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Deep brain stimulation: a mechanistic and clinical update

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Deep brain stimulation (DBS), the practice of placing electrodes deep into the brain to stimulate subcortical structures with electrical current, has been increasing as a neurosurgical procedure over the past 15 years. Originally a treatment for essential tremor, DBS is now used and under investigation across a wide spectrum of neurological and psychiatric disorders. In addition to applying electrical stimulation for clinical symptomatic relief, the electrodes implanted can also be used to record local electrical activity in the brain, making DBS a useful research tool. Human single-neuron recordings and local field potentials are now often recorded intraoperatively as electrodes are implanted. Thus, the increasing scope of DBS clinical applications is being matched by an increase in investigational use, leading to a rapidly evolving understanding of cortical and subcortical neurocircuitry. In this review, the authors discuss recent innovations in the clinical use of DBS, both in approved indications as well as in indications under investigation. Deep brain stimulation as an investigational tool is also reviewed, paying special attention to evolving models of basal ganglia and cortical function in health and disease. Finally, the authors look to the future across several indications, highlighting gaps in knowledge and possible future directions of DBS treatment.
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Key Words • **deep brain stimulation** • **review** • **mechanism** • **Parkinson disease** • **essential tremor** • **dystonia**

Since its approval by the FDA in 1997 for the treatment of essential tremor, deep brain stimulation (DBS) has revolutionized functional neurosurgery. Electrical current has been known to be critical for biological signal transduction since Luigi Galvani's work in the 18th century, and reports from the middle of the previous century detail first attempts to harness the effects of electrical stimulation of the CNS.[24] However, the use of chronic electrical stimulation to directly alter brain function was not shown to be safe or effective until pioneering publications by Alim Benabid.[17] Soon after the approval of DBS for essential tremor, approvals for applications in Parkinson disease (PD) and dystonia followed. The last decade has seen remarkable progress in the development of new applications for DBS. In the present review we aim to provide an overview of the current understanding of the mechanisms and applications of DBS. We then discuss emerging indications with a focus on psychiatric disease. Finally, we discuss future possibilities for DBS technology, including tandem stimulation and rational target development.

Abbreviations used in this paper: BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; DBS = deep brain stimulation; ET = essential tremor; GABA = γ-aminobutyric acid; GPe = globus pallidus externus; GPi = globus pallidus internus; LFP = local field potential; OCD = obsessive-compulsive disorder; PD = Parkinson disease; SCC = subgenual cingulate cortex; STN = subthalamic nucleus; TS = Tourette syndrome; VIM = ventralis intermedius; YBOCS = Yale-Brown Obsessive Compulsive Scale.

Mechanisms of DBS

It has become clear that the "reversible functional lesion" paradigm that inspired the development of DBS from lesion procedures is no longer adequate to describe its effects.[16] Early theories focused on depolarization block of efferent activity and local γ-aminobutyric acid (GABA)-mediated inhibitory effects.[21] These notions were supported by acute stimulation experiments in animals, but paired electrode recordings and other advanced techniques complicated this picture. Proposed mechanisms of DBS can be grouped into 4 main categories: 1) inhibition of the target, the classic reversible functional lesioning paradigm; 2) activation of the target; 3) combined inhibition and activation; and 4) disruption of pathological oscillations to restore rhythmic activity and synchronization, the "noisy signal hypothesis."[134,141] Recent findings have mostly supported the view that therapeutic effects are related to alterations in ongoing oscillations. In PD, subthalamic nucleus (STN) field potentials have been found to exhibit abnormal phase-amplitude coupling and spike–local field potential (LFP) coupling to primary motor cortex.[45,177] Furthermore, globus pallidus internus (GPi) neurons were found to entrain high-frequency stimulation at therapeutic parameters.[42] The "modulation of brain rhythms" hypothesis will likely provide a useful framework from which to make predictions about possible therapeutic targets for DBS.

Part of the difficulty in identifying a mechanism for the physiological effect of DBS is due to the incomplete

understanding of the pathophysiology of the diverse array of movement, neuropsychiatric, and cognitive disorders currently under investigation for DBS intervention. In the following sections, we discuss recent findings in DBS research, with a focus on reviewing the evolving view of DBS target circuits.

DBS in Parkinson Disease

Mechanistic Understanding

The current understanding of PD pathophysiology centers around abnormal β band oscillations (13–30 Hz) in the basal ganglia–cortical loop.[30] These pathological oscillations are suppressed by movement, dopaminergic medications, and DBS[203] and are believed to be closely related to the bradykinesia characteristic of PD.

The antikinetic nature of β oscillations has led to investigations of how they affect the relationship between the STN and primary motor cortex. An animal model of the therapeutic effects of DBS using optogenetics technology has further supported the hypothesis that high-frequency stimulation affects this relationship.[67] Importantly, high-frequency stimulation to primary motor (M1) afferents in the STN decreased bradykinesia, while stimulation in the β range exacerbated symptomatology. However, the mechanism by which β synchrony interferes with voluntary movement continues to be an area of intense study.

Local field potential recordings of M1 in patients undergoing DBS for PD suggest increased phase-amplitude coupling of M1 β-phase (13–30 Hz) and γ-amplitude (50–200 Hz) in PD patients.[45] Moreover, phase-amplitude coupling between M1 and STN revealed M1 LFP γ-power peaks occurring at a specific phase of the STN β rhythm in PD at a much higher magnitude than that of the STN β–M1 β coherence. This M1 β phase-coupled M1 broadband γ activity actually precedes STN β troughs, suggesting the existence of a feedback loop between the structures. It appears that pathological M1 broadband γ activity may be an important driver in maintaining aberrant STN oscillations. In turn, excessively synchronized STN and GPi β oscillations reinforce the pathological cortical β-phase and broadband γ-amplitude coupling. Another publication by the same group showed that epochs of M1 phase-amplitude coupling predicted STN spikes.[177] This theory contrasts with older literature emphasizing the importance of intrastriatal β-synchrony as the driver of pathological oscillations.[19]

Oscillatory activity in the motor cortex is now also being studied with magnetoencephalography as a possible biomarker for PD. The planning, execution, and termination of movement are known to be associated with consistent within-subject patterns of M1, primary sensory, and supplementary motor area oscillatory activity. Movement is preceded by a strong β desynchronization, beginning 600 msec prior to movement and lasting roughly 400 msec after the onset of movement. After this initial desynchronization, there is a strong β resynchronization called the postmovement β rebound that begins 500–800 msec after initiation of movement and lasts for 1000 msec.[64] A brief period (100–200 msec) of increased γ band activity is also associated with movement onset. Beta desynchronization is believed to be associated with movement selection,[85] and therefore excess β synchrony may underlie difficulty with movement initiation. In addition to excess β, PD patients were found to have diminished γ response amplitude and peak frequency.[78]

Taken together, these data fit into the model proposed by Shimamoto and colleagues in which excess motor cortical β synchrony, manifesting clinically as hypokinesia, is a result of strong pathological β oscillations passed from the basal ganglia.[177] This increased cortical β synchronization, in turn, leads to reinforcement of the basal ganglia β oscillations through pathological M1 β-phase γ-amplitude coupling (Fig. 1). This aberrant coupling decreases the cortex's capacity for activation-related γ activity, leading to difficulty initiating movement. Subthalamic nucleus DBS may have its effect on β oscillations and therefore movement initiation by altering the timing of M1 firing via orthodromic stimulation of afferents, limiting aberrant phase-amplitude coupling.

