Deep Brain Stimulation for Psychiatric Disorders

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Abstract

Medications, psychotherapy, and other treatments are effective for many patients with psychiatric disorders. However, with currently available interventions, a substantial number of patients experience incomplete resolution of symptoms, and relapse rates are high. In the search for better treatments, increasing interest has focused on focal neuromodulation. This focus has been driven by improved neuroanatomical models of mood, thought, and behavior regulation, as well as by more advanced strategies for directly and focally altering neural activity. Deep brain stimulation (DBS) is one of the most invasive focal neuromodulation techniques available; data have supported its safety and efficacy in a number of movement disorders. Investigators have produced preliminary data on the safety and efficacy of DBS for several psychiatric disorders, as well. In this review, we describe the development and justification for testing DBS for various psychiatric disorders, carefully consider the available clinical data, and briefly discuss potential mechanisms of action.

Contents

INTRODUCTION

Diseases desperate grown,

By desperate alliances are relieved,

Or not at all.

William Shakespeare, *Hamlet*, Act 4, Scene 3

Psychiatric disorders are among the most prevalent and costly ailments worldwide. Nearly 50% of all Americans will meet criteria for a mental disorder diagnosis in their lifetime, more than 28% will meet criteria for an anxiety disorder, and more than 20% will meet criteria for a depressive disorder (Kessler et al. 2005a). Depressive disorders alone are the highest contributor to the burden of disease in middle- and high-income countries and are the third highest contributor worldwide (WHO 2008). Suicide, which is almost always associated with the presence of a mental disorder, is the eleventh leading cause of death in the United States, third among persons aged 15–24 years, and fourth among persons aged 18–65 years (**http://www.cdc.gov/violenceprevention/suicide**).

Established treatments for many psychiatric disorders include medications and psychotherapy. Various other interventions have demonstrated efficacy for specific disorders [e.g., electroconvulsive therapy (ECT) for depression, mania, and catatonia; light therapy for seasonal affective disorder; and vagus nerve stimulation (VNS) and transcranial magnetic stimulation (TMS) for medication-resistant depression]. However, despite the proven effectiveness of available treatments, a substantial number of patients fail to fully remit (i.e., become symptom free) or maintain symptomatic improvement over time. This lack of effectiveness for some has led to the search for novel strategies, with more invasive approaches being considered and tested for the most severe and treatment-resistant patients.

Deep brain stimulation (DBS) is an invasive neurosurgical intervention being investigated for several psychiatric disorders, most notably treatment-resistant depression (TRD) and treatment-refractory obsessive-compulsive disorder (OCD), but also Tourette's Syndrome (TS), Alzheimer's dementia (AD), and addiction. The rationale for using DBS in the treatment of psychiatric disorders is based on its effectiveness in several movement disorders and the development of detailed neuroanatomical models for regulating emotion, cognition, and behavior.

DBS is achieved by implanting one or more electrode arrays (leads) into a specific region of the brain via burr holes in the skull using neuroimaging-guided stereotactic neurosurgical techniques (where the target for implantation is calculated within a three-dimensional coordinate system based on external landmarks) (**Figure 1**). Each array generally contains several (typically four) electrode contacts spanning 10–20 mm. DBS leads are connected via subcutaneous extension wires to one or more subcutaneously implanted pulse generators (IPGs) containing the system battery and the computer that drives stimulation; therefore, the system is completely internalized within the patient's body. Parameters can be noninvasively set and adjusted via a handheld computer interface. Stimulation parameters can vary widely, e.g., in terms of frequency, pulse width, and voltage/amplitude. In the clinical setting, common DBS parameters are 60–130 Hz, 60–200 μs

