Neuromodulation for Brain Disorders: Challenges and Opportunities

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***Abstract*—The field of neuromodulation encompasses a wide spectrum of interventional technologies that modify pathological activity within the nervous system to achieve a therapeutic effect. Therapies including deep brain stimulation, intracranial cortical stimulation, transcranial direct current stimulation, and transcranial magnetic stimulation have all shown promising results across a range of neurological and neuropsychiatric disorders. While the mechanisms of therapeutic action are invariably different among these approaches, there are several fundamental neuroengineering challenges that are commonly applicable to improving neuromodulation efficacy. This paper reviews the state-of-the-art of neuromodulation for brain disorders and discusses the challenges and opportunities available for clinicians and researchers interested in advancing neuromodulation therapies.**

***Index Terms*—Deep brain stimulation (DBS), intracranial cortical stimulation (ICS), neuroengineering, neuromodulation, transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS).**

I. Introduction

NEUROMODULATION is a rapidly growing field of study, encompassing a wide spectrum of implantable and noninvasive technology-based approaches for the treatment of neurological and neuropsychiatric disorders. Neuromodulation refers to interfacing and intervening with the nervous system through electrical, electromagnetic, chemical, or optogenetic methodologies with the goal of long-term activation, inhibition, modification, and/or regulation of neural activity [1]. While oral medication and ablative neurosurgical procedures can achieve similar therapeutic outcomes, neuromodulation has the advantage of higher spatiotemporal precision than oral medication combined with reversibility that is absent in ablative procedures. To date, neuromodulation has been used to treat movement disorders (Parkinson's disease, dystonia, tremor), tics associated with Tourette syndrome, obsessive–compulsive disorder, depression, tinnitus, sensory disabilities, bladder control, epilepsy, headache, chronic pain, spasticity, stroke, minimally conscious state, and spinal cord injury, among others. With these successes, there is tremendous impetus to refine existing technologies and develop new approaches to modulate the nervous system for existing indications as well as emerging indications, including but not limited to memory disorders, schizophrenia, addiction, eating disorders, hyperacusis, and traumatic brain injury.

Central to advancing the field of neuromodulation and treating these emerging clinical indications is developing a more thorough understanding of the neuroscience mechanisms by which neuromodulation generates a therapeutic effect and, at times, elicits untoward side effects. Biophysics and molecular biology have helped in developing a framework to understand how neuromodulation therapies affect single neurons. However, understanding how network scale dynamics emerge from single-cell dynamics and in turn relate to behavioral outcomes remains poorly understood. Bridging multiple spatial and temporal scales requires a *systems-level approach be brought to the field of neuromodulation*.

It is also important to acknowledge at the outset that there is no single mechanism by which all neuromodulation therapies act. The short- and long-term effects of neuromodulation depend upon the clinical disorder, the patient's anatomy and comorbidities, the neural pathway(s) targeted, the modality of stimulation, the duration of stimulation, and the applied stimulation settings, which can range in terms of amplitude, polarity, frequency, pulse width, and phase relative to the underlying neural activity. The nervous system is a dynamic entity and the application of neuromodulation can depend on plasticity and brain state. The myriad of experimental factors and parameters make probing the physiological mechanisms of neuromodulation challenging and important to understand. Future engineering and clinical advances in neuromodulation therapies will no doubt depend on the successful translation of knowledge related to these mechanisms of action (see Table I).

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TABLE I
CHALLENGES AND OPPORTUNITIES IN BRAIN NEUROMODULATION THERAPIES

	Challenges	Implications	Approach
Physiology	To better understand the physiological changes occurring within different regions of the brain during therapeutic neuromodulation	• Identify biomarkers for closed-loop stimulation therapy • Identify more effective and localized regions for stimulation • Provide engineering guidelines to improve device design and programming procedures	DBS, ICS, tDCS, TMS
	To better understand the temporal dynamics of neuromodulation therapy upon cycling the stimulator on and off	• Lower duty cycle stimulation • Reduce power consumption	DBS, ICS, tDCS, TMS
Engineering	To develop algorithms for programming neuromodulation systems	• Reduce time to identify effective stimulation parameters • Optimize therapeutic outcomes	DBS, ICS, tDCS, TMS
	To improve the stimulator circuitry such as: multi-channel current control, onboard sensing, rechargeable batteries	• Improve current steering within the brain • Sense for closed-loop control • Negate battery replacement	DBS, ICS
	To target brain regions more focally using high-field MRI for localization, higher-density arrays, and customized coils	• Improve therapy with fewer side-effects • Make the therapy more consistent among patients	DBS, ICS, tDCS, TMS
	To minimize tissue damage from DBS lead implantation	• Minimize post-operative side effects	DBS
Clinical	To identify new targets for existing indications of neuromodulation	• Expand coverage over multiple symptoms of a disorder • Target regions with fewer chances of side-effects	DBS, ICS, tDCS, TMS
	To identify new targets for emerging indications of neuromodulation	• Provide alternative therapies to patients who are not treated adequately with traditional medication or psychotherapy	DBS, ICS, tDCS, TMS
	To assess therapeutic efficacy through double-blinded clinical trials	• Understand outcome variability among patients • Identify variability (outcome) • Consensus on methodological issues	DBS, ICS, tDCS, TMS

The goal of this perspective paper is to provide a systematic overview of the challenges and opportunities for four clinical neuromodulation technologies that directly interface with the brain: 1) deep brain stimulation (DBS); 2) intracranial cortical stimulation; 3) transcranial direct current stimulation (tDCS); and 4) transcranial magnetic stimulation (TMS). The field of neuromodulation is poised to see explosive growth over the next decade. Dedicating research activities to the interdisciplinary challenges in neuromodulation will be critical to further improve the quality of life for individuals living with neurological and neuropsychiatric disorders.

II. DEEP BRAIN STIMULATION

A. Current Technology

DBS is an intracranial, electrical neuromodulation therapy that has FDA approval for the treatment of medication-refractory Parkinson's disease and essential tremor, and has humanitarian device exemption for dystonia and severe obsessive–compulsive disorder. DBS therapy involves surgical implantation of a lead of electrodes into a nucleus or fiber tract within the brain. Because precise targeting is of paramount importance to achieving therapy, neurosurgical stereotactic navigation coupled with preoperative MRI and intraoperative microelectrode mapping is often used to accurately target DBS lead(s) within selected structures in the brain. An implantable pulse generator (IPG), containing battery and stimulation hardware, is implanted subcutaneously in the chest of the patient, and an extension cable is tunneled under the skin to connect the IPG to the DBS lead. After these implantation procedures, a clinician titrates the patient's medication and telemetrically configures the IPG parameters to optimize therapy for the patient. Stimulation generally consists of a continuous, high-frequency (60–185 Hz), biphasic pulse train with amplitudes ranging from 0 to 10 V and pulse widths between 60–450 μs, applied through one or more cylindrical electrodes along the DBS lead.

Treating brain disorders with high-frequency, pulsatile stimulation was first introduced in humans through the pioneering work of Hassler and colleagues in the 1950s [2]. They described a series of parkinsonian patients who received electrical stimulation via wires that were inserted into the globus pallidus. Low-frequency stimulation ($<$25 Hz) exacerbated contralateral tremor, whereas high-frequency stimulation (25–100 Hz) through the same electrode alleviated or abolished tremor. They suggested that low- and high-frequency electrical stimulation could serve as useful tools to pinpoint regions of the brain conducive to surgical ablation therapy for treating movement disorders. Since then, DBS has largely supplanted neurosurgical ablation therapies because of the reversibility and capacity of DBS to tailor stimulation settings to a patient's symptoms. While approximately 100 000 patients have been implanted with DBS systems worldwide, the mechanisms of action of DBS therapy are still a matter of debate in the research and medical fields.

