# Chained Lightning: Advances in Neuromodulation

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The cornerstone of functional neurosurgery historically has been the modulation of known neural circuits and neuroanatomic pathways to achieve a predictable therapeutic effect. A lack of suitable alternatives once made lesioning the primary treatment for certain severe medically refractory movement, psychiatric, and chronic pain disorders. Vast improvements in lesioning techniques were accomplished with refinement of stereotactic radiosurgery. These have improved the safety, accuracy, and fidelity of such irreversible neuromodulatory interventions. However, lesioning remains hindered both by being a static intervention and by causing irreversible destruction of neural tissue. In contrast, stimulation-based neuromodulation holds the advantages of being reversible, nondestructive, and dynamic. Although stimulation-based animal research to achieve antinociception was attempted in the early 20th century, clinical application of reversible, nondestructive, and dynamic neuromodulatory stimulation was not pioneered until the 1960s and 1970s.[30,34,51] In 1987, Benabid et al.[6] first recognized the potential for a durable motor effect during a thalamotomy for essential tremor. When applied during mapping, high-frequency stimulation resulted in nearly immediate tremor suppression. This recognition spawned the use of high-frequency electrical stimulation as a reversible, nondestructive treatment for afflictions of both the peripheral and central nervous systems.

Continuous high-frequency stimulation of the deep gray matter, deep brain stimulation (DBS), is currently indicated for essential tremor, some forms of dystonia, and Parkinson's Disease. Respective targets include the ventral intermediate nucleus of the thalamus, internal segment of the globus pallidum, and subthalamic nucleus (STN). A human device exemption has also been granted for treatment of medically refractory obsessive-compulsive disorder. Vigorous clinical research, through physician- and industry-sponsored trials are currently pursuing alternative indications. These include but are not limited to cluster headache, minimally conscious state, obsessive-compulsive disorder, Tourette's syndrome, depression, chronic pain, obesity, and anorexia. In parallel, engineering insights and advancements from basic, translational, and clinical research studies promise to vastly improve the current technologies used in DBS. These include improvement in hardware design, introduction of the concept of dynamic targeting and programming strategies, and an exploration of the neuromodulatory potential of biologics-based therapeutics.


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## ENVISIONING AN OPTIMIZATION OF CURRENT TECHNOLOGY

### Current Generation DBS Technology[14]

The current state-of-the-art in DBS uses a quadripolar lead serial electrode array. Currently, the Medtronic 3387 and 3389 models (Medtronic, Inc., Minneapolis, MN) are both approved by the US Food and Drug Administration for clinical use. The 3389 differs only in a shortened intercontact distance (0.5 mm as opposed to 1.5 mm). A more recent version, the Medtronic 3391, is a larger electrode (3-mm contact length and 4-mm intercontact distance) that permits use of increased voltages while retaining an overall acceptable charge density of less than 30 $\mu C/cm^2$/phase. Delgado[15] initially provided detailed instructions for individual construction of multicontact brain stimulation electrodes in the 1950s. DBS leads underwent multiple advancements in electrode design over the next two decades. These included use of in-line platinum iridium contacts and intraoperative placement with a distal wire loop designed to engage a targeting stylet introduced in tandem. By contrast, current-generation electrodes use a hollow-core lead placed with the use of a removable tungsten stylet. The smooth distal interface, pioneered with spinal cord stimulation, was recognized to lessen the likelihood of postoperative tissue ingrowth and adhesion.

Early-generation DBS systems used an external programmable neurostimulator with a doughnut-shaped radiofrequency (RF) antennae. The transmitter antenna were placed over an infraclavicular pocket that contained the proximal electrode lead end and RF receiver. Because the RF receiver only contained a positive and negative pole, two of the four available electrode lead extensions were clipped and discarded after optimization during the percutaneous trial period. Therefore, although stimulation parameters could be modified after the trial period, the final implanted electrode configuration was permanent. By contrast, current-generation

internal pulse generators (IPGs) are fully implantable and capable of postimplant electrode programming with use of a telemetric programmer. Therefore, both electrode configuration and stimulation parameters may be optimized with a handheld programmer in an outpatient setting. While Coffey[14] has recently presented a more detailed review of historical and current-generation DBS technology, the remainder of this section explores near-term advances that may be expected in the design of DBS hardware and associated targeting modalities.