The GPi remains a common target for stimulation, although the mechanism of action of GPi DBS is still debated. Cleary and colleagues found that therapeutic GPi stimulation reduced mean firing rate and increased firing regularity of local neurons during electrical stimulation, importantly decreasing burst firing for a short period of time after firing.[42] Because stimulation of both the GPi and STN increase the regularity of thalamic neuronal firing,[7,206] as well as create complex "entrained" firing patterns in local GPi neurons,[39,42,197] it is likely that stimulation of the two regions has a similar mechanism of action. Alternative models of GPi stimulation suggest therapeutic benefit derives from stimulation of adjacent axonal projections, such as the medial medullary lamina (bradykinesia) and the internal capsule (rigidity).[83]

Current Approach to Therapy

Deep brain stimulation is a well-accepted approach to managing PD in patients with inadequate control of symptoms or with significant side effects from levodopa.[149] Class 1 evidence supports the use of STN DBS when compared with best medical therapy,[102,198,202] and in trials comparing the stimulation-on state versus the stimulation-off state.[150] However, several aspects of this accepted standard are in flux. Stimulation of the GPi has achieved wide acceptance after it was found to cause less decline in visuomotor function and decreased depression while maintaining equivalent primary outcome compared with STN stimulation, although the latter allowed greater reduction in medication dose.[59]

In addition to the STN and GPi, several other nuclei are accepted or under investigation for stimulation. The nucleus ventralis intermedius (VIM) of the thalamus is a standard target for alleviating tremor in PD.[125] The pedunculopontine tegmental nucleus is a target for gait disorder[25,171] and sleep modulation,[159] sometimes in tandem with stimulation of other nuclei.[90,195] Other targets in early stages of exploration include the posterior subthalamic area, caudal zona incerta, prelemniscal radiation, thalamic centromedian-parafascicular complex, and cerebral cortex.[53] As the currently approved targets only address

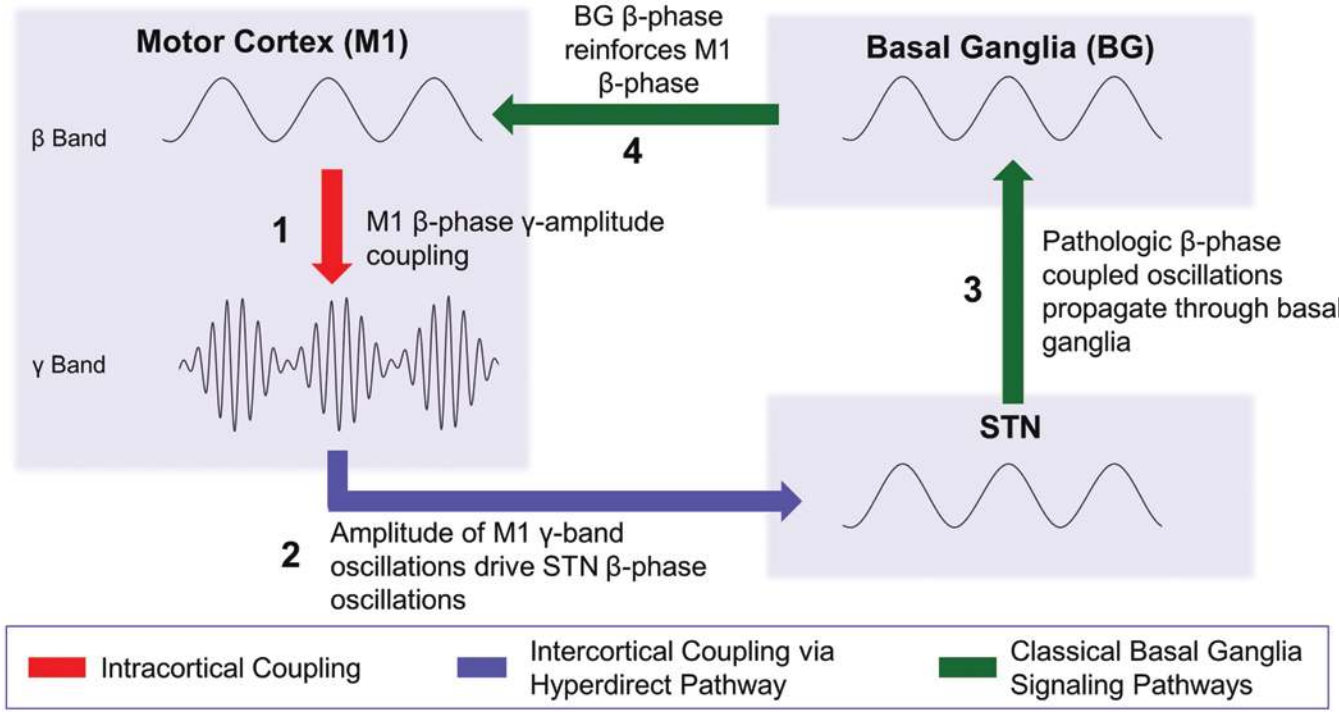

Fig. 1. Pathological phase-amplitude coupling in PD creates a self-reinforcing loop. **1:** Motor cortex (M1) β-phase oscillations drive M1 γ-amplitude changes reflected by intracortical β-phase γ-amplitude coupling. **2:** Changing M1 γ amplitude drives/reinforces STN β-phase oscillations via the glutamatergic hyperdirect pathway. **3:** Beta-phase oscillations propagate throughout basal ganglia via glutamatergic STN-to-GPe, STN-to-GPi, and STN-to-substantia nigra pars reticulata neurons. **4:** Beta-phase oscillations in the basal ganglia reinforce β-phase oscillations in M1. Reinforced β-phase oscillations in M1 prevent M1 β desynchronization necessary to initiate movement, leading to bradykinesia. M1 β-phase–M1 γ-amplitude coupling may also prevent the normal increase in γ band activity associated with initiation of movement.

motor symptoms of PD, more work is needed to identify the appropriateness of DBS for nonmotor PD symptoms.[53]

Cognitive Effects of DBS in the PD Population

The cognitive or nonmotor effects of PD are not as well defined as the motor effects. Motor effects are more commonly associated with presentation and disease burden, as they occur early in the course of the disease when the patient is in the most active and productive years of life. Cognitive decline is observed in advanced PD, a time during which DBS has historically been offered to the patient. However, the deleterious effect of compounding the natural progression of cognitive changes with the effects of DBS may outweigh DBS-derived motor improvement.