B. Mechanisms of Action

DBS involves applying electric current through small regions of brain tissue, changing the extracellular potential of cells and fibers near the stimulated electrode. The distance of the neuron and the orientation of its processes to the electrode affect how strongly the electrical stimulus modulates the excitability of the neuron [3]. The original mechanistic hypothesis for DBS equated the neurophysiological effect of DBS to a surgical lesion, since clinical outcomes were similar between the two therapies. Experimental evidence supports this hypothesis in part, in that the majority of neurons within a stimulated nucleus exhibit decreased firing rates during stimulation [4]. This effect was explained by various theories including depolarization block, activation of inhibitory synapses, and depression of excitatory synapses. In contrast, the majority of recordings downstream of

the stimulated target show distinct patterns of modulation that are not necessarily indicative of inhibition within the stimulated nucleus. In the case of DBS in the subthalamic nucleus (STN) for Parkinson's disease, for instance, there is an increased firing rate in the globus pallidus, even though excitatory STN neurons that project to globus pallidus are suppressed [5]. Further, globus pallidus neurons exhibit spike activity that is entrained to the pulses of stimulation. Combining these two experimental results, DBS is thought to dissociate dendritic/somatic activity from axonal output activity, inhibiting the former while driving the latter at or near the frequency of stimulation [3]. Indeed, the typical DBS setting used clinically consists of a short cathodic pulse followed by a long anodic pulse, which is known to initiate action potentials more easily in axons than in cell bodies [6].

Axonal fibers of passage coursing through or near a DBS electrode may also be directly modulated by stimulation, leading in some cases to an augmented therapeutic effect or alternatively to generation of untoward side effects. STN-DBS, for instance, may directly activate axonal fibers from the globus pallidus traversing around the STN and entering into the thalamus, which may provide an additional therapeutic effect on parkinsonian motor signs [7]. On the other hand, STN-DBS can also result in suprathreshold current extending into the corticospinal tract of internal capsule, which lies adjacent to the STN and can lead to involuntary motor contractions [8]. The concept of activating fibers of passage becomes important in the application of DBS to disorders like depression and obsessive–compulsive disorder in which the DBS electrodes are placed in white matter. In this case, the electrodes are surrounded by numerous fiber tracts that project to and from many cortical and subcortical brain regions.

The connection between modulating populations of neurons with DBS and inducing a behavioral effect is not fully understood. One hypothesis suggests that an "informational lesion" is generated by driving the output of the targeted nucleus with pulse trains above the natural frequency of the stimulated neuronal population, replacing pathological spike activity with more regularized activity patterns [9]. Thus, the pattern of stimulation, and not just the rate, appears to be important for effective treatment [10]. Disrupting the pathological network with DBS may allow other pathways to compensate for the underlying dysfunction [11]. Alternatively, the regularization of activity may increase the overall fidelity of information transmission through the stimulated nucleus. Recent experimental work shows that, despite overall changes in firing rate and pattern, neuronal activity in a nucleus targeted by DBS still correlates with behavior [12].

Another approach to disrupt pathological activity in the brain is to stimulate different parts of a neuronal population using separate electrodes. This method, called coordinated reset [13], involves stimulating through multiple electrodes at different phases, each entraining a subset of the population thereby disrupting global synchrony. Many output neurons of the basal ganglia act as autonomous oscillators [14], suggesting that periodic forcing of periodic systems at certain frequencies can induce chaotic patterns of activity. The defining feature of chaotic activity is that two neurons starting nearly synchronized will respond differently and their differences grow exponentially until they are no longer synchronized. Thus, the periodic stimulation used by DBS may work through a "chaotic desynchronization" [15].

Neural plasticity may also play a role, as DBS therapy can take seconds to hours to develop after stimulation onset [16], and in some cases effects can persist long after stimulation is terminated [17]. These temporal dynamics of DBS are not well understood and likely depend on the target of stimulation, the neurological disorder treated, and the particular symptom under investigation. In Parkinson's disease, for example, resting tremor is suppressed within seconds, while relief from bradykinesia takes minutes, and improvement in gait and posture can require continuous stimulation for hours to days before achieving a maximum effect. Compensatory networks and plasticity in the context of DBS require more attention than currently given.

C. Clinical Applications

DBS therapy is now in a period of rapid expansion to a broad range of clinical applications. At present, an open-label clinical trial is testing the efficacy and safety of DBS in the subgenual cingulate and anterior limb of internal capsule as adjunctive treatment for severe treatment-refractory major depressive disorder [18]. A randomized, double-blinded trial is also evaluating stimulation of the anterior limb of internal capsule against sham DBS for depression [19]. Recent efforts have also investigated DBS in the anterior nucleus of thalamus for reduction in seizure frequency through a double-blinded randomized trial with 3- and 25-month assessments [20]. While seizure frequency reduced by 40% on average, in this study, only 6 of the 81 patients became seizure free. The success of this trial provides support for DBS therapy as an alternative to surgical resection for patients with medically intractable epilepsy. However, the FDA has not yet granted full approval for use in the USA without further improvement in efficacy. Clinical trials are also underway for DBS of the fornix and Papez circuit to potentially delay or reverse the progression of Alzheimer's disease [21]. Targets for other brain disorders are still in the experimental phase due to inconsistent results or low recruitment numbers. In terms of the latter, stimulation of the central thalamus shows promise to activate the arousal system in minimally conscious state patients [22], but the relatively small number of patients affected by this condition makes large-scale clinical trials difficult. Several DBS targets, including the periaqueductal gray, have been stimulated to manage chronic pain [23], but the distributed nature of the nociceptive system also makes identifying an appropriate target difficult.

D. Challenges and Opportunities

There are a multitude of challenges and opportunities in the field of DBS research for physiologists, engineers, and clinicians (see Table I and Fig. 1). While DBS can improve the quality of life for patients with brain disorders, the therapy is far from optimal. One challenge is the lack of knowledge pertaining to the neurophysiological mechanisms of DBS, which limits opportunities to optimize targeting and stimulation for more consistent and effective therapy. This stems in part from the lack of animal

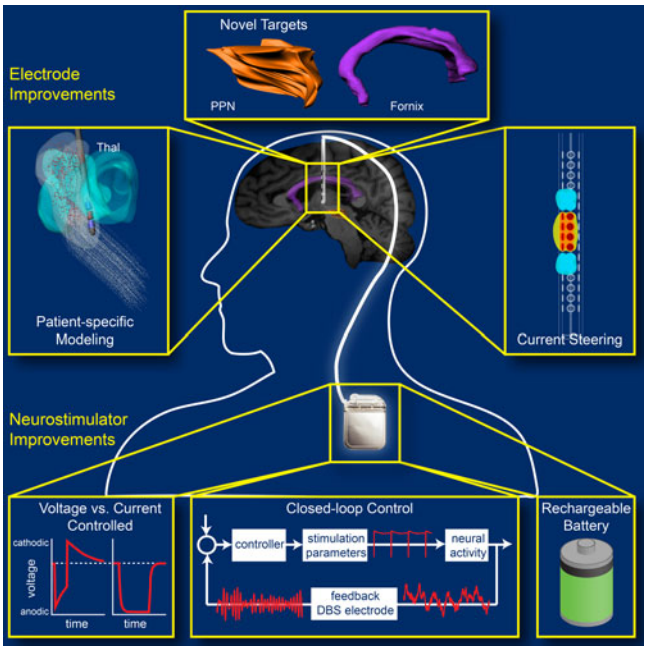

Fig. 1. Overview of future directions for DBS neuromodulation research. Improved therapy at the patient level, development of novel electrode configurations to sculpt voltage fields, patient-specific models to guide programming of stimulation parameters, and identification of new targets for stimulation are needed. On the hardware side, implementation of current-controlled stimulation with multiple independent sources, closed-loop algorithms to manage symptoms in real time, and improved battery longevity need to be implemented.