DBS: deep brain stimulation

TRD: treatment-resistant depression

OCD: obsessive-compulsive disorder

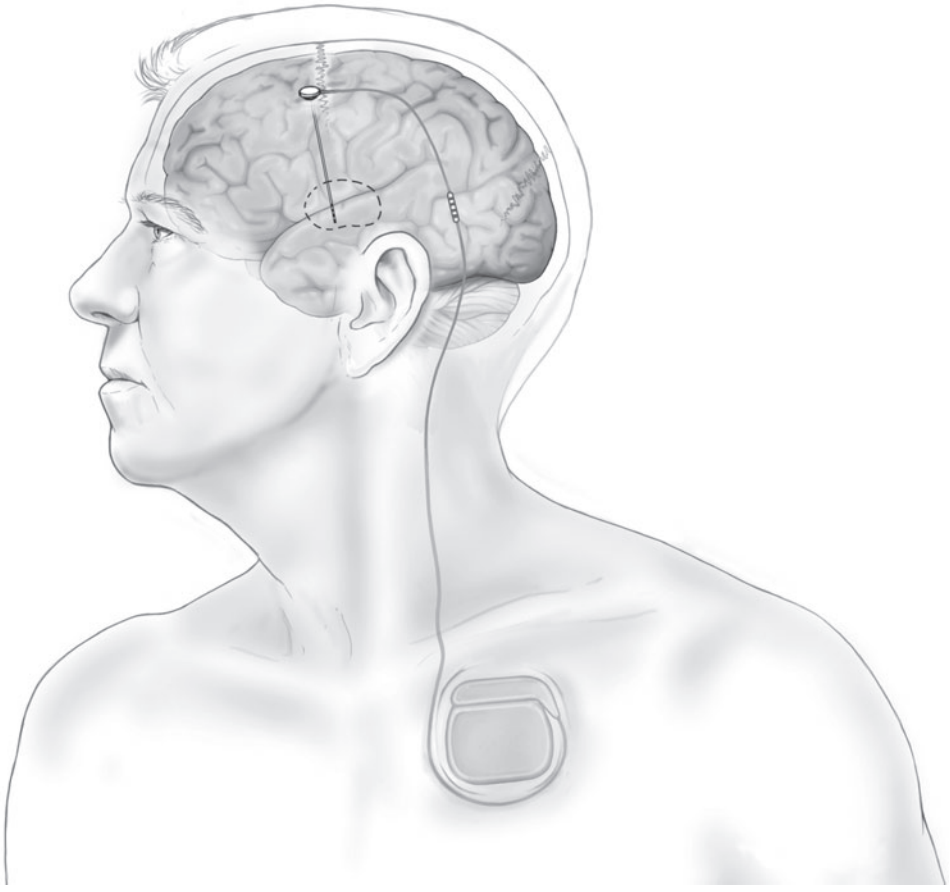

Figure 1

Diagram of a deep brain stimulation (DBS) system. Electrodes are implanted via stereotactic neurosurgery and attached to an implanted pulse generator via subcutaneous extension wires. Image courtesy of David Peace, Department of Neurosurgery, University of Florida School of Medicine.

pulse width, and 2–10 volts (V). Stimulation can be either monopolar (with one or more DBS contacts serving as the cathode and the IPG serving as the anode) or bipolar (with individual DBS contacts serving as the cathode and anode). In some systems, a duty cycle can be used such that stimulation is on and off for specified periods of time. Serious risks associated with DBS surgery include intracranial hemorrhage, infection, and complications associated with anesthesia. The DBS system could malfunction or break, making replacement of one or more components necessary. Finally, repeated minor surgery is needed to replace the IPG. Acute and chronic effects of stimulation depend on the site of stimulation.

In this review, we briefly describe the history of neurosurgery for psychiatric disorders to emphasize that this approach is not new, but has been previously limited by the neuroanatomical models used to select targets and by available neurosurgical techniques. We then describe, with a focus on movement disorders, how the refinement of neuroanatomical models and neurosurgical techniques led to the establishment of ablative neurosurgery and DBS as reasonable approaches for severe, treatment-refractory brain disorders. Next, the available

PD: Parkinson's disease

GPi: internal globus pallidus

data on the safety and efficacy of DBS for psychiatric disorders are presented and critically evaluated, with a brief discussion of the small but growing database on potential mechanisms of action. We conclude with recommendations for a research agenda going forward.