Initial long-term studies suggested an absence of significant change in cognition 5 years after STN DBS,[98] suggesting the promise of the technology's neuroprotective effects. However, other early studies comparing STN and GPi DBS targets reveal increased adverse cognitive and behavioral effects after STN DBS.[8,196] Speculation as to the potential cause of cognitive decline in early versus more recent studies may stem from the close anatomical apposition of motor, associative, and limbic pathways in the STN. As targeting techniques have improved, side effects of stimulation of these nonmotor pathways may have decreased. Definitive conclusions may also have been elusive due to small sample size and the study design. Woods and colleagues evaluated 30 studies investigating cognitive changes after DBS and identified only 2 that had sufficient statistical power on which to base conclusions.[205] Another meta-analysis found STN DBS to be relatively safe from a cognitive standpoint, except for a measurable decline in verbal fluency.[158]

Recent investigations in the US have corroborated the persistent decline in verbal fluency in the STN cohort,[207] as well as worsened dementia rating scores.[199] However, a European randomized controlled study evaluating the effects of STN versus GPi DBS in 128 patients with PD found no significant difference in cognitive side effects (a composite of multiple factors such as depression, anxiety, psychosis) in either group.[148] In fact, the authors recommended STN DBS due to superior overall outcomes of secondary investigative endpoints.

Areas of Evolving Practice

Although DBS has traditionally been reserved for PD patients with intractable symptoms, dyskinesias, or severe levodopa side effects, a recent study in patients with early motor symptoms of PD showed promising results.[173] This randomized prospective trial compared DBS combined with medication against medication alone in patients with early motor signs of PD (average duration of disease of 7.5 years). The primary outcome, quality of life (assessed using the Parkinson Disease Questionnaire-39), improved by 7.8 points in patients receiving a combination of DBS and medication, compared with a decrease of 0.2 points in pa-

tients receiving medication only. Patients who underwent surgery also experienced improved secondary outcomes, including decreased motor disability, improvement in performing activities of daily living, and fewer levodopa side effects. There was also an average of 1.9 hours/day increase in time with good movement and no dyskinesia, along with an average of 1.8 hours/day decrease in poor mobility time. Although patients in the stimulation group had slightly higher rates of mild adverse events, the authors argued that neurostimulation can and should be used to optimize treatment early in PD, before significant disabling motor and cognitive symptoms arise. It is also likely that performing surgery in patients who are younger and likely healthier will afford better surgical outcomes and a decreased risk of operative morbidity and death.

Other future directions of DBS for PD include tailoring the selection of nuclei to the individual's exact symptomatology, although target selection remains an area of debate.[54] Different modes of stimulation are also being attempted, including constant stimulation[151] and interleaved stimulation.[14]

DBS for Essential Tremor

Mechanistic Understanding

The disease formerly known as senile tremor, or benign essential tremor, has traditionally been underestimated by physicians. As the shedding of misleading labels has progressed (there is general agreement that it is neither benign nor confined to the elderly), a new understanding of its true public health cost has come into focus. The best estimates place its prevalence in patients over age 60 at 13–50 cases per 1000 people,[124] roughly the same as epilepsy.[12] In view of the aging population, there is new urgency to understanding the pathogenesis of essential tremor (ET).

The origin of pathological oscillations in ET has been debated. It has been known since the 1970s from animal lesion models that interactions between the inferior olive and the cerebellum are capable of driving ET-like tremor.[46] The view that olivocerebellar fibers represent a key node in ET pathophysiology was later confirmed with PET,[26] although functional MRI studies have yielded poor evidence for intrinsic olivary dysfunction.[31] Recent evidence suggests that GABA-receptor downregulation and/or dysfunction in the dentate nucleus (downstream of the Purkinje cells to which the inferior olive's climbing fibers project) correlates with tremor progression in a postmortem histopathological study.[157] The circuit targeted by effective DBS in ET has been probed with diffusion tensor imaging; effective contacts had robust connectivity to a circuit comprising the superior cerebellar peduncle (and presumably the dentate) as well as the primary motor cortex, supplementary motor area, lateral premotor cortex, and pallidum.[91] Source analysis of electroencephalography-electromyography coherence has supported a similar circuit.[143]

Current Approach

Essential tremor was the original indication for DBS, resulting in FDA approval in 1997.[16] Two multicenter studies were subsequently conducted in Europe with good tremor control and acceptable side-effect profiles found at both 1-year and 6-year follow-up.[117,187] An early randomized trial compared thalamotomy with DBS and showed superiority of efficacy with thalamic DBS, although there was 1 fatal hemorrhage after DBS.[174] After approval, the question of whether to implant 1 or both sides simultaneously was somewhat controversial. A small experience supported a stepwise benefit to a second, contralateral electrode in ET but not PD,[152] supporting the frequent practice of staging placement, starting with either the dominant hand or the more symptomatic side. Microelectrode recording is also variably practiced for VIM surgery.

Areas of Evolving Practice

More recent DBS approaches have included intraoperative CT-guided surgery, which appears to be accurate in the VIM thalamus.[33] There is also some experience with intraoperative MRI in VIM DBS.[111]

Initial enthusiasm for Gamma Knife thalamotomy[93] was tempered by a blinded study showing modest efficacy and a serious side-effect profile.[115] Additionally, many surgeons are accustomed to immediate physiological verification of treatment effect with test stimulation.[51] A larger retrospective series suggested that Gamma Knife thalamotomy could yield clinically significant reductions in tremor with an acceptable side-effect profile.[95]

Two groups have recently reported the use of focused ultrasonography for thalamotomy, combining the benefits of intraoperative testing with minimally invasive surgery.[52,120] Its efficacy is difficult to compare directly with DBS, as there has not been a direct comparison, but the results appear comparable.[146]

DBS in Dystonia

Dystonia is a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both. Hyperkinetic movements such as these can be observed in a plethora of neurological disorders and can make diagnosis challenging.[167] Dystonia is currently the leading indication for DBS in the pediatric population.