models of brain disorders and the application of DBS to them. The 6-OHDA and MPTP models of Parkinson's disease have yielded important insight into the mechanisms of DBS in the basal ganglia (e.g., [5] and [24]), but most brain disorders do not yet have adequate animal models for translational DBS therapy. Optogenetics is one neuroengineering tool that may prove useful for identifying the cell-specific physiological changes necessary to achieve a therapeutic outcome with DBS, especially in cases of DBS targeting white matter tracts [25]. With optogenetics, transfection of rhodopsin genes can be made to express channel rhodopsin proteins in specific cell types. Depending on the protein inserted, various wavelengths of light can be used to depolarize or hyperpolarize specific cells. Because light does not create electrical artifacts that interfere with electrophysiology or functional magnetic resonance imaging, optogenetics may become an important tool to probe the mechanisms of DBS [26]. However, because optogenetics involves viral transfection, its use will be restricted to animal research in the near future.

With a more thorough understanding of the mechanisms of DBS, hardware and software components of DBS devices and implantation procedures will need adaptation. Potential improvements include more accurate targeting of DBS lead(s) and enabling more precise shaping of the electric field within the brain. Most DBS targets are adjacent to neural populations that, if modulated by DBS, lead to untoward motor, sensory, and cognitive side effects. Improvements in high-field imaging that directly visualizes small nuclei and subnuclei will aid in neurosurgical targeting of DBS leads. In addition, DBS leads containing radially segmented [27] or multiprong electrodes [28] will enable clinicians to more precisely sculpt electric fields generated around a DBS lead.

There is also a push in the medical device industry to develop closed-loop strategies for DBS to make the initial programming of the IPG more streamlined and provide the patient with more consistent therapy. Implementation of a closed-loop system, however, requires identifying robust biomarkers that reflect the degree of DBS therapy, feeding this information back into a control algorithm. In the case of Parkinson's disease, studies suggest that beta-band activity (13–35 Hz) in the STN could be a biomarker of a parkinsonian state since the signal is abolished by dopaminergic [29] and DBS therapies [30]. However, changes in beta activity are inconsistent across patients, with some studies seeing beta-band activity in as few as 50% of Parkinson's disease patients [31]. In this case, the transfer function describing the effects of stimulation parameters on neurophysiological biomarkers of therapy needs further characterization before closed-loop control will be feasible and will be approved by regulatory agencies. An IPG employing closed-loop control must also compensate for increased computational resources of the sensors and controllers, which demand more efficient hardware and increased battery power.

Introducing rechargeable batteries would reduce, but not completely eliminate, the number of replacement IPG surgeries for the patient and offset the increased computational demands from complex software algorithms, but they would also require more patient compliance [32]. Reducing the need for IPG replacement surgeries or lead revision surgeries would drastically reduce cost of chronic DBS therapy, as the reimbursement rate for each IPG replacement ranges between $12500 and $26000. Improving therapeutic outcomes and reducing patient complications (e.g., infection, lead fracture, device dislocation, poorly targeted leads) also have the potential to reduce costs associated with DBS therapy.

With the extension of DBS to new targets and new clinical indications, it is important that future clinical studies are well controlled. Patient-to-patient variability is a large unknown in the context of DBS therapy, and can only be understood through randomized, double-blinded clinical trials that are coupled with detailed DBS lead localization through imaging, complete description of stimulation settings, and integration of patient-specific computational models that predict the volume of tissue activated by DBS [33]. Such an investigation goes beyond the scope of any one field and requires intensive collaboration. Neurologists, neurosurgeons, and radiologists interface with patients to collect electrophysiology and imaging data, which are then analyzed by neuroscientists and biomedical engineers.

In addition to the traditional devices used for DBS, there have been significant developments in implantable devices in other fields that can be used for deep brain neuromodulation, such as deep brain implants for hearing restoration. The rapid developments in auditory neuroprosthetics stemmed from the success of the cochlear implant (CI), which is positioned within the cochlea and stimulates the remaining auditory nerve fibers to restore hearing (see Fig. 2) [34]–[36]. There are now more than 200 000 patients implanted with CIs worldwide. The device consists of a stimulator that is implanted underneath the skin in

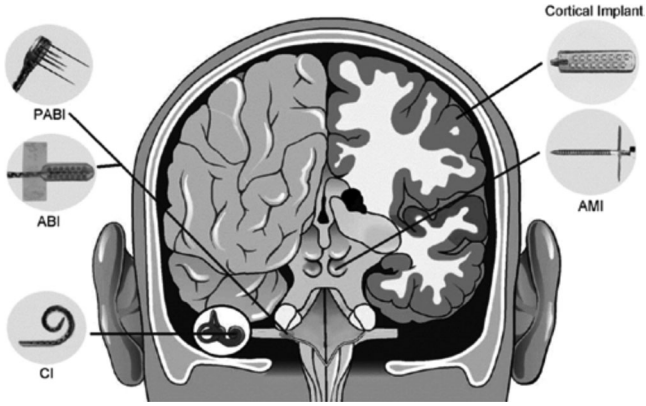

Fig. 2. Simplified schematic of the brain showing the location of electrode arrays currently implanted in humans for restoring hearing or suppressing tinnitus. The CI, ABI, PABI, and AMI are example arrays developed by Cochlear Limited (N.S.W., Australia) and the cortical implant is an example array developed by St. Jude Medical (TX, USA). Similar types of devices have been developed by several other neuroprosthetic companies. From [40] with permission.

a bony bed within the skull behind the ear and connects to the electrode array via a cable tunneling through the skull to the cochlea. A transmitter is positioned over the skin and aligned with the stimulator using a magnet. A behind-the-ear processor is able to record the incoming sound with a microphone, convert the signal into stimulation patterns, and transmit this information to the implanted stimulator through a telemetry interface. The success of CIs has been unparalleled in that deaf children and adults can understand speech and even converse over the telephone, allowing them to integrate into mainstream society. This success has pushed forward the rapid development of miniaturized processors, advanced electrode array technologies, new current-steering approaches, and semiautomated fitting and signal processing algorithms [34], [36]–[38]—all of which could benefit DBS research and clinical practice in the future.

For those not indicated for CIs (e.g., those without an implantable cochlea or functional auditory nerve for activation), new electrode arrays were developed to stimulate more central brain regions using the same implant technology as the CI (see Fig. 2). The auditory brainstem implant consists of either a surface array (ABI) or a multishank penetrating array (PABI) while the auditory midbrain implant (AMI) consists of a single shank array [39]. There are over 1000 children and adults implanted with the ABI, 10 adults with the PABI, and 5 adults with the AMI. These devices have proven safe for many years and have improved hearing performance in deaf patients, leading to an increase in the number of implanted patients over the past decade.