NEUROSURGERY FOR PSYCHIATRIC DISORDERS

The development of neurosurgical techniques for focal ablation and stimulation have historically been driven by attempts to treat intractable psychiatric disease [for an overview, please see the comprehensive historical review by Hariz and colleagues (2010)]. Prior to the 1950s, no specific medications existed for the treatment of severe psychiatric disorders. Given the disabling and often lethal nature of these illnesses, aggressive and often invasive treatments were pursued, including malarial pyrotherapy (Epstein 1936), hypoglycemic coma (Sakel 1937), electroconvulsive therapy (Bini 1938), and neurosurgery. The first surgical attempts to treat severely psychotic patients occurred as early as 1891 (Burckhardt 1891) with limited success. With the emergence of relatively crude models of the functional and structural neuroanatomy of mood and behavior regulation [e.g., Papez' circuit (Papez 1937)], researchers hypothesized that abnormal mood and behavioral regulation derived from dysfunctional thalamo-cortical communication (Moniz 1937). Neurosurgical treatments thus shifted to disrupting the white matter tracts connecting these regions, culminating in the prefrontal leucotomy (Moniz 1937) which was later referred to as the prefrontal lobotomy. The surgical methods available for severing these tracts were limited; procedures were often done blindly and resulted in relatively large lesions.

The mid-twentieth-century discovery of medications with antimanic (Cade 1949, Schou et al. 1954), antipsychotic (Bower 1954, Winkelman 1954), and antidepressant effects (Bailey et al. 1959, Kiloh et al. 1960, Kuhn 1958) essentially ended the lobotomy era. However, using novel stereotactic neurosurgical techniques allowing more focal ablation (initially viewed as a potential substitute for prefrontal leucotomy in psychiatric patients) (Hariz et al. 2010, Spiegel et al. 1947), surgery for severe, intractable psychiatric disorders has continued in a limited fashion. Current approaches include subcaudate tractotomy, dorsal anterior cingulotomy, anterior capsulotomy, and limbic leucotomy (combing a subcaudate tractotomy with a cingulotomy) (**Figure 2**) (Cosgrove 2000). Naturalistic and nondisease-specific response rates of 22%–75% for these procedures have been reported for patients with severe, treatment-resistant psychiatric illness, including treatment-resistant OCD and depression (Cosgrove 2000, Cosgrove & Rauch 2003, Sachdev & Sacher 2005, Shields et al. 2008). Risks include weight gain, cognitive impairments, personality change, and epilepsy (Moreines et al. 2011, Sachdev & Sacher 2005).

DBS FOR MOVEMENT DISORDERS

As neurosurgery for psychiatric disorders diminished in popularity, stereotactic neurosurgery continued as a strategy to treat severe movement disorders. On the basis of early motor regulation models and preliminary nonstereotactic surgical results, Spiegel and colleagues attempted subcortical lesions for the treatment of Huntington's chorea (Spiegel & Wycis 1950). A variety of subcortical targets were then proposed for treating tremor in Parkinson's disease (PD) (Andy et al. 1963). The refinement of neuroanatomical models (Alexander et al. 1986, Bergman et al. 1990) further established lesions of the internal globus pallidus (GPi), ventrolateral thalamus, and/or subthalamus as accepted treatments for a number of medication-refractory movement disorders, including PD (Burchiel 1995, Walter & Vitek 2004), essential tremor (Burchiel 1995, Pahwa et al. 2000), and dystonia (Tasker 1990, Vitek et al. 1998). With the recognition that high-frequency (50–200 Hz) stimulation of the thalamus and subthalamus achieved beneficial effects similar to thalamotomy (Benabid et al.