Dystonia can be classified as either primary or secondary. Primary generalized or idiopathic torsion dystonia is defined by involvement of more than one body part, familial predisposition, and a lack of additional neurological symptoms of other origin. Primary dystonia has been linked with multiple gene loci, the most common and best-studied being *DYT1*. Secondary dystonia can be caused by many environmental factors that injure the brain, including stroke, encephalopathy, trauma, hypoxic injury, or infection.[6,194] Even though the most common type of secondary dystonia is categorized as cerebral palsy, secondary dystonia comprises a varied patient population that has many different underlying pathophysiologies and potential responses to treatment.

Neurobiology of Dystonia

Dystonia is believed to result from abnormal motor

patterning within the basal ganglia circuit.[144] Animal and human studies in dystonia show evidence that cortical excitation causes abnormally strong and prolonged GPi inhibition through the direct pathway.[41] Decreased GPi output ultimately leads to decreased cortical inhibition, which manifests in spastic movements characteristic of dystonia. Through this circuit, a small amount of cortical excitation leads to prolonged cortical disinhibition, creating a self-reinforced feedback loop. Faulty firing patterns in motor cortical regions are generated, and become self-reinforcing because of the abnormal basal ganglia circuit. Studies have also found that the normal somatotopic organization of the GPi and globus pallidus externus (GPe) are changed in dystonia.[145] This disorganization likely allows GPi disinhibition to influence multiple areas of cortex and may be implicated in the diverse extremity and axial involvement noted in dystonia.

Pathological oscillatory activity has also been implicated in dystonia. Pallidal firing rates are abnormal and are characterized by reduced spontaneous firing, along with irregularly grouped burst discharges and pauses.[181] Additionally, increased pallidal LFP oscillations in θ through low β bands (3–20 Hz) were found to precede dystonic movements.[122] The mean discharge rate of STN neurons is also increased in dystonia.[172] We still do not fully understand the neurocircuitry in regards to different patterns of dystonia.

Treatment of Dystonia

At this time, there is no cure for dystonia. The goal of treatment is to provide a better quality of life for the patient. This can be accomplished directly by relieving pain and immobility related to dystonic contractions and thereby improving functional ability, and indirectly by providing caregivers with a more manageable child. Dystonia can be treated medically with anticholinergics, antidopaminergic agents, baclofen (oral or intrathecal), or benzodiazepines. Botulinum toxin can be injected in patients with focal or segmental dystonia but is not very effective in patients with generalized dystonia.[166]

Patients with dystonia who undergo an unsuccessful adequate trial of medical treatment are considered for surgery. Neurosurgical treatments of dystonia have included thalamotomy, dorsal column stimulation, cerebellar stimulation, pallidotomy, and intrathecal baclofen therapy via an implanted pump. Pallidotomy has been shown to improve primary dystonia, but unilateral pallidotomy may not sufficiently treat generalized symptoms, and bilateral pallidotomy is associated with significant risk.[153] Also, the irreversibility of parenchymal lesioning favors the use of nonablative DBS technology.

Deep brain stimulation has been shown to be most effective in patients with primary generalized dystonia, and those patients with the *DYT1* mutation are reported to have the best response. Coubes and colleagues published one of the earliest case reports of an 8-year-old child who underwent pallidal DBS for primary dystonia with significant functional improvement.[166] Haridas and colleagues followed with a case series of 22 patients with primary dystonia who had 94% median improvement in their functional scores with a decrease in their oral and intrathecal medications.[76] More recently, this same group published their experience with 47 *DYT1* patients who received pallidal DBS over 10 years with symptom reduction to less than 20% of baseline. In addition, 61% of their patients discontinued all dystonia-related medications after surgery.[156]

Although patients with primary dystonia respond best, patients with secondary dystonia have also been shown to improve with DBS.[97] Vayssiere and colleagues reported a series of 35 children with dystonia treated with DBS. The 10 children who had secondary dystonia had a 31% improvement in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) scores.[194] Similarly, Alterman and Tagliati showed a 33% improvement in BFMDRS motor scores in the 5 pediatric patients with secondary dystonia in their series.[6] Ghosh and colleagues reported a 31.3% improvement in the BFMDRS motor scores and a 37.5% improvement in the BFMDRS disability scores in their 2 pediatric patients with secondary dystonia.[65] Air and colleagues had 11 pediatric patients with secondary dystonia in their series; however, they only reported outcomes in 4 and their results were more modest than the prior studies.[4] Three patients had a 10% improvement in the BFMDRS motor score and a 20% improvement in the disability score. Zorzi and colleagues reported on 3 patients with secondary dystonia treated with DBS. The 2 patients who were not in status dystonicus experienced overall improvement in BFMDRS scores of 31% and 71%. The 1 patient with secondary dystonia who was in status dystonicus prior to surgery experienced resolution of status dystonicus 1 week after surgery.[208] Lipsman and colleagues reported 1 patient with secondary dystonia who was treated with DBS in their series, but they did not have any follow-up available for this patient.[118] A recent meta-analysis of 20 articles comprising 68 pediatric and adult patients with cerebral palsy showed a 23.6% improvement in the BFMDRS motor score and a 9.2% improvement in the BFMDRS disability score after DBS.[97]

Additional Areas of Evolving Practice

Clinical practice is also evolving in the choice of stimulator settings for DBS in dystonia. No difference was found between groups when right and left GPi leads were set to monopolar, double monopolar, or triple monopolar modes.[192] Interleaved stimulation, or independent stimulation of adjacent contacts with different amplitude and pulse-width values, may hold promise for patients who do not respond to other modes of stimulation. In a small case series, 4 patients classified as nonresponders (< 25% improvement) after 6–9 months of single monopolar stimulation were initially switched to double monopolar stimulation with no improvement. These patients were then changed to an interleaved setting and quickly improved.[96] The same group of investigators is currently recruiting subjects for a Phase IV prospective, randomized, double-blind crossover study to investigate the effect of stimulation settings on severity of segmental or generalized primary dystonia in patients with bilateral GPi stimulators. One group will receive interleaved stimulation, and the other group will receive double monopolar stimulation.

Although pallidal stimulation is the current standard

of treatment, additional targets are being investigated. For example, a Phase I/II open-label clinical trial of bilateral STN DBS is currently recruiting patients with primary dystonia.

DBS in Major Depression

Mechanistic Understanding

Depression is a common disorder affecting as many as 30 million Americans.[89] Moreover, from 20% to 50% of depressed patients eventually fail standard pharmacotherapy.[55] Recent advances in treatment, including DBS, have yielded insights into the pathophysiology of this disorder.