These auditory neuromodulation implant technologies are now under investigation for managing tinnitus, which is a phantom sound generated within the brain in the absence of an external sound source. Since tinnitus is linked to hearing loss and many deaf patients implanted with central auditory prostheses also have tinnitus, it has been possible to assess the effects of DBS on phantom sound perception. Encouragingly, ABI stimulation appears to mask and modulate the tinnitus percept in some patients [41]. Recent attempts have also shown the ability to interfere with tinnitus with the AMI [42]. However, due to variability in effects across patients, further studies are needed to assess if specific regions within the brainstem or midbrain could be targeted with alternative stimulation strategies to more effectively suppress tinnitus across patients.

Technologies for hearing applications consist of several components more advanced than the traditional DBS devices, such as smaller and more dense electrode arrays, constant-current stimulators with current steering capabilities, neural recording hardware and monitoring, and wireless interfacing. These advanced features can help address some of the challenges faced by DBS research (see Table I and Fig. 1). Therefore, there needs to be greater collaboration among the different fields to combine technologies and more effectively tackle different neural applications. One challenge will be in fostering collaborations across different implant companies and opening up new opportunities to develop improved technologies while overcoming FDA criteria for mainstream implementation.

III. Intracranial Cortical Stimulation

A. Current Technology

Based upon the pioneering work of Penfield and colleagues in the 1950s [43], intracranial cortical stimulation has become an increasingly popular investigational approach for treating patients with epilepsy, tinnitus, pain, depression, stroke, tremor, dystonia, and Parkinson's disease among others. The approach involves first implanting an array of electrodes over or into cortex, and then delivering electrical stimulation through these electrodes using stimulation parameters comparable to those used in DBS therapy [44]. Epidural electrode arrays, which are placed between the cranium and dura, are the most commonly used clinically. Northstar Neuroscience, for instance, has developed a two- and six-electrode epidural array with electrode diameters of 3 and 3.75 mm, respectively [45]. St. Jude Medical produced an 8- and 16-electrode epidural array with 4×2.5 mm electrodes (see Fig. 2) [46]. Similarly, Medtronic developed a four-electrode array with 4 mm diameter electrodes [47]. Because epidural arrays are separated from the cortical surface, the spatial precision of neuronal activation is most likely less than for subdural arrays implanted between the dura and cortical surface [48]. Penetrating cortical electrodes have also been pioneered for clinical use in brain–machine interface applications [49], but have yet to be broadly used for clinical neuromodulation applications. That being said, penetrating cortical arrays have strong potential for encoding information into the brain through auditory and visual neuroprosthetics [50].

B. Mechanisms of Action

Thresholds for activating cortical neurons with surface electrodes depend on several factors, including stimulation waveform and polarity, electrode geometry and configuration, and proximity of the electrode array to neuronal processes within cortical columns and layers [48]. Bipolar electrode configurations are more effective at confining the modulatory effects of stimulation to regions directly below the electrode. However,

the presence of axonal tracts projecting across cortical columns likely results in a sparse penumbra of modulation within cortex that extends beyond the proximal region of a stimulated electrode [51]. This penumbra also includes subthreshold changes in excitability that also can produce modulatory effects. It is also important to consider the placement of anode(s) and cathode(s) in bipolar configurations as neuronal populations under both sets of electrodes will be modulated [48].

Location and morphology of cortical neurons are also factors in the mechanisms of action [48]. Cortical neurons within a sulcus most likely have higher thresholds for modulation than neurons located along a gyrus. In addition, dendritic morphologies and orientations of axons can have significant effects on activation threshold, suggesting that each interneuron and pyramidal cell type may be affected differently during cortical stimulation. Understanding the direct and indirect effects of cortical stimulation on these populations is not well understood and is an important area of research for improving cortical stimulation therapies.

C. Clinical Applications

1) Epilepsy: Intracranial cortical stimulation at a seizure focus has been shown to suppress EEG activity as well as seizures. NeuroPace developed a device that analyzes electrocorticogram (ECoG) recordings and stimulates through the same electrodes to suppress seizures. When aberrant epileptiform activity is detected, stimulation is turned on to prevent seizures from occurring. Closed-loop systems have several advantages over open-loop counterparts. For one, they may reduce side effects by limiting stimulation to times when patients are at risk for seizures. Also they could potentially warn patients of seizure onset through the use of sophisticated seizure detection algorithms. The NeuroPace closed-loop system has been shown to reduce seizure frequency by about 40% [52], [53], which is comparable to the aforementioned clinical trial with thalamic DBS. Although clinical trials using closed-loop technology hold promise, the technology has not yet received FDA approval. Identifying patients for which stimulation is likely to be effective, improving detection of a preseizure state, and increasing efficacy are necessary for this approach to become a viable therapy. A unique challenge to treating epilepsy with cortical electrical stimulation is that epileptiform activity is transient. Open-loop periodic stimulation may be effective for certain pathologies, but may exacerbate others. Alternatively, closed-loop stimulation can determine when stimulation is effective and modulate stimulus waveforms accordingly to maximize efficacy.

2) Tinnitus: In the past, patients with tinnitus undergoing epilepsy surgery in which the auditory cortex is already exposed have been stimulated to assess the effects of cortical stimulation on tinnitus [54]. These early cases demonstrated that cortical stimulation could modulate and suppress the tinnitus percept. More recently, there have been significant developments in implanting surface electrode arrays over the auditory cortex for those with severe tinnitus. There are now over 50 patients who have been implanted with epidural arrays over the secondary auditory cortex (see Fig. 2) [46], [55]. The goal is to disrupt cortical and subcortical (via descending pathways) neurons involved with the tinnitus network with patterned stimuli. Overall, cortical stimulation for tinnitus has been encouraging with more than 50% of implanted patients obtaining improvements in their condition. However, due to the variability across patients and inability to fully suppress tinnitus in most patients, further studies are needed to identify consistent stimulation locations and strategies across different groups of tinnitus patients (e.g., those with noise-like versus tonal tinnitus or different causes and durations of tinnitus) to make cortical stimulation a standard treatment.

There are several key challenges that still need to be overcome with neuromodulation approaches for tinnitus. It is still unknown how tinnitus is coded throughout the auditory system, and if there is one region that can be targeted across patients with different types of tinnitus. There are several animal models of tinnitus (e.g., tinnitus caused by noise damage or ototoxic drugs) [56]–[58] that show some properties similar to those observed in humans that may be used to identify optimal target regions. However, no animal model captures the dynamics and variability observed in tinnitus patients. More clinical research using functional imaging and psychophysical methods in tinnitus patients will be important for advancing cortical stimulation therapy [59]–[61]. Currently, tinnitus does not justify implantation of electrodes for therapy in most patients. However, in some patients already implanted with electrodes for other applications, such as for hearing restoration, epilepsy treatment, or tremor suppression, it is possible to directly record neural activity from and stimulate neurons in humans with tinnitus to then validate the results from animals. There are a few recent reports in which patients being implanted with a DBS lead for Parkinson's disease or essential tremor were stimulated in a brain region (e.g., caudate nucleus) that suppressed tinnitus [62].

It is also important to continue developing less invasive approaches to manage brain disorders. Epidural stimulation is less invasive than traditional DBS approaches and thus can benefit a larger patient population with lower surgical risks. However, other minimally or noninvasive approaches need to be considered to further reduce risks while improving performance.