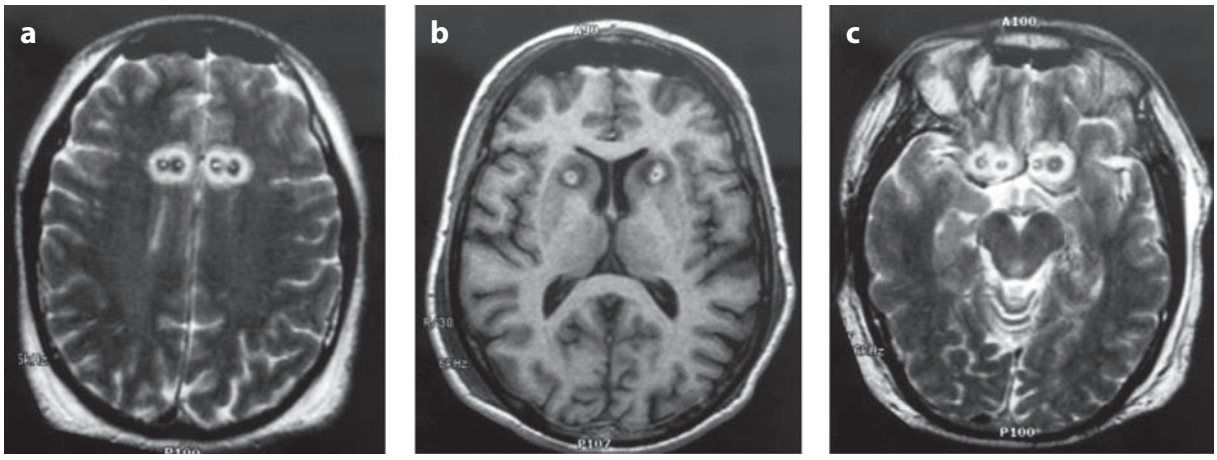

Figure 2

Postoperative MRI scans of three ablative neurosurgical procedures currently available for psychiatric disorders: (*a*) anterior cingulotomy, (*b*) anterior capsulotomy, and (*c*) subcaudate tractotomy. A limbic leucotomy is achieved by combining an anterior cingulotomy (*a*) with a subcaudate tractotomy (*c*). Images courtesy of G. Rees Cosgrove, Department of Neurosurgery, Brown University.

1991, Benabid et al. 1987, Hariz et al. 2010), DBS became a realistic alternative to ablation. Currently, DBS has largely replaced ablative surgery for the treatment of severe, refractory PD, essential tremor, and dystonia (Wichmann & Delong 2006). Targets include the thalamus for tremor and the subthalamic nucleus (STN) and GPi for PD (Moro et al. 2010b) and dystonia (Hung et al. 2007, Krause et al. 2004, Lozano & Abosch 2004, Sun et al. 2007). On the basis of more detailed models of motor regulation, investigators have proposed additional DBS targets for specific PD symptoms, such as the pedunculopontine nucleus for postural instability (Moro et al. 2010a, Plaha & Gill 2005). This historical progression highlights how the joint development of improved neuroanatomical models and neurosurgical techniques has been critical to establishing DBS as a valuable treatment option.

DBS FOR PSYCHIATRIC DISORDERS

Investigators began exploring the effects of intracranial stimulation in psychiatric patients as early as the 1950s, although reports are largely anecdotal (Hariz et al. 2010, Heath 1963, Heath et al. 1955). As such, DBS was not viewed as a viable treatment alternative until 1999 when Nuttin et al. (1999) published results of chronic, high-frequency stimulation of the bilateral anterior limbs of the internal capsule in four patients with severe, treatment-refractory OCD. Over the past decade, several reports have emerged that described effects of DBS at various targets and for various psychiatric indications (**Figure 3**). In general, these data derive from small, open-label studies without a comparator group and must therefore be viewed as encouraging but highly preliminary.