Depression is now viewed as a disorder arising from abnormal communications among systems of limbic-cortical pathways. Various methods, including neuroimaging, lesion studies, clinical trials, neuronal recordings, and postmortem autopsies have contributed to our understanding of the neural networks underpinning mood disorders. Anatomical structures across the brain are implicated, including the amygdala, ventromedial prefrontal cortex, orbitofrontal cortex, subgenual and pregenual anterior cingulate cortex, posterior cingulate cortex, ventral striatum, pallidum, medial thalamus, hypothalamus, and brainstem.[155,163] Deep brain stimulation has itself provided a remarkable opportunity to study cortical areas implicated in depression. One recent study of single neuron recordings in the subgenual cingulate cortex (SCC) showed that certain populations of neurons are specific for emotional category.[108] The authors defined 5 emotional categories (disturbing, sad, neutral, happy, and exhilarating) to represent different combinations of high or low valence and arousal. While some neurons responded only to valence or to arousal levels, others responded to 1 specific emotional category. Moreover, a majority of sampled neurons responded selectively to negative emotions, suggesting that SCC targeting in depression may inhibit this negatively prone bias. Another study, this time in the ventromedial prefrontal cortex, found coherent activation in low β-band (15–20 Hz) frequencies just prior to patients' passing a negative affective judgment in ambiguous (neutral valence) cases.[119] The authors concluded that coherent β-band activation reflects ventromedial prefrontal cortex communication to downstream targets, suggesting that abnormal ventromedial prefrontal cortex β coherence could play a role in the negative affective bias or indecisiveness experienced by depressed patents. Further study will be required to know if modulation of β activity, as in PD, is a therapeutic mechanism of DBS in this region. Another study of frontal activity showed that increases in frontal θ coherence were positively correlated with better clinical response to SCC DBS at 6 months.[28] As illustrated by this example, a better understanding of circuit abnormalities could aid in developing control signals for SCC stimulation and in providing mechanistic insights.

The field of optogenetics is also contributing to our understanding of depression neurocircuitry through the use of animal models of depression. One study employed an optogenetic 100-Hz burst stimulation on the medial prefrontal cortex in a mouse model of depression, resulting in a reversal of symptoms.[44] Optogenetics has also been used to explore the role of dopaminergic signaling in depression.[123] Using optogenetic probes, phasic activation of ventral tegmental area neurons projecting to the nucleus accumbens promoted a depression-like phenotype in mice,[40] whereas stimulation of medial prefrontal cortex–projecting cells was associated with resilience to the depressed phenotype. Further efforts will be required to harness this knowledge of the relevant circuitry to improve treatment options.

Current Practice

All current targets of stimulation for the treatment of depression are still under investigation. The SCC, and specifically Brodmann area 25 (Cg25) within the SCC, has emerged as one of the leading targets for stimulation,[74] and several series have demonstrated promising results.[80,88,128,132,164] Unfortunately, all data from this target are currently from open-label trials, and there are reports of mixed outcomes.[126] A Phase III multicenter, randomized, sham-controlled trial is underway, with a goal of enrolling 200 patients. This trial should help clarify outstanding questions of efficacy and patient selection. Other targets under investigation include the ventral striatum/nucleus accumbens,[22,23] inferior thalamic peduncle, and habenula.

Areas of Evolving Practice

As discussed in a recent review,[127] there is a lack of specific biomarkers for depression. Furthermore, because the clinical presentation of depression is broad and the anatomy of involved structures is diverse, it is likely that multiple different neuropathological abnormalities can manifest as depression. Further research is needed to define concrete predictors of response for different targets of stimulation in depression.

DBS in OCD

Mechanistic Understanding

As in PD, our understanding of the pathophysiology of obsessive-compulsive disorder (OCD) has evolved to include abnormal oscillatory activity through cortico-striatal-thalamic loops.[27] Cortical regions of the brain implicated in OCD include the orbitofrontal cortex, dorsolateral prefrontal cortex, ventromedial prefrontal cortex, and anterior cingulate cortex, while subcortical regions include the ventral striatum, mediodorsal thalamus, amygdala, and hippocampus. Overactivity of the orbitofrontal cortex correlates with anxiety levels[186] and likely impacts behavioral planning and reward expectation. Decreased medial orbitofrontal cortex activity and increased lateral orbitofrontal cortex activity may underlie an increased fear response and impaired positive valence processing.[99,137,138] The anterior cingulate cortex likely plays a role in conflict monitoring and error processing,[48,68,176] and has increased activity in OCD.[2,160] Increased caudate activity,[178] along with decreased caudate neuronal density[13] and abnormal dopamine management,[49,190] may lead to abnormal behavioral inhibition and release, similarly to how

basal ganglia abnormalities impact movement. Clinical symptoms in OCD also involve fear conditioning and the association of external stimuli with emotion, suggesting involvement of the hippocampus[131] and amygdala.[37] Both structures have been implicated in OCD,[10,81,104] although not in all cases.[20,170]

In the section on PD, hyperdirect pathways connecting the motor cortex with the STN play an important role in the ability of aberrant oscillatory propagation between cortex and basal ganglia structures. Thus, for a similar mechanism to be relevant for OCD, one would expect hyperdirect cortico-STN pathways to exist, connecting the cognitive and motivational cortical regions discussed above with the STN. Haynes and Haber recently illustrated the existence of a set of such prefrontal-STN hyperdirect connections in macaque monkeys.[77] Interestingly, projections from functionally diverse regions of cortex were found to converge on overlapping regions of the STN. This work, along with others,[5,106] also further helps to delineate the "associative-limbic" STN as the ventromedial STN, and includes the adjacent lateral hippocampus in the definition of the "limbic" STN.[77]

With the increasing use of DBS for OCD, LFP and single-neuron recordings are now beginning to shed light on abnormal oscillatory activity in this circuit. Early single-unit recording data in the caudate nucleus suggested that abnormally high frequency and increasingly variable interspike intervals occur during obsessions.[71] High-frequency burst firing, associated with motor loop dysfunction when occurring in the sensorimotor STN in patients with PD, has also been reported in the ventromedial STN of patients with OCD.[161] Moreover, low-frequency band (1–8 Hz) oscillatory and burst activity in the ventromedial STN correlates with OCD symptom severity and clinical improvement after STN stimulation.[200] A single-neuron recording study of ventromedial STN activity during a cognitive decision-making task in which some trials require repetitive checking showed that ventromedial STN neurons were more active during checking behavior.[32] The authors concluded that in addition to playing a role in the integration of multiple streams of information, ventromedial STN neurons are also involved in repetitive doubt-related thinking. Task-based, single-cell recordings have also helped to clarify the role of neurons in the dorsal anterior cingulate cortex. These neurons were observed to encode current and recent cognitive load, playing an important role in determining how much cognitive control is required in the task at hand.[176]

Most recently, optogenetics has been used to generate and suppress compulsive-like behaviors in a mouse model (Fig. 2). Multiple days of repeated hyperactivation of the orbitofrontal cortex neurons projecting to the ventromedial striatum was found to cause progressively increasing ventromedial striatum light-evoked firing in originally normal mice.[3] Moreover, this increasing ventromedial striatum firing occurred in parallel with a temporally linked increase in grooming activity in the mice, an OCD-like phenotype. The effects became self-sustained without orbitofrontal cortex–ventromedial striatum hyperactivation and were reversible with fluoxetine (Fig. 2A). In a different experiment, this time in a genetic mouse model of OCD, behavioral response inhibition was associated with defective downregulation in striatal neuron projections.[35] The authors were then able to improve behavior and correct abnormal microcircuit pathology with optogenetic stimulation of the lateral orbitofrontal cortex and its striatal terminals (Fig. 2B).