D. Challenges and Opportunities

Many of the grand challenges in the field of intracranial cortical stimulation are similar to those for DBS therapy. Both approaches will benefit from resolving issues relating to specificity and selectivity of stimulation, consistency of electrode array implantation across patients, and knowledge of how electrical stimulation modifies neuronal activity within cortex and how that then modulates to changes in network and behavioral function.

While intracranial cortical stimulation is less invasive than DBS, it comes with its own challenges. Sculpting the electric field with surface electrodes is complicated by the presence of gyri and sulci, whose neuronal populations are inevitably perturbed by different electrical gradients. Surface electrode arrays are also limited by their two-dimensional geometries, thus limiting opportunities to sculpt the electric field in depth.

For epidural arrays, the meningeal layers and cerebrospinal fluid will act as electrical shunts along the cortex, thereby limiting the spatial specificity of stimulation. The development of high-density subdural arrays that mold to the cortical surface [63], computational models that can predict the neurophysio-logical effects of cortical stimulation [48], and translational optogenetic approaches to target specific cell types [64] will be important to improve the sensitivity and selectivity of cortical stimulation approaches.

Stimulation of the cortex has a higher risk of inducing seizures than with DBS. Cortical stimulation in clinical trials for Parkinson's disease reported seizures in about 50% of the patients [65]. In contrast, following DBS lead implantation in the basal ganglia, less than 10% of patients have postoperative seizures, most often resulting from a hemorrhage during the implantation process [65]. Establishing safety guidelines for stimulation protocols and array configurations that maintain injected charge densities within safe limits for seizure induction will be important for current and future applications.

There also needs to be additional effort in making the therapy more consistent across patients through meticulous patient selection, imaging to localize cortical regions that are susceptible to neuromodulation, neurosurgical placement of the arrays, consistency of stimulation parameters, and patient-specific computational models to verify that the stimulation settings are appropriate for activation of the desired cortical region. It is important to consider that cortical stimulation may not be effective for all brain disorders, especially those with subcortical pathophysiologies. Thus, it is important going forward to rigorously investigate cortical stimulation in animal models to help guide in the translation of this approach.

Other than sensory neuroprosthetics, penetrating cortical electrodes have yet to see major neuromodulation-based applications in a clinical setting. One of the challenges with penetrating electrode arrays is finding a balance between minimizing the amount of brain tissue damaged when inserting an array and activating enough of the cortical surface to generate a behavioral effect. Identification of optimal regions for stimulation before implantation becomes even more critical for penetrating arrays to avoid excessive tissue damage associated with repeated placements. One possibility is to use a hybrid device consisting of surface and penetrating cortical arrays. Even if the arrays are not positioned in the exact target region, the electrodes located within the cortical tissue can be combined with the surface electrodes to achieve more localized and deeper activation of neurons using current-steering approaches. High-density electrode designs as well as current steering technology and theories developed in the auditory field [37] can help advance these efforts.

IV. Transcranial Direct Current Stimulation

A. Current Technology

Over the past decade, tDCS has emerged as a noninvasive tool to modulate the excitability of the cortex. tDCS is typically applied with a current intensity of 0.5–2 mA for a period of 10–20 min per session [66]. Most studies of tDCS have utilized saline-soaked sponge electrodes (25–35 cm^2) for stimulation, resulting in current densities at the scalp surface of up to $\sim$0.08 mA/cm^2. However, recent efforts to increase the spatial specificity of tDCS have led to the development of smaller, more focal stimulation electrodes ($\sim$1.4 cm^2), which result in current densities of up to 1.43 mA/cm^2. Computational studies of tDCS have demonstrated that these higher density stimulation electrodes result in more focal spatial distribution of current than traditional sponge electrodes [67], [68]. There is also strong evidence that increasing the current density and duration of stimulation can lead to more significant and longer lasting effects on cortical activity [66], [69]. However, it is important to maintain relatively weak currents in order to retain subthreshold effects of tDCS on cortical excitability, and avoid safety concerns with higher levels of electricity.

B. Mechanisms of Action

During tDCS, current flows across the cortex from the negatively polarized cathode to the positively polarized anode [70] [see Fig. 3(a) and (b)]. Through the application of weak electrical currents across the scalp surface, tDCS induces long-lasting, subthreshold changes in spontaneous neuronal activity and excitability [71]. Cortical neurons, such as pyramidal neurons, that have a major dendritic axis oriented along the gradient will generate an intracellular counter gradient that results in a change in transmembrane potential distribution, excitability [72], [73], and location of action potential initiation [74]. Neurons that do not have a major axis, such as stellate cells, or are compact, such as granule cells, may not be modulated regardless of their orientation to the field [75]. In cases of pyramidal cells, anodic stimulation generally has a facilitative effect through tonic depolarization of neuronal resting membrane potentials. Cathodic stimulation results in tonic hyperpolarization and an overall inhibition of the underlying neuronal population [76]. Tonic modulation of the excitability by tDCS can also induce changes in synaptic plasticity that persist for hours or even days following stimulation through modification of NMDA receptor efficiency [66]. Although there are no known significant risks associated with tDCS, the passing of weak electric currents across the scalp may result in itching, tingling, and burning sensations [77]. Such effects are the result of peripheral nerve stimulation and subside immediately after terminating stimulation.

Although the majority of tDCS studies to date have focused on behavioral effects, several groups have begun to assess the neurophysiological effects of tDCS in greater detail through the use of noninvasive functional imaging methods. Initial EEG studies showed that tDCS induces changes in resting state oscillatory activity, functional connectivity, and event-related EEG activity [78]–[81]. Electrode placement and stimulation polarity play complex roles in determining subsequent effects on cortical activity.

Functional MRI has also been used to assess the effects of transcranial electrical stimulation (TES) in both animal models and humans [82]. Multiple studies in humans indicate that tDCS is able to induce local, polarity-dependent effects on the

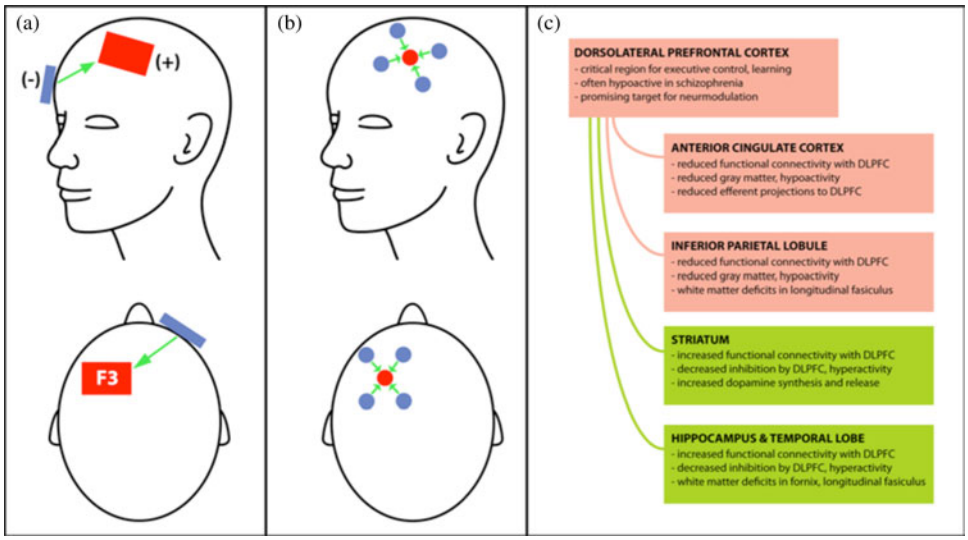

Fig. 3. Conventional and high-density tDCS of the DLPFC for cognitive rehabilitation in schizophrenia. (a) Anode (red, +) and cathode (blue, –) placement of conventional saline-soaked sponge electrodes for anodal stimulation of the left DLPFC. Anodal electrode placement corresponds to the F3 location of the International 10-20 EEG system. The direction of current flow is from the cathode to the anode (green arrows). (b) 4×1 ring electrode configuration for high-density anodal stimulation of the left DLPFC. The anode electrode is surrounded by four cathodal electrodes that collectively serve as the reference. (c) DLPFC network connectivity abnormalities in SZ. Red and green lines indicate decreased and increased functional connectivity with the DLPFC in SZ, respectively. Red and green boxes indicate hypoactive and hyperactive regional activity in SZ, respectively.