Obsessive-Compulsive Disorder

OCD is defined by the presence of one or more markedly distressing or functionally impairing obsessions (intrusive, ruminative thoughts, images, or impulses) and/or compulsions (highly repetitive mental or physical acts such as hand washing, checking locks, counting, praying, etc.); compulsions are often performed to diminish the anxiety/distress associated with obsessions. OCD affects about 1% of the U.S. population (Kessler et al. 2005b) and

STN: subthalamic nucleus

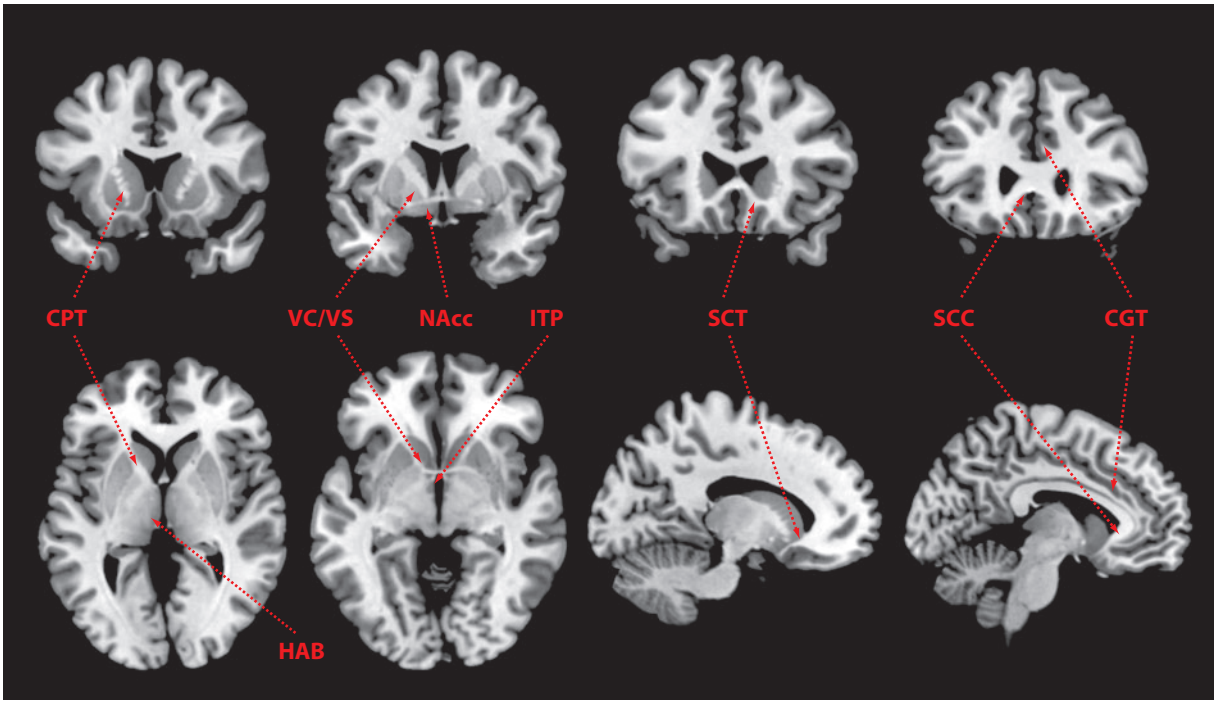

Figure 3

Location of various targets for ablation or DBS for psychiatric disorders. Abbreviations: CGT, cingulotomy; CPT, capsulotomy; HAB, habenula; ITP, inferior thalamic peduncle; SCC, subcallosal cingulate; SCT, subcaudate tractotomy; VC/VS, ventral capsule/ventral striatum. Note that the current VC/VS target is more posterior and inferior to the classic CPT target (Greenberg et al. 2010); the VC/VS and NAcc targets span a very similar area (Greenberg et al. 2010, Schlaepfer et al. 2008); the SCC target is more medial and anterior to the classic SCT target; and the classic CGT target is in the dorsal anterior cingulate (not rostral or subcallosal).

is associated with significant distress and disability (Hollander et al. 2010, Huppert et al. 2009). Evidence-based treatments include medications (primarily antidepressant and antipsychotic medications that modulate monoaminergic neurotransmission) (Goodman et al. 2000, Kellner 2010, Soomro et al. 2008) and cognitive-behavioral psychotherapy (Gava et al. 2007). However, up to 60% of patients do not respond adequately to available treatments (Goodman et al. 2000, Kellner 2010, Pallanti & Quercioli 2006, Simpson et al. 2008), making treatment-refractory OCD a serious public health problem.

