy was considered an acceptable treatment for patients experiencing debilitating parkinsonian tremor even though it resulted in hemiparesis.[11,12] During one of these ablative procedures, the American neurosurgeon Irving S. Cooper, who completed his neurosurgery residency at Mayo Clinic in 1951, encountered complications that resulted in a small stroke in the thalamus, forcing him to halt the surgery before ablation.[12] Upon awaking from anesthesia, his patient was surprisingly freed from tremor and rigidity, without any hemiparesis.[12] As such, Cooper serendipitously discovered that ablating tissue within the thalamus effectively eliminated hallmark symptoms of Parkinson disease (PD). This substantial finding ushered in decades of innovative ablative techniques to surgically lesion regions of the basal ganglia (BG)—thalamocortical circuitry to treat neurologic motor disorders. However, with the introduction of levodopa replacement therapy in 1969, surgical interventions temporarily fell out of favor to treat PD until it was apparent that the prolonged use of levodopa medication often leads to adverse effects such as dyskinesia.[13,14] Cooper continued to create innovative surgical methods, including implanting Medtronic DBS electrodes to electrically

stimulate the BG—thalamocortical circuitry to mimic the therapeutic effects of a thalamotomy.[15] Cooper's findings influenced a French neurosurgeon, Alim-Louis Benabid, whose seminal paper ushered in modern-day long-term high-frequency DBS as an alternative treatment to reduce tremor.[16]

In the 1990s, growing concerns over the adverse and irreversible effects of misplaced lesions led to DBS therapy replacing ablative techniques altogether.[17,18] Stereotactic and functional neurosurgery coupled with advances in structural neuroimaging technologies, such as magnetic resonance imaging (MRI) and computed tomography, enabled preoperative planning to identify the precise DBS anatomical target locations and map out the trajectory path for optimal electrode placement.[19-22] Complementary intraoperative microelectrode recordings allowed for the acquisition of neurophysiological data to fine-tune lead placement in the DBS anatomical target.[19,23] In 1997, the Food and Drug Administration (FDA) granted approval for Medtronic DBS system to provide long-term high-frequency stimulation to the thalamus to relieve debilitating symptoms of refractory essential tremor and parkinsonian tremor.[24] Although ventrolateral intermedius (VIM) stimulation reduces tremor, other BG were found to be more effective stimulation targets to reduce debilitating parkinsonian symptoms such as bradykinesia and rigidity, as well as dyskinesia-associated long-term levodopa therapy.[24] High-frequency stimulation of the subthalamic nucleus (STN) and globus pallidus internus (GPi) were indicated as an effective and safe treatment for movement disorders.[25,26] As such, the FDA approved STN and GPi DBS for refractory PD in 2002, followed by a Humanitarian Device Exemption (HDE) for dystonia in 2003.[27]

After nearly half a century since Dr Heath's early studies, neurosurgical interventions that apply electrical stimulation to targeted brain regions are reemerging as acceptable treatment options for refractory psychiatric disorders. Some patients receiving DBS therapy to treat refractory neurologic movement disorders also experienced adverse psychiatric effects.[28,29] These behavioral observations, coupled with advances in functional neuroimaging technologies, such as positron emission tomography and functional magnetic resonance imaging (fMRI), led to the discovery of other potential therapeutic stimulation targets and the extension of DBS therapy as an option for treatment-resistant neuropsychiatric disorders.[30-33] Much has been discovered over the last couple of decades regarding the overall neural network circuitry.[34,35] Characterization of the BG—thalamocortical circuitry describes structurally and functionally segregated pathways that are modulated to control movement and mood. The anatomical nodes of the BG circuitry include the following: putamen, globus pallidus, thalamus, STN, caudate nucleus, and substantia nigra. Each BG component contributes to the overall function—or dysfunction—of the motor, associative, and limbic circuits. These pathways are organized to include specific regions of the thalamus and cortex.[36,37] Additional components of the cortico-basal ganglia—thalamocortical circuitry, such as the ventral capsule/ventral striatum (VC/VS) and the NAc, were indicated as a treatment for refractory psychiatric disorders, including Tourette syndrome and obsessive-compulsive disorder (OCD).[1]

Deep Brain Stimulation System and Surgical Procedure

Currently, Medtronic is the primary manufacturer of clinical and investigative DBS systems, although Boston Scientific and St. Jude Medical are releasing similar devices. The Medtronic stimulating electrodes (model 3387 or 3389) are commonly used to deliver long-term DBS for clinical and investigative purposes. The DBS electrodes are connected via Medtronic lead extenders to their battery-powered IPG. Medtronic Activa series of open-loop neurostimulation devices (Activa SC, Activa PC, and Activa RC) are FDA approved and differ on the basis of dimensions, weight, and battery type. These IPG devices are capable of delivering single- or dual-channel electrical stimulation with a frequency of 2 to 250 Hz, a pulse width of 60 to 450 μs, and an amplitude of 0.0 to 10.5 V.