fMRI BOLD signal and significant changes in resting state functional connectivity [83], [84]. Resting state fMRI scans before and after tDCS of M1 have revealed both local and long distance increases in functional connectivity using cathodic and anodic stimulation, respectively [85]. Such distributed effects of tDCS detected by the fMRI BOLD signal appear to parallel those reported in EEG studies, further demonstrating that tDCS can have both local and global effects on cortical activity and connectivity [86], [87].

C. Clinical Applications

tDCS shows promise for treating several neuropsychiatric conditions including schizophrenia, addiction, and depression.

1) Schizophrenia: Schizophrenia is often characterized by aberrations in cortical functional connectivity [see Fig. 3(c)]. Auditory verbal hallucinations are reported in 50–70% of individuals with schizophrenia and are often resistant to pharmacological treatments [88]. A recent tDCS study found that anodic (excitatory) stimulation of the left dorsolateral prefrontal cortex (DLPFC) in conjunction with cathodic (inhibitory) stimulation of the left temporal-parietal junction could significantly reduce the occurrence of auditory verbal hallucinations in schizophrenia patients [88]. Importantly, the reduction in auditory verbal hallucinations persisted a full three-month period after the end of the tDCS treatment regimen. Hypoactivity of the prefrontal cortex is also associated with numerous learning and memory problems in schizophrenia, furthering its promise as a target for tDCS intervention. Anodic tDCS of the left DLPFC was able to improve probabilistic association learning in a subgroup of patients with schizophrenia [89]. Overall, attempts to utilize tDCS for treating schizophrenia highlight the heterogeneous nature of the disease and the challenges associated with neuromodulation intervention.

2) Addiction: Several studies have also attempted to reduce impulsivity and risk-taking behaviors in healthy populations using tDCS. Individuals with substance abuse problems generally exhibit increased impulsivity and risk-taking behavior when compared to controls, due to deficits in top-down cognitive control. Bilateral stimulation of the DLPFC was shown to elicit a significant decrease in ambiguous risk-taking behavior in healthy human subjects [90] and a decrease in impulsivity on a nonambiguous risk task [91]. These promising early results demonstrate that tDCS is indeed able to reduce impulsive behaviors associated with drug abuse and should encourage further development of tDCS-based therapies for addiction.

3) Depression: tDCS has also been investigated as a treatment for major depression, though controversy remains around its efficacy due to the inconsistency of published results. While some tDCS studies have noted that anodic stimulation of the left DLPFC can significantly reduce depression scores for up to 30 days following the treatment regimen, other studies have found no significant effects of tDCS on reported depression ratings. Optimizing DLPFC stimulation in a subject-specific manner and investigating additional tDCS of other cortical regions involved in mood and emotion, such as the parietal cortex [92], could improve efficacy of tDCS for treatment of depression.

D. Challenges and Opportunities

Despite many advances in tDCS research, there are still a number of technical challenges. First will be the establishment of optimal tDCS stimulation configurations and protocols for different cortical regions. Variations in electrode design beyond the traditional large sponge electrodes may improve the focality of tDCS [93], [94]. Electrode positioning and underlying cortical anatomy play a significant role in determining current flow and distribution during tDCS. The existing body of tDCS

literature reveals large variations in subject-specific effects of stimulation, even within a particular cortical region. Though current approaches generally utilize the international 10-20 EEG system for positioning tDCS electrodes, future work will benefit from the use of subject-specific computational models based on anatomical MRI and FEM/BEM for targeting of tDCS. fMRI activation maps, which are currently used for improving targeting of TMS, could also improve tDCS targeting [69]. Optimizing stimulation sequences and understanding polarity-related differences in tDCS-induced effects across cortical regions will also be critical to establishing tDCS as a clinical intervention.

Functional neuroimaging of tDCS also faces significant challenges. Currently, there have been very few attempts to simultaneously record EEG during tDCS stimulation. The majority of tDCS-EEG studies have collected EEG only before and after a period of tDCS stimulation. This is primarily due to the fact that traditional sponge electrodes are ill-suited for simultaneous EEG recordings. Not only are these electrodes bulky and difficult to position under an EEG cap, but they also induce widespread artifacts in the EEG signal and prevent EEG recordings at electrode positions that overlap with tDCS electrode locations. In contrast, high-density tDCS electrodes are much better suited for use during simultaneous EEG. A pilot study recently reported successful recording of EEG at 24 electrode locations during high-density tDCS in both healthy and epileptic human populations [95]. However, recording EEG directly at the site of stimulation is still not possible at this time. It is likely that the adoption of such novel electrode types and configurations for tDCS will significantly improve our capacity for simultaneously recording EEG during stimulation. Ultimately, the development of an EEG cap with electrodes capable of both stimulation and recording would benefit clinical studies with tDCS. Measuring fMRI signals during tDCS is possible [96], but tDCS-based artifacts may still occur near sites of stimulation due to the application of electrical current during the MR pulse sequence. These induced artifacts in the fMRI signal could potentially confound the observed changes in local BOLD signals during tDCS and must be carefully characterized prior to making any scientific conclusions.

Finally, given the low cost and relatively portable nature of tDCS, working toward novel closed-loop control systems for individualized cognitive training and rehabilitation should be the next major push in the field. Such a device would be able to monitor neural activity in real time, potentially using EEG, and trigger tDCS with high temporal and spatial specificity in response to changes in a given control signal. A recent study utilizing a closed-loop TES system was able to significantly reduce epileptic waveforms in rats in real time following detection of increased epileptic activity [97]. Although TES is different from tDCS because it is applied at an intensity high enough to trigger action potentials, an earlier pilot study using cathodal tDCS over the epileptogenic focus in a treatment-resistant human population also reported a significant reduction in epileptogenic waveforms [95]. These results suggest that a similar closed-loop device utilizing tDCS could be used to monitor and treat drug-resistant epilepsy in humans, among other neurological and neuropsychiatric conditions. However, since current procedures for tDCS are relatively limited in terms of temporal precision due to long stimulation durations, further investigation into the real-time effects of tDCS using functional imaging is essential.

Further study of existing and new tDCS approaches with neuroimaging will provide critical information about the effects on brain activity and connectivity induced by tDCS and how best to unlock its full potential as a noninvasive tool for the treatment of neuropsychiatric disorders.