## Device-Centric DBS Advancement

Multiple near-term advances in DBS hardware design may be expected predicated on the existence of relevant technology in related devices with intracranial application. Specifically, a cranium-mounted pulse generator, lead and wiring antimicrobial impregnation, and improvements in pulse generator longevity may be expected based on current use in US Food and Drug Administration–approved or experimental application. Furthermore, significant research has been devoted to generation of novel electrode geometries that will allow the generation of customizable current fields. Such "current steering" should minimize off-target effects by increasing the specificity of therapeutic current delivery to the anatomic target of interest.

### Cranially Mounted IPG

Infraclavicular placement of the proximal lead end dates to the use of RF receiver coils in early-generation DBS hardware and continues with contemporary programmable IPGs. This location provides bony protection, sufficient subcutaneous tissue to contain the hardware, and the well-vascularized pectoralis muscle should subfascial placement be required. However, infraclavicular placement increases the risk of lead breakage and is associated with perioperative discomfort because of soft-tissue tunneling. A cranium-mounted IPG, made possible through decreases in IPG size, mitigates each of these limitations.

The Neuropace responsive neurostimulator (Neuropace, Inc., Mountain View, CA) represents the first long-term implanted, cranially mounted neurostimulator. This device is a closed-loop neurostimulator designed to monitor and process electrical activity from seizure foci using both depth and subdural electrodes. Device volume is approximately one half that of the Soletra IPG (Medtronic, Inc.) (10.5 versus 22 $cm^3$). Subsequent therapeutic stimulation detects electrographic synchronization and prevents progression to a clinical seizure. Placement requires generation of a partial- or full-thickness craniectomy defect and anchoring of the stimulator mount (ferrule) and responsive neurostimulator flush with the outer cranial table. This experimental therapy recently underwent a prospective, multicenter, randomized, double-blind clinical trial to assess safety and efficacy with a significant reduction of seizures compared with the control group.[43,48,49] Initial abstract data from this trial (N = 65 patients) demonstrates "no serious unanticipated device-related AEs [adverse events]"[5] and that "responsive neurostimulation was well tolerated."[5] Other reports in the literature support the safety, durability, and tolerability of this cranially mounted neurostimulator. The implantation has been reported as safe and reproducible, and no infections have been reported at the site of the stimulator implant.[2] In this series, generator replacements were required at 20, 17, and 11 months. Furthermore, an additional report by Fountas et al.[19] of eight patients (mean follow-up, 9.2 months) reported no significant adverse events or dysfunction of the neurostimulator at follow-up periods exceeding 2 years.

### Reducing Infection: Best Practices and Hardware Modifications

Postoperative infection rates associated with DBS lead implantation vary from 0 to 23% in the literature. This discrepancy exists in part because of varying definitions and follow-up periods used for reporting postoperative infection. A recent retrospective study by Sillay et al.[52] examined implantation of 759 DBS leads and 615 IPGs by two surgeons in 420 patients. These authors reported a 4.5% rate of early hardware-related infection (2.5% per lead), defined as occurring at less than 6 months postoperatively. No intracranial infections were observed. Early detection and surgical intervention allowed salvage of the distal intracranial leads in 64% of patients. In this and other smaller series, the most common site of infection is at the chest IPG implantation site.[33,54] The lead connector has also been reported as the most common site of infection.[26] In the attempt to reduce hardware infection, a number of best-practice initiatives have been reported and are reviewed by Sillay et al.[52] and Rezai et al.[47] Recommendations included handling of the IPG only by the implanting surgeon and placement of the IPG under the pectoralis fascia instead of within the subcutaneous tissue. In a retrospective study of implanted neurostimulators and intrathecal pumps (n = 614), Miller et al.[40] studied the use of intravenous antibiotics alone (n = 455) or with wound application of a neomycin/polymyxin solution (n = 159). Postoperative infection rates requiring culture verification were 5.2% versus 1.9% at 18 months.