Ventral capsule/ventral striatum. As described above, several ablative procedures, including capsulotomy, had shown moderate efficacy in severe, treatment-refractory OCD. However, side effects, when they occurred, were generally irreversible, leading to an interest in DBS as a possible alternative. In the first report of bilateral DBS of the anterior internal capsule for OCD (Nuttin et al. 1999), four patients were implanted and three were reported to have beneficial effects (although the definition of improvement is not provided). More detailed data are presented for one subject: This patient had a 90% reduction in compulsive behavior per her family, and behavioral testing suggested acute positive effects with stimulation (Nuttin et al. 1999). A number of case reports/series followed that suggested beneficial effects of DBS of the ventral capsule (VC) and/or ventral striatum (VS) in treatment-refractory OCD (Abelson et al. 2005, Anderson & Ahmed 2003, Aouizerate et al. 2004).

VC: ventral capsule

VS: ventral striatum

An international, multicenter group implanted 26 patients over 8 years using similar but not identical protocols (Greenberg et al. 2010). All but three patients had a comorbid mood disorder. Response was defined as a decrease in the Yale-Brown Obsessive Compulsive Scale (YBOCS) of ≥35% from baseline. At 3 months ($N = 26$), 50% of patients were responders; at 6 months ($N = 24$), 46% were responders; at 1 year ($N = 21$), 48% were responders; at 2 years ($N = 17$), 65% were responders; and at 3 years ($N = 12$), 58% were responders. Significant decreases in depression severity and increases in global functioning were also observed. Over the course of this study, location of the DBS electrodes was moved posterior and inferior from the classical capsulotomy target on the basis of clinical results; this adjustment was associated with lower stimulation intensity and better response rates in the latter patients. Adverse events related to surgery, the device, or stimulation included intracranial hemorrhage ($N = 2$), seizure ($N = 1$), infection ($N = 1$), lead or extension wire break ($N = 2$), hypomania ($N = 1$), and increased suicidal ideation (in at least four patients, although it appears this result was associated with a planned stimulation off phase (i.e., no stimulation was provided during this phase) at one of the sites in at least some patients. Acute effects of stimulation included hypomania-like episodes, mood worsening, improved anxiety, worsened anxiety (including one panic attack), irritability, cognitive abnormalities, and sensorimotor effects; in general, these symptoms resolved with either continued stimulation or a parameter change. Battery life ranged from 6–18 months, and battery depletion (or cessation of stimulation due to other causes) was noted to be mostly associated with a return of depressive rather than OCD symptoms.

Goodman et al. (2010) recently reported a blinded, staggered-onset, sham-controlled study of DBS of the VC/VS for OCD. Six patients with severe, treatment-refractory OCD were included. At one month postsurgery (without stimulation), subjects were randomized to one month of active (on) versus sham (off) DBS. After another month, the sham patients received active stimulation and were followed for one month. No patient showed significant improvement during the one month postsurgery or during the one-month sham period; however, in the first few months of the study, there were no statistically significant differences between patients receiving early versus delayed stimulation. Following 12 months of chronic DBS, 4 of 6 patients were responders (≥35% decrease in the YBOCS score from baseline). Side effects were similar to those previously reported with DBS at this target, and battery depletion/stimulation cessation were similarly associated with a return of depressive rather than OCD symptoms. Most patients showed no cognitive changes with chronic stimulation, although some showed improvements and others showed decrements.

Nucleus accumbens. The VC/VS target for DBS includes the ventral portion of the anterior internal capsule and the VS. The nucleus accumbens (a major component of the VS) has also been explored as a discrete target for DBS treating OCD. In a sham-controlled, crossover study, Huff and colleagues (2010) implanted 10 patients with OCD with a DBS electrode in the right nucleus accumbens. Patients were randomized to three months of active versus sham DBS then crossed over to the other condition for three months; all patients received active stimulation after these six months. There were no statistically significant differences between active and sham DBS. After 12 months of active stimulation, one patient (10%) achieved a response (≥35% decrease in the YBOCS score from baseline) and five patients (50%) achieved a partial response (≥25% decrease in the YBOCS score from baseline). Adverse events were similar to those seen previously with VC/VS stimulation. Although preliminary, these data suggest that DBS of the internal capsule may be necessary to treat OCD. This finding may relate to a proposed mechanism of action of DBS involving activation of white matter fibers.