Surgical procedures vary from institution to institution, yet most use these neurosurgical technologies to ensure precise placement of the electrode lead(s). The overall DBS procedure consists of 4 parts: (1) preoperative assessment; (2) preoperative planning; (3) surgical

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implantation; and (4) postoperative assessment (Figure 2). The surgical procedure typically takes up to 6 to 8 hours to complete and involves an interdisciplinary team of neurosurgeons, neurologists, nurses, and technical support staff for the medical devices and associated software. After patient assessment and consensus of eligibility for DBS, the patient undergoes DBS. First, the exact placement and trajectory path for the electrode lead is determined. Next, burr holes are carefully drilled at the planned entry points for the electrodes. In some institutions, complementary intraoperative neurophysiological data are acquired to guide lead placement. A slight deviation from the optimal path to the target may result in adverse effects such as slurred speech and abnormal sensations. As such, the electrode location is adjusted to maximize therapeutic and minimize adverse effects. Once successful trial stimulation is achieved, the DBS electrode is secured to the skull and excess wires placed under the scalp. Intraoperative fluoroscopy and postoperative MRI or

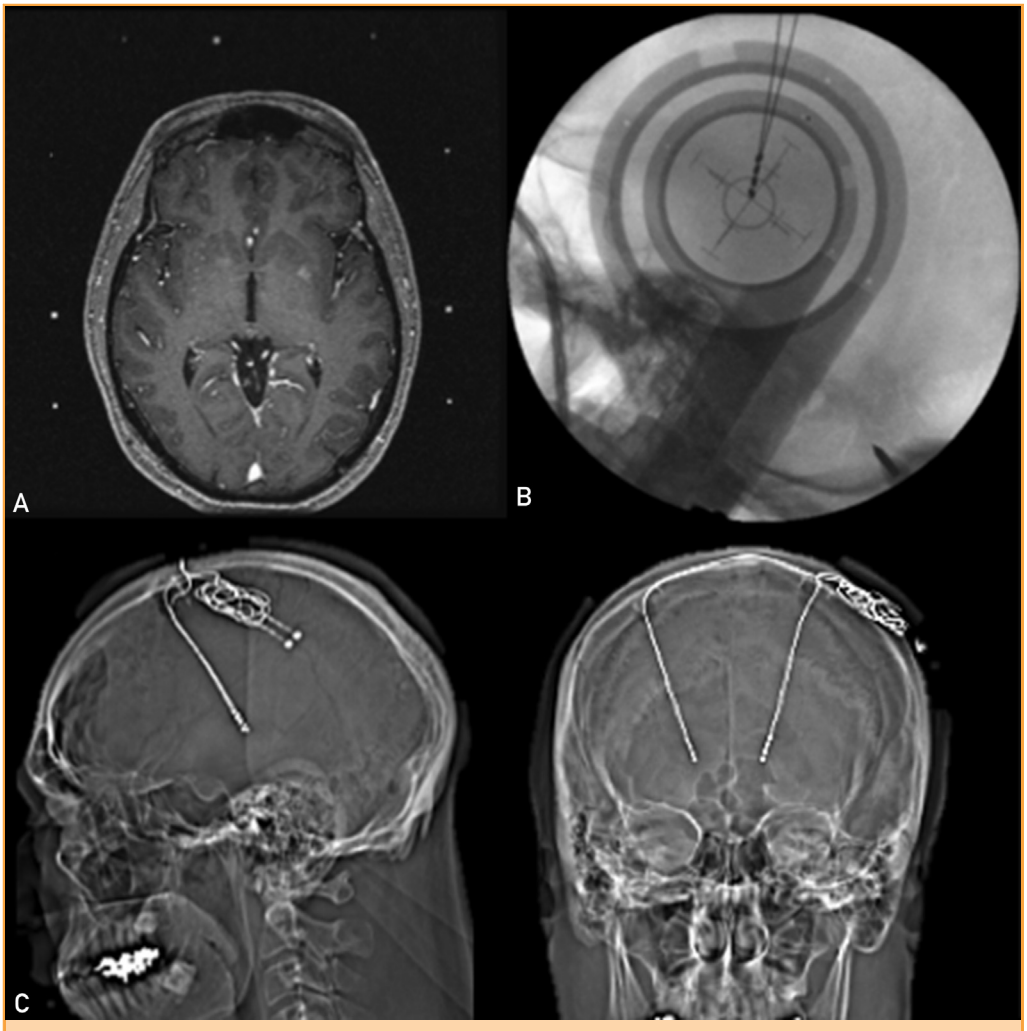

FIGURE 2. Deep brain stimulation (DBS). A, Intraoperative magnetic resonance imaging scan showing magnetic resonance fiducial markers that are used for stereotactic planning of the ventrolateral intermedius (VIM) thalamus for the treatment of essential tremor. B, Intraoperative fluoroscopy scan showing the accurate placement of bilateral VIM thalamic DBS leads. C, Postoperative head computed tomography scan showing the accurate placement of bilateral VIM thalamic DBS leads in the sagittal (left) and coronal (right) planes.

computed tomography scans are acquired to confirm electrode placement. Finally, lead extenders are tunneled subcutaneously down the neck to below the clavicle in which the pulse generator is implanted. After surgery, several postoperative outpatient sessions are conducted over 3 to 6 months by a trained DBS clinician who optimizes stimulation parameters on the basis of patient feedback and objective measurements.

Deep Brain Stimulation Clinical Indications

Currently, DBS therapy is FDA approved for medically refractory PD, essential tremor, dystonia, and OCD; in addition, other disorders under investigation include Tourette syndrome, treatment-resistant depression, chronic pain, alcohol and drug addiction, cluster headache, and Alzheimer disease.[25] Deep brain stimulation candidates are assessed and selected using an interdisciplinary team comprising neurosurgeons, neurologists, neuropsychologists, psychiatrists, speech-language pathologists, and biomedical ethicists.[38] The potential benefits and risks to the patient are considered on a case-by-case basis. The benefits of DBS are well documented; however, there are also motor and psychological adverse effects to consider. For instance, stimulation-induced adverse effects such as worsened gait disturbances, dysarthria, and dysphagia have been published.[39,40] Furthermore, neuropsychiatric and cognitive symptoms have been documented with stimulation in/near regions associated with sensorimotor, associative, and limbic functions.[41-43] Patients with medically refractory psychiatric and advanced neurodegenerative disorders often have comorbidities (eg, severe depression and cognitive deficits) that must be carefully considered during the selection process.[38,44-47]