Hardware modifications also provide the opportunity for reduction of postoperative infection. Because device infections often necessitate removal of the entire system, cranial placement of a smaller IPG and antimicrobial impregnation of the proximal lead extender may reduce postoperative device infection rates. Results from the literature for antimicrobial impregnation of external ventricular drains and shunt catheters support the use of antibiotic-impregnated indwelling hardware. In a multicenter prospective study with well-balanced treatment and control groups (n = 306, 288 under-

 

went final analysis) by Zabramski et al.,[66] patients who received external ventricular drains impregnated with rifampin/minocycline (VentriClear; Cook, Inc., Bloomington, IN) were one half as likely (17.9% versus 36.7%) to develop a positive cerebrospinal fluid culture after placement. Govender et al.[25] assessed a clindamycin/rifampin-impregnated catheter (Bactiseal; Codman, Johnson & Johnson, Boston, MA) when using internalized shunts for the treatment of hydrocephalus. These authors found a significant reduction in shunt infection at a follow-up 2 months when compared with control catheters ($p = 0.038$). A meta-analysis by Ratilal et al.[45,46] assessing multiple outcomes when comparing infection between antibiotic-impregnated and control catheters found odds ratios favoring the use of treated catheters in both the externalized (Zabramski et al.[66]: odds ratio, 0.13 [95% confidence interval, 0.03–0.6]) and internalized (Govender et al.[25]: odds ratio, 0.32 [95% confidence interval, 0.08–1.32]) studies. When the results of these studies were pooled, an odds ratio of 0.21 [95% confidence interval, 0.08–0.55] was obtained.

**Improving Stimulator Longevity**

Currently, IPG neurostimulators must be replaced within 1 to 5 years. This wide variation depends largely on the disease being treated, the stimulation parameters required, and the IPG model. The most significant improvements in stimulator longevity may be achieved by a multifactorial approach to device optimization. Advances already discussed that may improve IPG life span include smaller, more efficient microprocessors and improved battery design. Reductions in current draw may also be achieved through improvements in targeting. Targeting improvements may be achieved either through alteration of the size and 3-dimensional shape of the electrical field generated between the anode and cathode or through improvements in the accuracy and precision of initial electrode lead placement. Both are discussed in subsequent sections. Finally, device longevity may be meaningfully improved through alterations in battery design, either through increased efficiency or through use of a rechargeable cell.

The Restore (Medtronic, Inc.) is a lithium ion rechargeable IPG option, approved for 9-year use. It is specifically designed to address battery exhaustion associated with high-energy setting needs that necessitate spinal cord stimulation IPG replacement as often as every 2 years.[36] In a recent study of 41 patients, Van Buyten et al.[57] demonstrated that all patients were capable of successfully recharging their stimulators at a recommended 1-month interval and that 78.6% of patients found the recharging process to be easy. Physical dimensions for the RestoreUltra spinal cord stimulator are comparable to those of the Soletra unilateral DBS IPG, whereas those for the RestoreAdvanced fall between those of the Soletra and Kinetra DBS IPGs. In the spring of 2009, Medtronic introduced the first of a line of rechargeable DBS IPGs, the Activa RC.[39]

**Lead Geometry-Based Current Steering**

The electrical field surrounding the DBS lead is modified by electrode contact geometry, anode/cathode distribution, and local tissue properties.[9] Therefore, alteration of individual lead geometry or accommodation of more complex polarity combinations would permit greater flexibility regarding the shape and size of the induced electrical field. Finite-element computational modeling has played a crucial role in predictive modeling when making physical changes to electrode geometry, contact spacing, and the number and pattern of contacts that may be used. Using a custom computer model capable of estimating the volume of tissue activated (VTA) around the electrode, Butson and McIntyre[9] examined alternate electrode geometries with the intent of assessing the effect on VTA. In this model, increases in electrode contact height resulted in a linear increase in VTA, whereas increasing diameter achieved a logarithmic decrease in VTA when using adjacent contacts. The authors underscored the clinical utility of these findings through demonstration that ellipsoid, as opposed to spherical, VTA could more closely approximate the anatomy of deep nuclei.