V. Transcranial Magnetic Stimulation

A. Current Technology

TMS is a noninvasive neuromodulation therapy that is currently FDA approved for the treatment of medication-refractory depression and the stimulation of peripheral nerves. TMS is also emerging as a possible therapeutic intervention for stroke rehabilitation, schizophrenia, and other conditions affecting the brain. Unlike invasive neuromodulation techniques, TMS does not require surgical intervention. Instead, pulsed current is discharged through a coil placed near the surface of the scalp, creating a time-varying magnetic field perpendicular to the plane of the coil with durations of approximately 1 ms. The resulting eddy currents act to modulate neuronal activity within the cortex. Several TMS coils have been developed to tailor the intensity and focality of the electromagnetically induced cortical currents within the brain. TMS coils with a circular shape generate a loop of eddy current on the cortical surface [98], [99], affecting a relatively large cortical area. Figure-eight coils [99], [100], on the other hand, consist of two circular coils in which current flows in opposite directions between the two loops, summating at their intersection. Therefore, while cortical eddy currents are generated beneath both loops, the largest eddy currents occur at the intersection between the loops. Figure-eight coils require substantially less energy to provide stimulation when compared to circular coils. Moreover, figure-eight coils produce a smaller activation area when stimulation is provided at an appropriate threshold.

The location of the TMS coil can be guided to the cortical target using anatomical landmarks or, preferentially, by individual MRI data. Coil placement based on MRI requires a neuronavigation system that incorporates anatomical and functional MRI data and tracking the relative location of the TMS coil in real time. This allows for stimulation with increased accuracy and precision relative to the desired cortical targets. After placement of the hand-held coil, a clinician determines the motor threshold, as the stimulation intensity is often expressed as a percentage of the motor threshold. The resting motor threshold is defined as the lowest stimulation level for which a motor-evoked potential is seen 50% of the time in a relaxed target muscle via electromyography. Once motor threshold is determined, therapeutic stimulation generally consists of repetitive pulse trains with intensities ranging from 80% to 150% motor threshold (approximately 30–90% maximum stimulator output) at either a low (less than 1 Hz) or high (greater than 3 Hz) frequency. Intermittent stimulation, including periods of high-frequency TMS followed by periods without stimulation, have

also been used for therapeutic stimulation. The most commonly used form of intermittent TMS consists of short 50 Hz bursts of stimulation repeated at a frequency in the theta range (5 Hz), known as theta burst stimulation. Currently available stimulators and hand-held coils produce a magnetic field on the order of 1.5–2 T at the coil surface, resulting in currents changing at a rate of approximately 170 A/μs and induced cortical electric fields near 150 V/m [101].

B. Mechanisms of Action

The mechanism of TMS is based on the principle of electromagnetic induction [102], [103], which states that an electric field is proportional to the rate of change of its magnetic field. During TMS, a time-varying pulsed current is discharged through a hand-held coil, creating a time-varying magnetic field perpendicular to the plane of the coil. This changing magnetic field passes relatively unimpeded through the scalp and skull and generates small cortical currents. The resulting local eddy currents within cortex are thought to modulate neuron membrane excitability and lead to action potentials with large depolarization. TMS settings are often classified according to subthreshold or suprathreshold effects on a meaningful behavioral outcome that is indicative of major neuronal excitation or inhibition. The extent of depolarization or hyperpolarization depends on several factors including the direction of current flow parallel to the brain surface (e.g., anterior to posterior), waveform shape (e.g., monophasic or biphasic), conductivity of tissue (e.g., inhomogeneities and anisotropies), orientation and morphology of the neuron population under investigation (e.g., neurons in the gyrus versus sulcus), and cortical layer and cell type experiencing the largest degree of modulation.

TMS can be delivered using single pulses, pairs of pulses, or repetitive trains of pulses, each of which having different effects on brain networks underneath the stimulation coil. While the precise mechanisms of action for these stimulation sequences are not fully understood, general principles do exist. For instance, to probe short-interval intracortical inhibition related to $GABA_A$ interneuron activity, TMS can be applied with a subthreshold pulse followed by a suprathreshold pulse that is separated by 1–5 ms. In contrast, intracortical facilitation related to NMDA activity can be investigated using a subthreshold pulse followed 10–15 ms later by a suprathreshold pulse. TMS pulse trains with durations of minutes or longer, also called repetitive TMS (rTMS), have differing effects on neural tissue that depend on the stimulation frequency. High-frequency rTMS (i.e., $\geq$3 Hz) is considered to have an excitatory effect, while low-frequency rTMS ($\leq$1 Hz) is thought to have an inhibitory effect. The major risk associated with TMS is seizure, but this risk can be minimized if protocols follow published guidelines [101].

C. Clinical Applications

rTMS has been investigated as an interventional therapy for depression, stroke rehabilitation, pain, and neuro-psychiatric disorders, among others. Although several studies offer promising results for the therapeutic efficacy of rTMS for a variety of conditions, the effects of rTMS remain controversial due to the inconsistency of published results.

1) Depression: Medication-resistant depression remains the only FDA approved clinical application for rTMS. The application of rTMS for medication-resistant depression is based on the findings of functional neuroimaging studies in depressed patients [104]–[106], in which the left DLPFC exhibited reduced activity, along with abnormal cortico-subcortical activation patterns. To date, rTMS studies have primarily investigated either high-frequency (excitatory) rTMS applied to the left DLPFC or low-frequency (inhibitory) rTMS applied to the right DLPFC, to disinhibit the left DLPFC via transcallosal connections [107]. Studies applying low-frequency rTMS to the left DLPFC in a randomized double-blinded sham-controlled manner show conflicting results, with most reporting statistical efficacy with moderate improvement on a clinical level [108], [109] and others reporting improvements comparable to sham stimulation [110]. In the case of high-frequency rTMS, two multicenter randomized double-blinded sham-controlled trials have been conducted [111] again with conflicting results, with one study demonstrating efficacy of high-frequency rTMS beyond that of the sham treatment [112] and the other failing to report a significant difference active rTMS and sham rTMS groups [113]. Bilateral rTMS has also been investigated, in which both the left and right DLPFC are stimulated either simultaneously or sequentially, with moderate improvements in depressive symptoms [114]. MRI-based connectivity has recently shown that antidepressant efficacy of rTMS is associated with anticorrelation of DLPFC with the subgenual cingulate [115]. These results suggest that connectivity analysis may be useful to identify likely responders from nonresponders and to develop a strategy for targeting rTMS.

2) Stroke Rehabilitation: rTMS has also been investigated for stroke rehabilitation. Stimulation strategies for stroke are based on the notion that hemiparesis after stroke results not only from neuronal death due to the vascular insult within the lesioned hemisphere, but also from the down-regulation of surviving neurons within the peri-infact zone and other areas remote from the lesion (i.e., diaschisis). An example of diaschisis is the exaggerated interhemispheric inhibition (IHI) affecting surviving neurons in the lesional hemisphere thought to follow from the maladaptive overuse of the contralesional hemisphere. Thus, two rTMS neuromodulation strategies have been investigated to improve motor function after stroke: 1) high-frequency (excitatory) rTMS applied to lesional M1 or 2) low-frequency (inhibitory) rTMS applied to contralesional M1 (see Fig. 4). The former is thought to result in long-term potentiation and the latter in long-term depression in synaptic connectivity between cortical neurons [116]. For both, the supposition is that the resultant up-regulation of suppressed neurons in lesional M1 avails more neurons for voluntary recruitment during subsequent behavioral training. Several randomized double-blinded sham-controlled studies have demonstrated functional improvements in motor recovery after low-frequency rTMS applied to the contralesional motor cortex, without producing any adverse effects [117], [118]. Controlled studies also found improvements applying high-frequency rTMS to ipsilesional M1 [119], [120],