Parkinson Disease. Parkinson disease is a neurodegenerative disorder marked by the cardinal symptoms of tremor, rigidity, akinesia, and bradykinesia.[48] The disease hallmark is the loss of dopamine cells in the substantia nigra pars compacta. Indications for DBS in PD are motor fluctuations, dyskinesia, medication-refractory tremor, and medical intolerance. In general, DBS improves those symptoms that respond well to dopaminergic medications, including resting tremor, rigidity, upper extremity bradykinesia, and bradykinetic component of gait. Other symptoms such as freezing of gait (FOG), dysarthria, and dysphagia have varying responses to dopaminergic medications and may be worsened by DBS therapies.[49] Thus, the ideal candidate would have an excellent L-dopa responsiveness as assessed by the Unified Parkinson's Disease Rating Scale. An exception to the general rule that DBS treats only dopa-responsive symptoms is tremor, which is well treated by DBS.

Standard DBS targets for PD include the STN, GPi, and VIM for tremor-predominant PD.[25] High-frequency (eg, 130-Hz) stimulation of the STN or GPi may improve all cardinal symptoms of PD, whereas stimulation of the VIM improves only tremor.[25] A class III study evaluating the effectiveness of STN-DBS treatment of PD over a 10-year span for 18 patients found that the treatment sustained its therapeutic effects.[50] A prospective study evaluated the long-term outcomes of bilateral STN-DBS treatment with and without levodopa medication for 42 patients with PD over a span of 5 years. This study confirmed the efficacy of STN DBS to improve off-medication motor function, while also reducing dyskinesia associated with levodopa therapy.[51] However, this study also observed a decline in cognitive and motor functions, including speech difficulties and FOG, which are characteristic of the neurodegenerative nature of PD.[51] Furthermore, a small subset of patients receiving STN-DBS therapy experienced cognitive and psychiatric issues, including depression and mania, apart from the progression of PD.[51]

It was previously believed that compared with GPi DBS, STN DBS more effectively treated motor symptoms; however, there were concerns that patients receiving STN-DBS therapy also experience an increased risk of adverse cognitive and psychiatric effects.[52,53] In 2016, a meta-analysis of 4 randomized controlled trials, with a combined total of 521 patients with PD, evaluated cognitive and psychiatric effects associated with STN-DBS vs GPi-DBS treatment.[54] This study concluded that the psychiatric effects (eg, depression and anxiety) and quality of life for patients receiving STN-DBS and GPi-DBS therapies were comparable;

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however, a greater decline in specific cognitive functions (eg, verbal fluency, learning, and memory) was observed in patients receiving STN-DBS therapy.

In addition, although FOG occurrences may be minimally reduced with dopaminergic medications, conventional DBS strategies for PD are ineffective and could worsen this type of gait disturbance.[48,55] Studies indicate that different DBS strategies may effectively reduce the occurrences of FOG. For instance, increased occurrences of FOG episodes often occurs as PD progresses and with long-term high-frequency STN DBS; however, studies found that lowering the stimulation frequency to 60 Hz markedly reduced the number of FOG episodes.[55,56] Furthermore, studies indicate that the pedunculopontine nucleus is showing promise as an effective alternative DBS target to reduce the occurrences of FOG.[48,57-59]

Essential Tremor. Essential tremor is the most common neurologic movement disorder characterized by rhythmic and regular oscillations. Candidates for DBS should be restricted to those patients with disabling action, postural, or rest tremors that significantly impair the ability to carry out their daily tasks. The optimum DBS target for tremor is the VIM.[30,60] Adverse effects of VIM stimulation may include dysarthria and paresthesias due to current spread into the thalamic nucleus just posterior to the VIM called ventralis caudalis (somatosensory thalamus).

Dystonia. Dystonia is an uncommon but severely debilitating movement disorder that involves involuntary sustained muscle contraction, causing repetitive twisting movement that results in abnormal posture.[61] The most often used target for DBS in dystonia is the GPi. There has been only 1 randomized blinded study of bilateral GPi DBS.[62] However, DBS for dystonia received an HDE from the US FDA in 2003. Complications of GPi DBS include visual deficits due to the anatomy of the optic tracts lying just ventral to the GPi; thus not inserting the DBS electrode too deeply is important. Another possible adverse effect of improperly placed electrode leads includes tetanic muscle contractions from the current spread to the cortical spinal tract, which lies just medial to the GPi.[63]

Obsessive-Compulsive Disorder. Obsessive-compulsive disorder is a psychiatric disorder that affects 2% of the population in the United States. It is characterized by intrusive anxiety-generating thoughts known as *obsessions*, with repetitive behavior or rituals (eg, counting, checking, or cleaning) known as *compulsions* that are perceived by the patient as necessary to reduce anxiety. The DBS targets for OCD include the VC/VS, NAc, STN, and inferior thalamic peduncle. Among early reports of outcome, Nuttin and colleagues found that 3 of 4 patients with OCD benefited from bilateral DBS, whereas a study by Greenberg et al found positive outcomes in 16 of 26.[64-66] Interestingly, several studies found that DBS in the region of the VC/VS resulted in smiling and laughter during surgery, indicating that this circuitry may be related to mood alteration.[67,68] Because of these positive results, an HDE from the US FDA was obtained in 2009.[1,69-71]