In addition to changing contact shape and configuration, electric field shape can be modulated through altering anode/cathode combinations. Butson and McIntyre[10] emphasized this point by using the same model to observe significant changes in VTA and VTA shape by dividing current between adjacent or nearby electrodes of the same polarity while using the IPG as the anodic return. The Kinetra and Soletra IPGs (Medtronic, Inc.) only allow use of two electrodes with opposed polarity or a contact serving as the cathode with the IPG serving as the anode. However, the recently introduced Activa RC (Medtronic, Inc.) is capable of powering multiple contacts by alternating current supply between separate contacts during different cycles. These studies highlight the utility of customizing electrode diameter and length, alternative spacing options between electrode contacts, and contact-specific current supplies to be adapted on an individual patient or target-specific basis.

## Targeting Optimization: Interim Improvements and Paradigm Shifts

Significant technological advances over the past decade have affected the standard of practice for DBS electrode targeting. Frameless stereotaxy and intraoperative microelectrode targeting have become commonplace navigational and targeting aids. Furthermore, improved imaging resolution now allows specific deep nuclei to be clearly observed on preoperative magnetic resonance imaging (MRI). A report by Toda et al.[56] demonstrates targeting improvements to the STN solely based on the use of 3-T versus 1.5-T preoperative

 

MRI. Continued imaging advancements, new strategies for DBS atlas design, and improvements in neurophysiologic targeting techniques are poised to further advance the armamentarium of indirect and direct targeting techniques. Together, these advances are poised to improve both indirect and direct targeting techniques, broadly defined as noninvasive and invasive targeting techniques. Recent studies that promise to contribute to both indirect and direct targeting techniques are reviewed below.

**Indirect Targeting Advances**

Two-dimensional DBS atlases represent the traditional indirect targeting strategy. However, because they are generated from relatively small patient samples, the potential for sampling bias exists. Attempts to minimize these errors have focused on the use of 3-dimensional atlases that are able to conform, or warp, to preoperative patient neuroimaging. Multiple different registration techniques have been explored and discussed.[4,11,12] An alteration of these approaches uses probabilistic data from previous successful implantation procedures to customize electrode trajectory[13] for individual patients. Advances in imaging techniques that are making patient-customized atlases a reality are also applicable to real-time intraoperative targeting.

Use of preoperative neuroimaging in surgical planning for DBS electrode implantation has traditionally been limited by insufficient visual resolution to accurately delineate deep intracerebral nuclei and an inability to account for intraoperative tissue shifts. Furthermore, long wait times and a significant sacrifice in imaging resolution have obviated the potential gains achievable with real-time assessment of lead localization using intraoperative MRI. Martin et al.[38] recently reported the utility of intraoperative targeting using frameless stereotaxy with a 1.5-T intraoperative MRI scanner. Before human studies, an in vitro phantom model demonstrated average lead placement at 0.8 $\pm$ 0.5 mm from the intended target.[37] In a subsequent series of 30 patients and 25 bilateral implantations, first-pass lead placement was achieved in 49 cases (86%), second-pass lead placement was achieved in seven cases (12%), and third-pass placement in one case. One system was explanted secondary to infection near the IPG. Cases that required alignment revision had accuracy nearly identical to that of first-pass placements. These were 1.1 $\pm$ 0.7 mm for first-pass placement and 1.2 $\pm$ 0.7 mm for second pass placement. Importantly, the authors report bilateral lead placement times of 220 $\pm$ 32 minutes with a minimum of 177 minutes for bilateral placement and 123 minutes for unilateral placement. Briefly, use of electrodes with alternate physical properties may further advance the practice of intraoperative targeting by both improving imaging quality and addressing associated concerns of diathermy with use of high-resolution scanners. Dunn et al.[16] successfully tested a carbon fiber–based electrode in a 9.4-T scanner, without histological evidence of diathermy-induced tissue damage in the Evans-Long rat. Furthermore, while in the scanner, the electrode was used to generate an electroencephalographic seizure assessed by BOLD (blood oxygen level dependent)-based functional MRI.