Current Practice

Since 2009, DBS has been an accepted treatment for refractory OCD under an FDA Humanitarian Device Exemption. Current targets in practice and under investigation include the ventral capsule/ventral striatum, anterior limb of the internal capsule, STN, ventral caudate nucleus, nucleus accumbens, and inferior thalamic peduncle (reviewed by Mian et al., 2010[136]). The Yale-Brown Obsessive-Compulsive Scale (YBOCS) score[66] is commonly used to track patient outcomes in clinical trials. Data from lesional capsulotomy treatment for OCD served as initial motivation for using the ventral capsule/ventral striatum and anterior limb of the internal capsule as targets for DBS. A review of 4 centers performing anterior limb of the internal capsule and ventral capsule/ventral striatum DBS demonstrated clinical improvement (> 35% reduction in YBOCS score) in more than two-thirds of patients. Moreover, there was an improvement in results depending on location of the implantation, allowing the authors to conclude that the optimal location for ventral capsule/ventral striatum stimulation is at the junction of the anterior commissure, anterior capsule, and posterior ventral striatum.[69] Recently, a study in 16 patients with OCD after at least 1 year of nucleus accumbens stimulation showed a 50% increase in symptoms after turning patients' stimulators off. They also used functional MRI, resting state functional MRI, and electroencephalography to suggest that nucleus accumbens DBS reinstates normal nucleus accumbens function and decreases the overactive fronto-striatal network connectivity characteristic of OCD.[57] A report of inferior thalamic peduncle stimulation in 6 patients with OCD showed a 51% mean decrease in YBOCS score after 12 months.[82] While efficacy has been shown in numerous stimulation targets, randomized controlled clinical trials are still needed to prove efficacy and determine optimal targets.

DBS for Other Emerging Indications

Tourette Syndrome

Tourette syndrome (TS) is a neuropsychiatric syndrome characterized by multiple chronic, brief, involuntary movements and sounds, often called tics.[135,139] Notably, TS has a high comorbid incidence with OCD and attention-deficit hyperactivity disorder,[60,103] reflecting possible mechanistic overlaps. Current models of pathophysiology in TS suggest a reduction in GABAergic and cholinergic striatal interneurons, as well as decreased changes in numbers of parvalbumin-positive GABAergic neurons in the GPi (increased) and GPe (decreased).[86,87] Parvalbumin is a calcium binding protein that has recently been found to play a role in rhythm generation in fast spiking interneurons, as well as in preventing narrow frequency

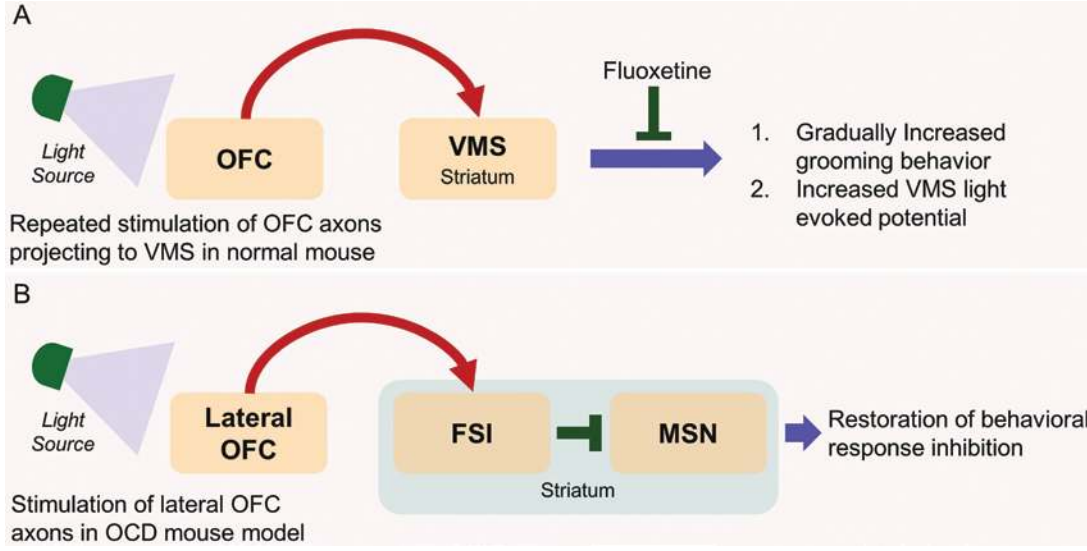

Fig. 2. Optogenetic stimulation of unique orbitofrontal cortex cell types creates and inhibits OCD phenotypes in mice. **A:** Illustration of the experiment of Ahmari and colleagues. In normal mice, repeated light stimulation of optogenetically modified orbitofrontal cortex (OFC) glutamatergic axons projecting onto the ventromedial striatum (VMS) leads to increased grooming behavior that persists after termination of light stimulation. **B:** Illustration of the experiment of Burguière and colleagues. In a genetic mouse model of OCD, increased activity of striatal medium spiny neurons (MSNs) was correlated with OCD-like behavior. Light stimulation of lateral orbitofrontal cortex axons that project onto fast-spiking striatal interneurons (FSIs) in the centromedial striatum led to increased FSI activity. Increased FSI activity led to increased inhibition of MSNs in the striatum, and OCD-like behavior was instantly eliminated.

synaptic facilitation at striatal neuron synapses on outside targets.[154] Other research has also suggested that striatal disinhibition and aberrant oscillations in basal ganglia structures lead to cortex disinhibition and tic production.[29] Clinical symptoms have also been found to correlate with the temporal power γ-band activity in the centromedian sulcus of the thalamus. Moreover, modulation of γ-band activity with DBS was found to influence clinical symptoms.[130] Motor tics have also been associated with changes in normal rhythms throughout cerebro-basal ganglia-cerebellar networks.[133] Although evidence continues to accumulate, an overarching model for the pathophysiology of TS remains a work in progress.