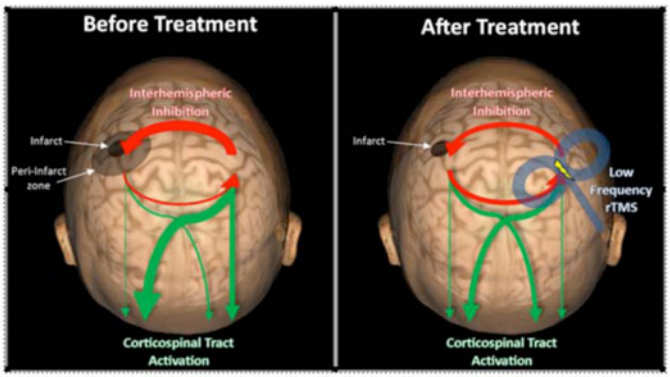

Fig. 4. Theorized depiction of the exaggerated IHI before treatment (thickened red line) acting on the lesional hemisphere through transcallosal pathways stemming from compensatory overuse (thickened green lines) of the contralesional hemisphere. The consequence is down-regulated excitability of surviving neurons (shaded circle) surrounding the neurons damaged by the stroke (black circle). After repetitive transcranial magnetic stimulation (rTMS) to the contralesional hemisphere, the peri-infarct zone becomes disinhibited, restoring function to some of its crossed corticospinal tract pathways.

though low-frequency rTMS over contralesional M1 appears to provide greater motor improvement [121]. Bilateral rTMS, combining alternated low- and high-frequency stimulation over contralesional M1 and lesional M1, respectively, has promise for enhanced motor recovery over unilateral stimulation [122].

D. Challenges and Opportunities

Despite the multitude of studies conducted and recent advances in TMS research, several physiology, engineering, and clinical challenges remain regarding the use of TMS as a treatment for clinical conditions.

First, the physiological changes associated with therapeutic rTMS need to be further characterized to allow for the development of more effective stimulation parameters and TMS machine designs. Although TMS has been applied to many subjects as a neuromodulation therapy, the physiological mechanisms of action of TMS require further characterization to improve therapeutic efficacy and investigate additional applications. For example, two successive forms of intervention (e.g., paired associative stimulation followed by behavioral training), each with excitatory after-effects when acting alone, can interact under certain timing conditions through homeostatic plasticity mechanisms to yield suppressive rather than excitatory after-effects [123]. Thus, a remaining challenge is to identify the proper time interval between the conclusion of an rTMS session and the beginning of the subsequent behavioral therapy. It might seem logical to follow rTMS immediately with behavioral therapy. However, evidence shows that synaptic plasticity can be bidirectional [124]. Up-regulation of excitability from two successive excitatory sources, if applied with little time gap in between, can invoke homeostatic plasticity mechanisms that produce excitability changes in the direction opposite to that produced by one excitatory source alone [125]. Conversely, such plasticity of synaptic plasticity (i.e., metaplasticity) [126] can also be used to augment synaptic change toward a desired direction. It was demonstrated that applying a period of high-frequency priming rTMS immediately before a period of low-frequency rTMS to M1 in healthy humans caused a more pronounced and longer lasting inhibitory after-effect compared to sham-primed low-frequency rTMS [127]. Additionally, identifying anatomical or genetic factors separating responders from nonresponders to TMS, such as the amount of M1 and corticospinal tract preservation after stroke [128] or the presence versus absence of the brain-derived neurotrophic factor gene [129], will provide guidelines for selecting patient populations likely to benefit from TMS therapy. Identifying such factors could also lead to the development of therapies that address impeding factors within the population of nonresponders. The temporal dynamics of both the stimulation and the corresponding response need further characterization to identify the optimal frequency and duration of stimulation, along with the proper interval between stimulation and subsequent behavioral therapy.

From an engineering perspective, many challenges and opportunities remain regarding the design of software and hardware components of TMS systems. The associated circuitry of the TMS machine should be improved to reduce coil heating, allowing for stimulation at higher frequencies and longer train durations. Stimulators providing alternative pulse shapes, with regard to pulse width, polarity, and intensity, will also be important to facilitate more flexibility with TMS applications [130], [131]. The positioning of the stimulation coil plays a large role in determining the outcome of the therapy with regard to both efficacy and side effects. Therefore, future work would benefit from including not only accurate targeting methods [132], such as neuronavigation or stereotactic systems, but also subject-specific selection of optimal stimulation targets, based on both high-field anatomical MRI data and FEM/BEM models. TMS coils capable of subcortical stimulation without excessive cortical stimulation have begun to be developed [133] and investigated clinically [134]; however, even with such advanced coils the maximal stimulation always occurs at the cortical level. Further work with shielding or alternative stimulation coils will be required to target stimulation to only subcortical brain regions.

With regard to clinical applications, the identification of novel stimulation targets for both existing and new applications of TMS remains a challenge. For existing applications, new targets could allow for improved efficacy, by addressing a greater number of symptoms and minimizing the emergence of side effects. Initial research has identified alternative stimulation locations, such as the premotor cortex [135] and supplementary motor cortex [136] for stroke and the cerebellar vermis [92] for depression, that may lead to further improvement in therapy. However, additional evaluative work is necessary to characterize the effects of stimulation in such alternative targets. The identification of new targets for emerging areas of TMS would provide a noninvasive alternative therapy for patients who are not treated adequately with medication or other therapies. Similarly, identification of novel subcortical targets for TMS would provide a noninvasive therapy for patients who would otherwise require surgical intervention (ablation, resection, DBS, etc.). Reducing the size and cost of TMS systems would also help in the

translation of TMS to larger patient populations and new clinical indications. Finally, optimization and consistency of stimulation parameters, including frequency and duration and sham conditions, for a given application will also be important for establishing TMS as an effective noninvasive clinical intervention for a variety of neurological disorders. In recent meta-analysis of rTMS in stroke, stimulation intensities ranged from 80% to 130% of motor threshold, stimulation frequencies ranged from 1 to 20 Hz, and total pulses/day ranged from 160 to 2000 [137]. Future double-blinded clinical trials will be required to assess the therapeutic efficacy and outcome variability among patients.

VI. Discussion and Conclusion

Neuromodulation therapies show great promise for treating neurological and neuropsychiatric disorders that are not well controlled with traditional medication. Arguably, the most significant challenge facing the field of neuromodulation is identifying and classifying the multifaceted spectrum of physiological effects elicited when perturbing the nervous system with electrical, electromagnetic, chemical, and optogenetic interventions. A large disconnect remains between how each neuromodulation approach affects single cells and how these perturbations translate to network function and ultimately to behavior. To meet these challenges, significant efforts will need to be made:

1) identification of biomarkers of disease and therapy (i.e., knowing where, what, and how to stimulate);
2) development of technologies that deliver more spatial, temporal, cell-type, and patient-specific stimulation;
3) development of techniques to perform functional imaging or electrophysiology with neuromodulation therapy;
4) improvement in device–tissue interfaces with the goal of making neuromodulation therapies safer, less invasive, and more stable over time

Solving these issues will invariably lead to more consistent therapy with fewer side effects for all patients. Though beyond the scope of this paper, other neuromodulation approaches including sensory neuroprosthetics, spinal cord and peripheral nerve stimulation, controlled drug delivery, and optogenetics are also of strong clinical relevance. It will be important going forward for increased dialogue and collaborations among groups pursuing all different forms of neuromodulation to cross-pollinate ideas and findings to advance the field.

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