**Direct Targeting Advances**

Sterio et al.[53] commented on the utility of MER to aid in targeting of the lateral STN during DBS lead implantation for the treatment of idiopathic Parkinson's disease. Use of direct neurophysiologic monitoring during lead trajectory assessment has become a widely accepted practice. Amirnovin et al.[1] reported that MER modified final electrode placement in 58% of their cases. Zonenshayn et al.[71] concluded that the most accurate lead placement in a bilateral STN implantation occurred with use of a multimodal targeting approach, including the use of invasive neurophysiologic monitoring. Furthermore, Sani et al.[50] report MER as an accurate determinant of target localization when mapping the posterior hypothalamus for treatment of cluster headache. Novel invasive imaging applications and exploration of new direct targeting modalities may soon expand the spatial resolution and overall accuracy obtained with invasive monitoring techniques.

Giller et al.[22] reported on the use of optical feedback as a determinant of tissue type. Using a fiberoptic probe and near-infrared wavelengths, tissue type–specific changes in reflectance allow differentiation between white and gray matter. Giller et al.[23] previously reported detection of white matter layers as thin as 0.3 mm. These authors recently completed a study examining human insertion of 203 near-infrared probes with multiple probe types. They included use of forward, side-sensing, side-sending with combined MER electrode, and side-sending fiberoptic with a hollow channel for DBS electrode insertion. Advantages over MER-based targeting reported by the authors include fast acquisition times ($<$10 minutes) and a high reliability for use in thalamic surgeries. They concluded that centers with a high volume and proficiency with performance of STN DBS surgeries may prefer continued use of MER for this target. Furthermore, near-infrared–based targeting is immune to electrical interference, allowing simultaneous MER or macrostimulation through a DBS electrode when using a hollow working channel. Given the fast acquisition times and ability to insert multiple instruments through a hollow working channel, incorporation of this technology may be ideal in exploring new targets for novel indications.

## INTERPRETING CEREBRAL ACTIVITY: CONSIDERING A CLOSED LOOP INTERFACE

Real-time detection of either disease-specific pathologic signal waveforms or quantification of observed symptomatology may serve as the basis for a closed-loop interface.

In this model, applied stimulation parameter settings are modified based on interpretation of electrical indicators of disease activity. In contrast, current applications of DBS use a static open-loop interface. This is similar to the high-frequency stimulation initially recognized by Benabid et al.[6] to ameliorate tremor during current application to the STN. Currently, stimulation parameters are optimized by an iterative modification of an applied square wave, including contact combination, amplitude, frequency, and pulse width.[58] However, intraoperative neurophysiologic mapping during treatment of movement disorders has since revealed the presence of underlying signal waveforms associated with disease activity, a potential feedback for a closed-loop interface. Additionally, an association between the clinical effect of stimulation and changes in underlying signal waveforms has been identified.[7,35,61] Both potential inputs for a closed-loop interface and a paradigm for using a closed-loop interface as a mechanism to improve stimulation parameter evaluation and selection are introduced.