Current investigational targets for DBS include the medial thalamus (nucleus ventrooralis internis, centromedian nucleus, and substantia periventricularis),[175] anterior medial (limbic) GPi,[47] STN, nucleus accumbens, and anterior limb of the internal capsule. A small, double-blind, randomized crossover trial of stimulation targeting the thalamic intersection of the centromedian sulcus, the substantia periventricularis, and nucleus ventrooralis internus showed a 37% improvement on the Yale Global Tic Severity Scale in patients on stimulation compared with off stimulation.[1] An open-label study of centromedian/parafascicular complex stimulation in 3 patients with medically intractable TS resulted in a 60%–80% reduction in Yale Global Tic Severity Scale score for each patient at 1 year.[169] Despite early promising trials, there are also reports of no benefit after stimulation.[34,50] Further work is needed to clarify stimulation targets, define appropriate selection criteria,[140] and determine how target stimulation may effect comorbid psychiatric disorders.

Obesity and Anorexia

Obesity is a growing epidemic in the US and worldwide. Stimulation targets for obesity are based on two complementary mechanisms that lead to overfeeding: reward circuitry and satiety centers.[73] Hypothalamic structures are also under investigation, including the ventromedial hypothalamus and lateral hypothalamus. An initial pilot study in 3 patients of lateral hypothalamic DBS for refractory obesity reported no overall weight loss when stimulation was programmed with settings derived from experience with movement disorders.[201]

Foods with high caloric content reinforce eating behaviors through reward circuitry, including the nucleus accumbens, suggesting that this structure may serve as a target for stimulation. Other studies have accumulated evidence implicating the subgenual cingulate and ventral tegmental area in addition to the nucleus accumbens.[188] As stimulation targets in the hypothalamus have had limited success, a current clinical trial is recruiting patients refractory to gastric bypass for evaluation of targets involved in dysregulated reward circuitry. While gastric bypass is currently the gold standard therapy for morbid obesity, a recent study used decision analysis to note that DBS for obesity would only need an 83% success rate to achieve equivalence to bypass surgery.[162]

Anorexia nervosa is another psychiatric disorder involving limbic circuits. Up to 70% of patients suffering from anorexia have a chronic refractory course, and it is one of the deadliest psychiatric disorders, with a mortality rate of 10%.[147] Initial trials of DBS[121] showed promising clinical results, as well as changes in metabolic activity in cortical and limbic regions associated with the subcallosal

cingulate. Regions of the brain believed to be abnormal in anorexia nervosa include the parietal cortex, anterior and subgenual cingulate, and superior frontal, dorsolateral prefrontal, and orbitofrontal cortex.[191] Many of these regions overlap with other psychiatric indications, notably major depressive disorder and OCD.

A Phase 1 clinical trial of SCC DBS is currently recruiting patients with refractory anorexia nervosa for initial safety and efficacy estimation. This study is a continuation of a pilot study in which 6 patients underwent SCC stimulation for 9 months.[121] Initial results after 9 months included 3 of 6 patients increasing and maintaining their body mass index, and improvement in mood, anxiety, obsessions, and compulsions in 4 of 6 patients. Another trial is currently recruiting similar patients for implantation and stimulation of the nucleus accumbens.

Learning and Memory

Another active area of investigation is whether DBS may be effective for treating disorders of learning and memory. Applications are being developed for memory impairment due to Alzheimer disease, traumatic brain injury, temporal lobe epilepsy, stroke, and encephalitis. Improvements in our understanding of the anatomy of the hippocampal entorhinal cortex circuit (reviewed in Squire et al., 2004[180]), the role of phase-phase and phase-amplitude coupling in learning and memory (reviewed in Fell and Axmacher, 2011[56]), and the role of DBS in augmenting learning and memory (reviewed in Suthana and Fried, 2013[184]) are stimulating interest and research in the field.

The presence of phase-phase and phase-amplitude coupling has important implications in DBS for memory. Hippocampal stimulation, for example, has been found to both disrupt[72,105] and enhance memory. The fact that memory enhancement requires the stimulation to be spatially and temporally matched to existing hippocampal input activity[18,75] suggests that some sort of oscillatory coupling mechanism is involved and that DBS can augment this mechanism. In the medial temporal lobe, increases in the amplitude of θ band (3–8 Hz) LFP oscillations can predict whether an experience is encoded in memory,[70,113] and reinforcing these θ oscillations with DBS has been shown to improve spatial working memory.[110] Theta-phase γ-amplitude coupling has also been implicated in successful learning and is believed to play a role in communicating across large dispersed cortical brain networks.[38] Oscillatory mechanisms are increasingly being used to tie together theories of brain function, as illustrated in a recent paper unifying the dual role of the hippocampus in memory and physical navigation.[36]

Multiple stimulation targets are currently under exploration for memory improvement. A Phase I trial of fornix/hypothalamus stimulation in 6 patients with mild Alzheimer disease did not show significant improvement in clinical symptoms, but showed reversal of decreased glucose metabolism in parietal and temporal lobes after 12 months of stimulation.[109] Stimulation of the entorhinal cortex has been shown to improve spatial learning,[183,185] and stimulation of the medial septal nucleus has been shown to improve spatial working memory after traumatic brain injury.[110] While studies performed to date provide promising evidence, randomized controlled trials are still needed. Fortunately, multiple clinical trials are currently underway to clarify the role of DBS in Alzheimer disease and other types of cognitive impairment.

Addiction

Drug addiction is characterized by the compulsion to consume a substance, the loss of control in limiting its intake, and the development of a withdrawal state when the substance is withheld. This cycle becomes a chronic relapsing disease that affects approximately 2.9% of the adult US population (5.4 million) with illicit drugs and 7.7% (18 million) with alcohol. In addition, an estimated 28.6% (70.9 million) of Americans aged 12 or older are current tobacco users. Koob and Volkow, in their review of addiction and its neurocircuitry, describe 3 stages of addiction that they map to key regions of the brain: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation.[94] In the first stage, binge/intoxication, the nucleus accumbens and the ventral tegmentum are believed to play key roles, whereas in the withdrawal/negative affect stage, the amygdala is the central structure. Finally, the last stage, preoccupation/anticipation, appears to involve multiple structures including the prefrontal cortex, striatum, amygdala, hippocampus, insula, and cingulate gyrus.[94,129] Given this network, DBS could potentially target any of these structures to interfere with addiction circuitry.