MOTOR CORTEX STIMULATION

Historical Perspective

Another fortuitous discovery in neurosurgery came in the early 1990s, when Tsubokawa hypothesized that stimulation of the somatosensory cortex could alleviate central pain and implanted cortical electrodes into patients with central pain syndromes. To his surprise, these electrodes covering the sensory cortex did not alleviate pain, but at times worsened it. Serendipitously, the stimulating electrodes just anterior to the somatosensory cortex, on the primary motor cortex, inhibited pain.[72,73] Since this initial discovery, there have been many additional studies to understand the therapeutic mechanisms of MCS, in comparison to DBS and SCS techniques, to alleviate chronic pain.[9,74]

Motor Cortex Stimulation System and Surgical Procedure

Currently, there are not any specific FDA-approved cortical stimulation electrodes; therefore, most centers use the paddle leads borrowed from epidural SCS for pain, which are FDA approved. Unlike DBS, cortical stimulation requires a craniotomy to implant either electrocorticography-like grids or paddle electrodes. Although the precise procedure varies

from center to center, most centers use image guidance for accurate electrode implantation. A craniotome is used to perform the craniotomy, exposing the dura underneath. Some centers place the electrode in the epidural space. In contrast, other centers have reported placing the cortical stimulating electrodes in the subdural space. Once the electrode is appropriately placed, the dura is closed, the bone flap placed back and secured with plates and screws, and the scalp is closed. Finally, a battery is implanted below the clavicle and connected subcutaneously to the cortical electrode wire (Figure 3).

It is estimated that 5% of the population lives with medically intractable pain, with a subset experiencing unbearable excruciating pain. Decades of use indicate that MCS is an effective therapy to provide pain relief for those patients who are affected by various medically intractable pain syndromes. Clinical MCS studies indicate a significant reduction in pain for neuropathic facial pain and poststroke pain. In a study of 100 patients with neuropathic facial pain, 84% experienced at least a 40% reduction in pain symptoms.[74]

RESPONSIVE NEUROSTIMULATION

Historical Perspective

Epilepsy is a common neurologic disorder that results in regular occurring seizures, which may be broadly categorized as partial or generalized, and manifest in various ways, such as a person having a blank stare for a couple of seconds to incapacitating convulsions and loss of consciousness. Approximately 1% to 2% of the US population has experienced epileptic seizures, with nearly 30% of those patients having treatment-refractory seizures that are unresponsive to antiepileptic drugs.[75] In those cases, only neurosurgical interventions are capable of reducing or eliminating the seizure activity. This includes resective surgery to remove the brain region(s) responsible for initiating the seizure activity or reversible neurostimulation therapy that is capable of significantly reducing the frequency of clinically evident seizures.

As early as the mid-20th century, it was observed that intracranial electrodes delivering high-frequency stimulation were capable of halting seizure activity.[2] Cooper, who pioneered reversible long-term neurostimulation methods, started with cerebellar stimulation and then moved on to other more effective deep brain structures such as the internal capsule and regions of the thalamus to reduce epileptic seizures.[15] Neurostimulation therapies to treat medically intractable epilepsy continued to evolve as advances in neurotechnologies enabled a more complete understanding of the pathological brain circuitry. As such, abnormal electrocortical activity was observed before clinically evident epileptic seizures. This discovery enabled the creation of an innovative closed-loop RNS system, which delivers therapeutic stimulation upon the detection of precursor signals to potentially halt epileptic seizure activity.[75] In 2013, the FDA approved NeuroPace RNS system (NeuroPace, Inc.) for the treatment of medically refractory

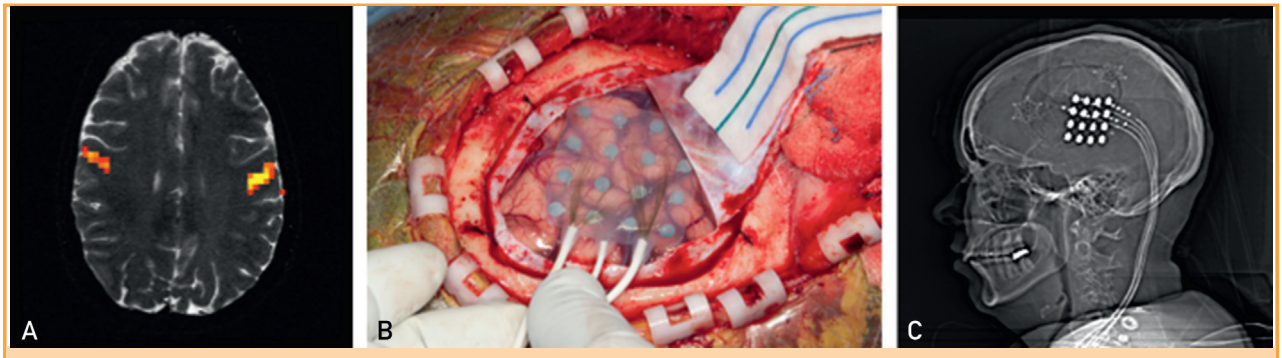

FIGURE 3. Motor cortex stimulation. A, Functional magnetic resonance imaging scan of the patient with tongue-tapping task that show the precise location of the motor area of the tongue. B, Intraoperative photograph showing the placement of the temporary grid on the cortical surface for test stimulation. C, Postoperative computed tomography scan of the head showing the precise location of the permanent grid for cortical stimulation.