### Selecting the Appropriate Input Signal

Significant evidence suggests that neuronal synchronization within the basal ganglia, related to dopamine depletion and neuronal death in the substantia nigra contributes to the symptomatology observed in Parkinson's disease. Use of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in primate models and long-term depth electrode recording–based findings of pathologic local field potential (LFP) synchrony in the globus pallidus and STN bands appear to colocalize to the dorsal STN. This occurs in the $\beta$ (13–30 Hz) and low $\gamma$ (35–80 Hz) ranges. Recent studies suggest their respective contributions to the akinetic (rigidity, bradykinesia)[35] and kinetic (rest tremor)[59] manifestations of Parkinson's disease. Synchronous neuronal activity has also been associated with oscillatory cortical electroencephalographic activity and the development of symptomatology. Furthermore, both dopaminergic agonists and direct high-frequency stimulation suppress this synchronization within both the STN and motor cortex, suggesting a mechanistic foundation for the effects observed during DBS.[18] Nevertheless, development of a closed-loop interface will require a more complete understanding of the role of synchronized STN LFPs in symptom development and an approach to both detect the oscillatory LFP waveform and provide therapeutic stimulation.

A primary drawback to the use of $\beta$- and $\gamma$-range oscillations as a signature of disease activity is their amplitude in relation to that of therapeutic stimulation. Because these signals are considerably smaller than the applied stimulation waveform, they are difficult to detect while stimulating. Researchers have indirectly detected the effect of stimulation on the $\beta$- and $\gamma$-range waveforms in the rare circumstance of dual unilateral lead placement or through detection of a latency associated with return of the LFP waveform after cessation of stimulation.[35] A surrogate marker of disease activity could be obtained from grid placement and cortical electroencephalography to modulate stimulation parameters in response to electrophysiologic evidence of tremor activity.

### A Near-Term Alternative: A Perioperative Closed-Loop Interface

In addition to real-time DBS output modulation in response to pathologic oscillatory signal waveforms, a closed-loop interface could be selectively used intraoperatively or during the perioperative trial period to quickly process and identify optimal stimulation parameters. Monitoring and quantification of a clinical indicator (e.g., tremor activity through subdural grid placement and cortical electroencephalography), using an external workstation, as opposed to continuous waveform processing by the IPG, would minimize required hardware and software modifications. Furthermore, Feng et al.[19] have proposed the use of a computational approach strategy that modulates lead and stimulation parameters based on feedback from a pathophysiologic input (e.g., tremor activity or waveform) to automatically and iteratively process contact combinations and stimulation parameters to improve stimulation efficacy.

## LEVERAGING BIOLOGICS-BASED DISCOVERIES FOR NEUROMODULATORY APPLICATIONS

Treatment approaches that depend on long-term placement of indwelling hardware carry inherent limitations, including the risk of infection, need for revision associated with device malfunction or end of life, and potential for lead breakage. Furthermore, electrical stimulation–based treatment modalities are capable only of achieving anatomic specificity. By lacking implanted hardware, gene-based neuromodulatory techniques have none of these limitations and are capable of achieving targeting specificity at a subcellular level. In this section, a brief overview of strategies for modulating synaptic transmission and achieving titration of transgene control are introduced, including a hybrid optogenetic approach that uses an implantable fiberoptic light source.

### Modifying Synaptic Transmission, Myriad Targets, and Approaches

Gene-based efforts to modulate synaptic transmission have broadly focused on either potentiation or inhibition of synaptic transmission. Efforts to potentiate synaptic transmission have included the addition of rate-limiting enzymes in neurotransmitter production and the incorporation of ion channels designed to promote presynaptic depolarization. Application of transgenes encoding enzymes has been at-

 

tempted for treatment of conditions ranging from treatment of chronic pain to striatal injection of adeno-associated virus encoding human aromatic L-amino acid decarboxylase in Parkinson's disease.[20] Because of the tropism of herpes simplex virus for retrograde axonal transport, several investigators have used this vector as a vehicle to deliver transgenes to the dorsal root ganglion for the treatment of neuropathic pain syndromes. Attempts have been made to deliver the gene-encoding preproenkephalin[24,44] as well as the gene encoding endomorphin,[62] both endogenous analgesics, as well as glutamatergic acid decarboxylase,[28] the enzyme encoding the inhibitory neurotransmitter, γ-aminobutyric acid. Attempts to supplement dopamine production in Parkinson's disease have progressed from large animal nonhuman primate studies[20] to a phase I clinical trial (n = 10) that, to date, supports the safety of this intervention. Additionally, it has demonstrated positron-emission tomography–based evidence of sustained human aromatic L-amino acid decarboxylase production at the implant sites.[17]