Several stimulation targets are under investigation, with the nucleus accumbens and STN receiving the most attention. In 2007, Kuhn and colleagues published a case report of a 54-year-old male with severe agoraphobia and panic attacks, with concomitant alcohol dependence, who received bilateral DBS of the nucleus accumbens for treatment of his anxiety disorder. He had no reduction in his anxiety, but he did experience a remarkable change in his alcohol dependency. Prior to DBS, he was consuming alcohol daily with an average of 10 drinks per day, with multiple hospitalizations for intoxications and withdrawal. After DBS, the patient claimed to have lost the desire to drink, and he only occasionally had 1–2 drinks in the year following his treatment.[101] In 2009, the same group published a retrospective review of 20 patients who received nucleus accumbens DBS for OCD and TS. Of these patients, 10 were daily smokers and 4 had attempted smoking cessation unsuccessfully prior to DBS. Of the latter 4, 2 attempted and were successful at smoking cessation after DBS.[100] Several preclinical studies in rats have investigated the effect of high-frequency DBS on ethanol consumption and cocaine/narcotic-seeking behavior.[15,79,92,165,193] These studies showed a significant reduction in drug-seeking behaviors following DBS.

Müller and colleagues reported a pilot study of 5 patients who received bilateral nucleus accumbens DBS for chronic alcoholism.[142] Two of the 5 patients were abstinent for at least 5 years following DBS and the remaining 3 had marked decreases in their alcohol consumption. One patient had a 2-week hypomanic episode that resolved after changes in stimulation settings. Of note, they also reported that 1 patient agreed to additional studies; when the DBS was turned off, the patient experienced increased

risky behavior during gambling paradigms administered when compared with the same tests with the DBS on. These studies suggest that nucleus accumbens DBS appeared to normalize reward processing, which may be dysregulated in patients with addictive disorders.

Subthalamic nucleus stimulation has not had as promising results as nucleus accumbens stimulation. Rouaud and colleagues investigated high-frequency STN stimulation on cocaine and food-seeking behavior in rats.[165] Stimulation made the animals less willing to work for drugs but did not affect consumption of readily available cocaine. Human case reports looked at patients with PD and found that STN DBS could either reduce or induce addictive behavior.[9,11,204] Several studies have also linked STN stimulation with increased impulsiveness.[116,179] Given these mixed results, the overall consensus is that STN stimulation is not as effective and safe as nucleus accumbens stimulation in addiction.

Additional target areas have included the dorsal striatum, lateral habenula, medial prefrontal cortex, and lateral hypothalamus. Animal studies showed no effect on drug-related behaviors after stimulation of the dorsal striatum[193] and lateral hypothalamus.[114] Lateral habenula stimulation was effective in controlling drug consumption but also decreased food consumption, which was considered an undesirable side effect.[62,63] Medial prefrontal cortex stimulation also appeared effective in animal studies, but no human cases have been reported.[129,142]

Neuromodulation of the nucleus accumbens has been shown to be effective and safe in the treatment of refractory addiction in small cohorts of patients. Given the societal burden imposed by addictive disorders, additional work in this area is warranted.

Others Indications: Epilepsy, Aggression, and PTSD

Epilepsy has been extensively studied as an indication for DBS (reviewed in Lega et al., 2010[112] and Kahane and Depaulis, 2010[84]). Initial results of the Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial, testing stimulation against placebo in patients with severely refractory epilepsy, were promising.[58] Five-year follow-up data were recently presented showing a median 69% reduction in seizure frequency, increased from a 56% reduction at 2 years. The 5-year response rate (patients with > 50% seizure frequency reduction) was 69%, and patients also had improvement in quality of life measures (Long Term Efficacy of the SANTE Trial. Presented at American Epilepsy Society 66th Annual Meeting. Abstract 1.272, Platform A.04. December 2, 2012). Other targets under active investigation include the hippocampus, caudate, and centromedian nucleus.[61]

Another psychiatric indication under early investigation is treatment-refractory aggression. Based on early lesioning studies, as well as lesion/stimulation work,[168] the mediobasal hypothalamus ("hypothalamic aggression area") has emerged as a target for stimulation. A recently published retrospective chart review on long-term results of posteromedial hypothalamic DBS for refractory aggression showed a significant decrease in the number of violent outbursts in 5 of the 6 patients reviewed.[189] Although significant care was taken in patient selection and consent (each patient was evaluated by 2 psychiatrists, a local ethics committee, and consent was obtained from patients' parents or legal guardians), DBS for aggression continues to have severe ethical implications that must be carefully considered before this indication is more widely studied.

Preclinical work is also ongoing for the treatment of posttraumatic stress disorder (PTSD), as well as improving the understanding of the brain circuitry involved in PTSD. Currently, the amygdala[107,182] and ventral striatum/ventral capsule[43] are preliminary targets.

The Future of Electrical Stimulation

Deep brain stimulation serves as a prime example of how advances in systems neuroscience are being translated into novel therapies. Deep brain stimulation is also gaining increasing acceptance for use on a case-by-case basis in a number of investigational indications. As noted in a recent review,[127] 100 Phase I/II and 21 Phase II/III trials of DBS were underway at the end of 2012. Many of the indications under investigation, such as obesity, addiction, depression, and Alzheimer disease, are extremely prevalent and represent a significant healthcare burden worldwide. Although other indications such as TS, OCD, dystonia, and Huntington disease are less prevalent, DBS may be able to return quality of life to patients not effectively treated by current medical technology. Promising preliminary results for several of these indications suggest that DBS will likely continue to increase in prevalence as a neurosurgical intervention.

In addition to potentially providing relief for millions of patients, DBS is also providing researchers with a window into the function of the human brain. As discussed above, our understanding of normal motor neurocircuitry, as well as the pathophysiology of PD, has changed drastically, thanks to cortical and subcortical single-neuron and LFP recordings obtained during implantation of DBS electrodes. Our understanding of mood and decision-making has also been transformed with this technology, providing new insights into how signals from broad areas of cortex are funneled into subcortical structures enabling decision-making and subsequent selection of action. Insights into mechanisms gained from DBS studies have also informed novel experimental designs: tractography studies (tracer studies in primates, diffusion tensor imaging), optogenetic manipulation of select neuron populations, and functional imaging (magnetoencephalography and resting state functional MRI) are sure to continue revolutionizing our understanding of brain circuitry and functional anatomy.

Finally, technology for stimulation continues to evolve. We have illustrated examples of how DBS targets are refined and targeted, and as our understanding of brain physiology improves, rational selection of targets for stimulation is becoming a reality. New stimulation settings, such as interleaved stimulation, continue to develop and are tested against current standards. In the near future, real-time LFP recordings may also be used to modulate stimulation settings, creating feedback loops for continuous stimulator setting modulation. Such de-

vices may help to extend battery life, as well as allow for intermittent stimulation in cases in which constant stimulation may not be needed, such as for augmentation in forming memories. Other forms of stimulation, such as transcranial magnetic stimulation, focused ultrasound, and possibly optogenetic stimulation, can also play a role in modulating aberrant neurocircuitry. As clinical applications of electrical stimulation continue to expand in the future, so too will our understanding of the brain as a collection of highly connected regions, speaking to each other in a language of oscillations and burst firing patterns that we are just beginning to decode.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors.

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