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epilepsy.[76] References to RNS in current literature are synonymous with the NeuroPace closed-loop device.[76-80]

Responsive Neurostimulation System and Surgical Procedure

The NeuroPace RNS "smart device" system includes a cranially implanted neurostimulator, connected to depth or cortical strip leads, with 4 electrodes each, that are used for both sensing and stimulating targeted brain areas. The components are implanted using standard stereotactic surgical techniques while the patient is under general anesthesia. The neurostimulator is implanted within the skull, in the parietal region, and the leads are implanted in predetermined regions in which the seizures are believed to originate. Surgery recovery time typically takes about a month for a patient to fully recover; however, optimal therapeutic results may not be achieved until up to 2 years. On a daily to weekly basis, the patient downloads data from the neurostimulator to a laptop with specialized software that transfers it to a secured database for access by the physician. For at least the first year, during monthly visits, the physician adjusts detection and stimulation parameters on the basis of data retrieved from the device and patient feedback. The neurostimulator is programmed to continuously monitor electrophysiological signals that are precursors to seizure activity. Upon detection of this activity, the neurostimulator administers therapeutic electrical stimulation to halt the seizure activity. The stimulation parameters are adjusted on the basis of this feedback information for optimal therapeutic results.[77]

Responsive Neurostimulation Clinical Indications

The RNS system was designed specifically to treat medically intractable partial onset epilepsy.[75] A 2-year multicenter double-blind controlled trial to assess the safety and effectiveness of responsive cortical stimulation for partial onset seizures in adults with medically refractory epilepsy was reported in 2011. A total of 191 adult patients with medically refractory epilepsy were implanted with the NeuroPace RNS system. As a result, seizures were reduced by 37.9% as compared with a sham group during the blinded period. This study provided class I evidence that responsive cortical stimulation is effective in reducing seizures. A 7-year extension study with 256 patients indicates that the frequency of seizures is reduced up to 66% in a span of 6 years.[78] Furthermore, other measures such as quality of life and cognitive functions noticeably improved with RNS therapy.[79] Clinical experience indicates the safety and efficacy of RNS to provide relief to those who experience debilitating seizures. As with all neurostimulation therapies, although the underlying mechanisms of action are not well understood, this therapy is providing hope for those disabled by seizure disorders.[80]

SPINAL CORD STIMULATION

Historical Perspective

In 1965, Ronald Melzack and Patrick Wall proposed the gate control theory of pain to describe the complex interaction between the central and peripheral nervous systems to process pain and haptic signals. The dorsal horn is thought of as the gate of the spinal cord, in which peripheral nerve fibers carrying pain signals are blocked from ascending the central nervous system, when nerve fibers carrying touch, pressure, or vibration signals are activated. During that time, DBS targets to treat intractable pain were being explored; however, inspired by the gate control theory, initial clinical studies indicated SCS for chronic pathological pain.[81,82] Today, SCS is used as an alternative therapy for refractory chronic pain, and it is showing promise as an option to counter the effects of spinal cord injuries.[9]

Spinal Cord Stimulation System and Surgical Procedure

Currently, SCS systems are available from Medtronic, Boston Scientific, and St. Jude Medical. Before the implantation of an SCS system, typically a 3- to 7-day trial is conducted using an external SCS system, composed of percutaneous stimulation electrode leads attached to an external pulse generator. Once the trial is complete and the efficacy of SCS is confirmed, the patient undergoes an outpatient surgical procedure for the implantation of an SCS system. First, the patient is brought to the operating room where general anesthesia is administered, and the patient is

placed in the prone position. Through a midline skin incision, paraspinal muscles are retracted laterally and then an intraoperative radiograph is acquired to localize the spinal level. Next, a laminotomy is performed to expose the epidural space. The stimulating electrode is inserted into the epidural space, and then secured to the fascia, before battery placement in the flank or abdominal wall.

Spinal Cord Stimulation Clinical Indications

Chronic Pain. Indications of SCS include a myriad of refractory chronic pain conditions, including failed back surgery syndrome, complex regional pain syndrome, angina pectoris, ischemic limb pain, and abdominal pain.[9,83,84] Literature reviews spanning decades of SCS therapy found that the procedure was safe and effective for treating various intractable pain conditions.[85-89] In a long-term study of 102 patients, 68% experienced a significant reduction in their chronic pain symptoms.[85] A multicenter randomized controlled trial of 100 patients with failed back surgery syndrome found that SCS treatment provided continuous pain relief over a period of 24 months.[90]

The treatment of medically intractable pain with SCS is a complex dynamic process, as found by a study that examined the complex pain patterns of patients with intractable lower back and leg pain.[91] Surgical techniques have evolved to mitigate the risk of lead migration.[92] Effective SCS therapy requires adaptable stimulation specifications. In 2011, the FDA approved the Medtronic AdaptiveStim with RestoreSensor SCS system for treatment of refractory chronic, intractable back and limb pain. This device acquires and assesses a patient's position as a feedback signal to optimize neurostimulation parameters for effective pain management.[93]

Functional Restoration. Recently, the SCS technology has shown promise for regaining volitional movement for those with spinal cord injuries. In a 2009 case study, an adult patient who had paraplegia from a motor vehicle accident years earlier underwent an epidural stimulation procedure. This involved more than 100 locomotor training sessions over about 2 years, followed by the implantation of a 16-electrode array on the epidural space overlying L1-S1 cord segments. As a result, the patient was able to achieve full-weight bearing with assistance only for balance for nearly 5 minutes of epidural stimulation. After training and adjusting stimulation parameters, the patient was able to regain some control of leg movement during periods of stimulation.[94] More recently, a team at Mayo Clinic implanted the Medtronic RestoreSensor SCS system in a patient with paraplegia from a spinal cord injury at the sixth spinal segment. Spinal cord stimulation therapy coupled with intense physical therapy led to remarkable results, in which the individual was able to regain task-specific volitional control of lower-limb movement.[95]