Attempts to inhibit synaptic transmission have included prevention of vesicle docking with the presynaptic membrane and incorporation of ion channels designed to hyperpolarize the presynaptic membrane. Clostridial toxin, a potent inhibitor of synaptic transmission, is composed of both heavy and light chains. It achieves neuronal uptake via the heavy chain and prevents vesicle release through light chain–mediated cleavage of the vesicle-docking protein synaptobrevin. In vitro neuronal PC12 cell culture preparations, when transduced with adenovirus-encoding light chain, have demonstrated selective depletion of synaptobrevin.[55] In vivo studies incorporating the light chain transgene into both adenoviral and adeno-associated viral vectors have been used to functionally inhibit synaptic transmission without resultant damage to the local neuronal population. These studies have included selective and reversible inhibition of nigrostriatal pathway transmission,[64] inhibition of penicillin-induced neocortical seizures,[63] reversible disruption of sensorimotor function when injected into the rat lumbar spinal cord,[55] and reductions of the cue-initiated fear-potentiated startle reflex.[70] Neuronal transduction with transgenes encoding ion channels that promote a hyperpolarized membrane potential may also be used to inhibit synaptic transmission. The Kir2.1 channel promotes maintenance of the resting membrane potential through generation of an inwardly rectifying $K^+$ current and has been demonstrated to selectively reduce synaptic transmission in a culture of superior cervical ganglion cells without observed neurotoxicity.[32] Furthermore, recent studies of Kir2.1 have demonstrated that delivery to chick embryos significantly reduces motor activity and alters the electrical properties of developing spinal motor neurons while in the ova.[65]

## Optogenetics: A Combined Neuromodulatory Intervention and New Therapeutic Precedent[29]

Selected photosensitive ion channels are capable of conformational alteration on exposure to specific energy wavelengths. Chromophores are present across a phylogenetically diverse spectrum, with conceptually similar proteins contributing to both mammalian photoreception as well as to algal and microbial photosensitivity. By changing shape in response to light, these photosensitive ion channels are capable of neuromodulation based on photochemical transduction. Conceptual proof of principle has been corroborated by several studies that examined optogenetic neuromodulation in both in vitro and small animal in vivo settings.

Early studies of light as a neuromodulatory trigger used caged neurotransmitter compounds in cultured neuronal preparations.[42] These light-sensitive compounds, inactive neurotransmitter analogues, release active neurotransmitters on exposure to light. Although this technique allowed kinetic exploration of neurotransmitter activity on the postsynaptic membrane, sustained activity was not achievable without replenishment of the caged compound.[60] Subsequent studies examined ectopic coexpression of critical elements of the Drosophila phototransduction cascade in rat hippocampal neuron culture. A significant increase in spiking was observed with administration of white light.[67] Furthermore, in vitro studies examined the use of rationally designed ion channels complete with a pore blocker that alternates between *cis* and *trans* configuration depending on the wavelength of light administered. This allowed a switch mechanism to control ion flux and the likelihood of neuronal spiking.[3] Additionally, in vivo Drosophila work has demonstrated significant behavioral escape pattern changes on exposure to light with ectopic expression of the *Rhodopsin* gene in the giant fiber system that these flies use for stereotyped escape flight patterns.[69] Shared among these studies was the lack of demonstration of sustainability or tight temporal onset and offset control of neuronal spiking, both prerequisites for consideration of this technology as a potential therapeutic modality.

Recent efforts have extended these findings to demonstrate both the capability of controlling ion flux alterations on a millisecond timescale and achievement of antagonistic neuromodulatory control. Both Boyden et al.[8] and Ishizuka et al.[31] generated data with the channelrhodopsin-2 gene (ChR2), initially described by Nagel et al.[41] This work demonstrated high-fidelity control over action potential train formation with use of 450 to 490 nm of blue light. In the former study, a lentiviral vector was used to transfect in vitro rat hippocampal neurons, whereas the latter study examined PC12 cell transfections and in vivo transduction of the murine hippocampus. In both in vitro and in vivo setups, high-fidelity millisecond timescale control over neuronal spiking was

achieved. Even more recent efforts examined presynaptic colocalization of excitatory and inhibitory optically active ion channels responsive to different wavelengths. Zhang et al.[68] introduced both the algal ChR2 channel, capable of depolarizing the presynaptic membrane, as well as the NpHR, an inhibitory ion channel, into the same cell population using an in vitro preparation of rat hippocampal neurons. These channels respond antagonistically to blue and yellow light, respectively. Although brief pulses of blue light resulted in reproducible neuronal spiking on a millisecond timescale, the addition of a constant yellow light source inhibited spiking. Together, these advances provide a high-fidelity mechanism for both temporal and excitatory versus inhibitory synaptic control.

Recently, Han et al.[27] extended this neuromodulatory approach to the primate brain. Nonhuman rhesus macaques underwent direct cortical injection of replication-incompetent lentiviral vectors encoding ChR2-GFP. To increase specificity of cell-type expression to excitatory neocortical neurons, the $\alpha$-CamKII promoter was used. Immunostaining for $\alpha$-CamKII, $\gamma$-aminobutyric acid, and glial fibrillary acidic protein demonstrated specificity only to excitatory neocortical neurons. Repeated injections and recording sessions, occurring over several months, failed to result in evidence of a local immune reaction. The authors noted the ability to achieve temporal control over neuronal spiking at approximately 1.2 mm from the applied blue laser light source. However, evidence of both excitatory neuronal spiking and inhibitory suppression was observed. Multiple lines of evidence supported inhibitory activity as a likely response of downstream network activity. Together, these data support the capability of safe and effective long-term control over excitatory neuronal activity in a large animal. Although future studies will need to elucidate the neural network contributions to local inhibition during excitatory stimulation, this remains an important step toward clinical implementation of this emerging technology. For a more detailed review of optogenetic neuromodulation, including past and current research, potential clinical applications, and barriers to translation, please see the recent review by Henderson et al.[29]

## CONCLUSION

Introduction of high-frequency electrical stimulation as a neuromodulatory technique represented a paradigm shift in the practice of functional neurosurgery. As opposed to lesioning techniques, stimulation-based treatment approaches are reversible, may be titrated through alteration of stimulation parameters, and spare neural tissue at the target location. This therapeutic technique will further mature through a broad expansion of treatment indications and iterative improvements in device design. Although approval had initially been granted for treatment of movement disorders, application to neuropsychiatric, primary headache, and neurobehavioral disorders is now under investigation. In tandem, technological barriers continue to be addressed and multiple near-term advances likely include smaller and more efficient IPGs, cranial IPG implantation, antimicrobial impregnated leads, and an increased array of contact geometry configurations. A combination of improvements in neurophysiologic mapping and imaging should further improve lead targeting accuracy. Additionally, a closed-loop interface and a computational approach to contact configuration and stimulation parameter optimization may further improve therapeutic efficacy or reduce off-target effects. Finally, gene-based neuromodulatory approaches hold the inherent advantages of being able to achieve subcellular specificity while lacking the limitations commonly associated with use of indwelling hardware. Future therapeutic paradigms may combine the benefits achievable with electrical stimulation and gene-based neuromodulatory techniques through use of a hybrid approach. One example, optogenetic neuromodulation, would allow targeting to a subcellular localization while maintaining control of transgene expression and activity through use of an implantable fiberoptic light source.

## Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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