VAGUS NERVE STIMULATION

Historical Perspective

The first publications on VNS were in 1990, and then in 1997 the US FDA's neurologic devices panel met to consider approval of the Cyberonics (now LivaNova) VNS device for the treatment of epilepsy.[96] The device consists of a pulse generator that is implanted under the skin below the patient's clavicle and lead wires that are tunneled up to the patient's neck and wrapped around the left vagus nerve at the carotid sheath. In addition, VNS has been used as a therapy for treatment-resistant depression.[97-99]

Vagus Nerve Stimulation System and Surgical Procedure

For VNS surgery, a linear incision is made in the mid left neck area—where the electrode will be placed carefully to avoid induction of bradycardia as occurs with stimulation of the right vagus nerve. Next, careful dissection is carried out through the platysma muscle, through the carotid sheath, to the left vagus nerve. Then, a portion of the vagus nerve is dissected such that a cuff-type electrode is placed around it. The wire is then tunneled through the subcutaneous tissue and connected to a battery that is placed just below the clavicle. The stimulation settings are typically 1.0 to 3.0 mA, with a frequency of 20 to 30 Hz and a pulse width of 130 to 500 μs. The device is programmed to provide regular intervals of on and off stimulation,

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typically 30 seconds on and 5 minutes off (epilepsy foundation, VNS).

Vagus Nerve Stimulation Clinical Indications

Vagus nerve stimulation is mostly used to treat epilepsy and treatment-resistant depression and is currently under study for several additional indications.[97-99]

Epilepsy. Vagus nerve stimulation is a currently accepted treatment for drug-resistant epilepsy. The afferent fibers projecting to the brain are thought to increase blood flow and metabolism in regions that are involved in the onset of epileptic seizures, though there is still much debate on this topic.[100] As of 2002, there were more than 16,000 patients implanted with VNS devices.[96]

Depression. Vagus nerve stimulation has also been shown to be effective in patients with mild to moderate treatment-resistant depression. The first report of VNS to treat depression was in 2000, with 30 patients having a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of major depressive disorder.[97] The follow-up results also concluded that VNS improved symptoms after 1 year.[99] Because of the minimally invasive nature of VNS compared with other neurosurgical options to treat depression, this therapy generated a great deal of attention.[98] However, there is still debate as to the level of its efficacy to treat depression.

ENABLING TECHNOLOGIES EVOLVING NEUROSTIMULATION THERAPIES

To date, the therapeutic mechanisms underlying neurostimulation therapies are not well understood; even so, such approaches are the only effective treatment option for several refractory neurologic disorders and are rapidly expanding to other clinical application domains. Decades of advances in neural activity monitoring technologies have resulted in powerful investigative and clinical tools that are providing remarkable noninvasive, in vivo, multimodal views of the brain. In 2013, the US White House announced the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative, which includes substantial investments in research to explore new methods to investigate the underlying mechanisms of brain function and dysfunction and potentially revolutionize treatment options for brain disorders. Resulting technologies are expected to accelerate the path forward to personalized long-term neuromodulation systems to treat a myriad of refractory neurologic disorders. Innovative multimodal neuroimaging and electrochemical monitoring techniques, along with hardware and software engineering advances, are setting the stage for innovative closed-loop neural control systems that maximize therapeutic effects, while minimizing adverse effects.

High-Resolution Stimulating Leads

Today, current-steering leads are of interest to improve the inherent variability of lead placement and adverse effect generation.[101] This approach arises from the idea that some of these adverse effects will be ameliorated with precise stimulation and conforming the electric field to the targeted structure. These recently developed leads provide precision in shaping the electrical field generated during stimulation. One such lead, the "directSTIM" (Aleva Neurotherapeutics) lead, consists of 4 rings with 3 independent electrodes on each ring.[102] This lead has been used for thalamic stimulation for tremor, which allowed for lower stimulation thresholds and decreased adverse effects as compared with a normal lead. Another lead design, the "SureSTIM" (Medtronic, Inc) lead, provides up to 32 small disc electrodes at a size of 0.4 mm^2 with both long-term stimulation and local field potential (LFP) recording technology. This device allows concurrent activation of electrodes, which enables directional current and shaping of the electric field.[103] The SureSTIM lead has shown its efficacy intraoperatively, allowing simultaneous stimulation and LFP recording.[104] These high-resolution leads will provide increased structural specificity in the nonlinear targets for DBS.

Neuroimaging and Electrochemical Monitoring

Innovative structural and functional neuroimaging technologies are creating enriched views of subject-specific anatomical and physiological brain circuitry. In particular, advances in MRI technologies are enabling

acquisition of structural image volumes with greater dynamic range, thus revealing finer details to discriminate anatomical brain regions.[105,106] Additional advances in ultra-high-field (including 7-T) structural imaging and body-transmit MRI technologies in patients with implanted stimulating devices show promise to enable therapeutic application and understanding of the effect.[107,108] Furthermore, MRI technologies have expanded to include techniques such as diffusion tensor imaging, which is sensitive to the diffusion properties of water through specific types of tissues.[109] In particular, diffusion tensor imaging is used to visualize and analyze the white matter tracts that connect brain regions.[22,110,111] Structural neuroimaging provides the anatomical contextual framework for functional brain data (eg, fMRI). Specific MRI protocols, which mitigate safety risks and reduce image artifacts associated with the interactions between the metallic components of the implanted devices and the scanner's magnetic field, are enabling the use of MRI technologies in conjunction with implanted neurostimulation devices.[108,112-115]

Linking multimodal in vivo neuroimaging with neurostimulation strategies is a powerful combination that is expected to significantly advance neurostimulation technologies and provide more precise and effective treatment for refractory neurologic disorders.[31,116,117] Structural, functional, and effective connectivity maps (ie, connectomes) are revealing insights into the pathogenesis of neurodegenerative and psychiatric disorders, leading to potential individualized biomarkers to aid diagnosis, predict prognosis, and quantify neuroplasticity.[118-125] Brain mapping techniques will enable investigation of the underlying mechanisms of therapeutic neurostimulation and the modulated brain circuitry that may lead to more effective stimulation targets and parameters. In particular, DBS-evoked functional brain maps, such as those acquired using fMRI, allow for the global assessment of the distributed patterns of activation corresponding to electrode placement, stimulation parameters, and behavioral results.[52,68,126-128] Furthermore, implementation of real-time fMRI techniques will potentially enable neurofeedback strategies to converge more quickly on optimal neurostimulation parameters. Subject-specific structural and functional macroscale connectomes, along with computational models that localize the volume of tissue activated by neurostimulation, will enable individualized precise therapeutic neuromodulation.[68,116,129,130]

Current advances in real-time MRI coupled with frameless stereotactic approaches (ie, NexFrame) are enabling faster, precise placement of DBS electrodes.[131] Combined with intraoperative neuroimaging, frameless stereotactic neuronavigation systems exhibit 3-dimensional spatial accuracy that is comparable to conventional frame-based stereotactic approaches, while also decreasing the time required for the surgical procedure.[131,132] Furthermore, higher-resolution neuroimaging technologies are enabling better visualization of brain target areas, which are potentially negating the need for microelectrode recordings and behavioral feedback to fine-tune the placement of DBS electrodes.[133]

In addition, intraoperative electrocorticography sensorimotor cortex recordings, with subcortical LFP recordings, are enabling discovery of biomarkers for dysfunctional motor circuitry, providing insights into the therapeutic mechanisms of DBS, and identifying potential feedback mechanisms for future closed-loop DBS systems. For instance, physiological studies report a pathological increase in beta band oscillations and hypersynchronization across the BG—thalamocortical circuitry associated with PD symptoms (eg, bradykinesia).[134-137] Also, chronic multisite brain recordings in patients with PD led to the discovery of pathological gamma oscillations in the BG—thalamocortical circuitry associated with dyskinesia.[135,138]

In vivo neurochemical monitoring techniques, such as fast-scan cyclic voltammetry (FSCV), are enabling real-time quantitative measures of evoked changes in neurotransmitter concentrations within targeted brain regions. In general, these techniques measure changes in electrical current corresponding to the oxidation and reduction of electroactive neurotransmitters (eg, dopamine, adenosine, and serotonin) at specific voltages applied to an implanted microelectrode fiber. The FSCV method quickly scans over a range of voltages, allowing for in vivo monitoring of multiple

neurotransmitters simultaneously. The Mayo Clinic Neural Engineering Laboratory developed an innovative system called Wireless Instantaneous Neurochemical Concentration Sensor, which leverages FSCV for real-time neurochemical monitoring during DBS surgical procedures. This compact, battery-operated device acquires electrochemical measurements via an implanted microelectrode sensor and wirelessly transmits these data to a base station with software that provides real-time visualization of neurochemical concentrations. This device has been safely used in animal and clinical studies, which observed, in real time, evoked neurotransmitter release correlated with DBS target location and stimulation parameters. These multimodal views of brain function in response to electrical stimulation provide a treasure trove of data to enrich our understanding of the evoked functional brain mappings that elucidate the therapeutic mechanisms of neurostimulation therapies and lead to a novel smart DBS system that enables individualized neuromodulation with the potential to expand to closed-loop stimulation (Figure 4).

Closed-Loop Adaptive Systems

Neurostimulation devices are continuing to evolve to support closed-loop strategies, with the motivation that these systems will potentially significantly improve the efficacy of neurostimulation therapies to treat a myriad

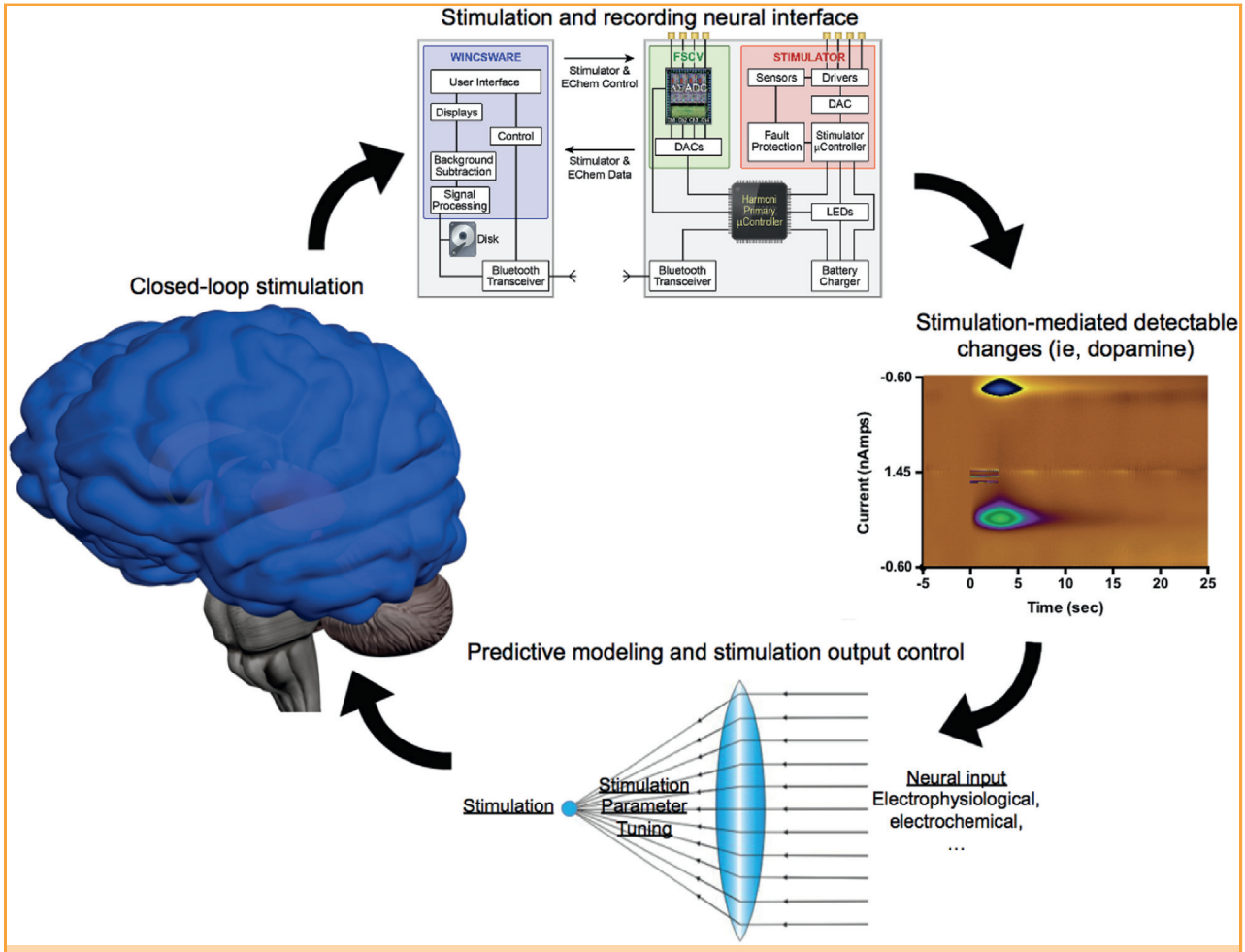

FIGURE 4. Toward closed-loop electrochemical sensing and stimulation. Neural interface (top) detects specific neurochemical changes in the brain (right) to drive stimulation parameter tuning (bottom) and deliver stimulation to the brain (left). ADC = analog-to-digital converter; DAC = digital-to-analog converter; LED = light emitting diode.

of refractory neurologic disorders. Currently, most neurostimulation systems have an open-loop design with static stimulation parameters (eg, amplitude, duration, and frequency) programmed by a clinician; however, there are a few FDA closed-loop neurostimulation systems that are providing further motivation for these personalized neuromodulation therapies. One such example is the closed-loop NeuroPace RNS device, which is the only FDA-approved device that provides direct stimulation to deep brain structures or cortical regions to treat medically intractable epilepsy.[76] Another FDA-approved example is the Medtronic SCS neurostimulation system AdaptiveStim with RestoreSensor, which incorporates an accelerometer to quantify a patient's position as a feedback signal to adapt neurostimulation parameters for optimal chronic pain management.[93]

Although DBS systems are primarily open-loop design, great strides continue to be made to create a closed-loop smart DBS device that provides more precisely regulated and customized stimulation.[139-144] In 2013, Medtronic announced the expansion of their Activa series of neurostimulators, including a new device called Activa PC+S and RC+S systems, that are capable of simultaneously sensing and recording brain activity while stimulating specific brain regions. Although these devices are not FDA approved for the sensing and diagnostic component, they are provided to institutions for investigational purposes. Several institutions are using this sensing neurostimulator device to further investigate using LFP recordings as a feedback signal to assess alpha, beta, and gamma band spectral power changes associated with dysfunctional circuitry vs those associated with effective DBS.[138,145-149]

CONCLUSION

As outlined, the rapid advancements in neurostimulation technologies are providing the necessary tools to treat patients living with many debilitating neurologic and psychiatric disorders. Here, we discussed the established invasive electrical stimulation systems used clinically to induce therapeutic neuromodulation of dysfunctional neural circuitry. Although we are on an accelerated path toward an adaptable and precise neuromodulation therapy, much remains to be accomplished. This includes advancements such as electrode design to enable long-term high-precision sensing and stimulating as well as computing approaches to acquire and assess meaningful feedback signals in real time to adapt stimulation parameters accordingly. More importantly, a more complete understanding of the therapeutic mechanisms of neurostimulation for various neurologic disorders is required, thus enabling the discovery of biomarker feedback signals that effectively inform the closed-loop system.

Abbreviations and Acronyms: **BG** = basal ganglia; **DBS** = deep brain stimulation; **FDA** = Food and Drug Administration; **fMRI** = functional magnetic resonance imaging; **FOG** = freezing of gait; **FSCV** = fast-scan cyclic voltammetry; **GPi** = globus pallidus internus; **HDE** = Humanitarian Device Exemption; **IPG** = internalized pulse generator; **LFP** = local field potential; **MCS** = motor cortex stimulation; **MRI** = magnetic resonance imaging; **NAc** = nucleus accumbens; **OCD** = obsessive-compulsive disorder; **PD** = Parkinson disease; **RNS** = responsive neurostimulation; **SCS** = spinal cord stimulation; **STN** = subthalamic nucleus; **VC/VS** = ventral capsule/ventral striatum; **VIM** = ventrolateral intermedius; **VNS** = vagus nerve stimulation

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