SCC: subcallosal cingulate

Subthalamic nucleus. On the basis of observations of decreased compulsive behaviors in PD patients following STN DBS, Mallet et al. (2008) conducted a double-blind, crossover, sham-controlled trial of STN DBS for treatment-refractory OCD. At three months postsurgery, patients were randomized to three months of active versus sham DBS, followed by a one-month washout (no stimulation) phase, then crossed over to the other condition for an additional three months. Active DBS was statistically superior to sham stimulation in reducing OCD symptoms. Following three months of active stimulation, 75% of subjects met response criteria (≥25% decrease in the YBOCS score from baseline) versus 38% of subjects meeting response criteria following three months of sham stimulation.

Inferior thalamic peduncle. The inferior thalamic peduncle (ITP) is a white matter bundle that includes fibers connecting thalamic nuclei with ventral prefrontal cortex. Presumably based on earlier models suggesting that disruption of thalamic-prefrontal connections could have beneficial effects in psychiatric disorders, one group has tested ITP DBS for treatment-refractory OCD in a small case series (Jimenez-Ponce et al. 2009). Following 12 months of open-label DBS, the authors report a 100% response rate (≥35% decrease in the YBOCS score from baseline). Acute stimulation was associated with anxiety and autonomic symptoms in all subjects and confusion/disorientation in one subject; however, these effects occurred at contacts that were not optimal for long-term stimulation. No other adverse events were described.

TRD

Major depressive disorder (MDD) is a syndrome characterized by depressed mood and/or anhedonia (decreased ability to experience pleasure) and a combination of additional symptoms, including sleep and appetite abnormalities, low energy, psychomotor retardation (or agitation in some patients), decreased attention/concentration, low self-esteem and feeling of guilt, and suicidal ideation. MDD has a one-year U.S. prevalence of 7% (Kessler et al. 2005b), is the leading cause of years lost due to disability worldwide, and represents the largest contributor to overall disease burden in middle- and high-income countries (WHO 2008). Treatments for depression include medications, psychotherapy, and a number of other somatic interventions (such as ECT and light therapy). Despite the availability of treatments, two-thirds of patients do not remit (i.e., become symptom free) with an initial medication, one-third do not remit with multiple treatments, and at least 20% remain significantly symptomatic despite multiple, often aggressive interventions (Holtzheimer & Mayberg 2011, Rush et al. 2006). For those patients that respond well to treatment, depressive relapse is quite common, occurring in 60% to nearly 100% of patients depending on prior history of relapse and level of treatment resistance (APA 2000, Rush et al. 2006, Sackeim et al. 2001). Treatment-resistant depression (TRD), therefore, has a prevalence of ~1%–3%, and better treatments for achieving and maintaining remission are clearly needed.

Subcallosal cingulate white matter. As neuroimaging techniques have greatly improved over the past three decades, an impressive literature has accumulated on the neuroanatomical bases of depression and the antidepressant treatment response. On the basis of a converging dataset (Mayberg 2009, Price & Drevets 2010), Mayberg hypothesized that DBS modulation of the subcallosal cingulate (SCC) white matter would help bring about the functional neuroanatomical changes previously associated with an antidepressant response (across a number of treatments) and lead to symptomatic improvement in severe TRD patients. Critically, this proposed target was not a prior site for ablative neurosurgery in psychiatric disorders: The standard target for a cingulotomy was located in the mid-cingulate cortex dorsal to the corpus callosum, and the target for a subcaudate tractotomy was several millimeters more lateral.

An initial, open-label pilot study demonstrated clear antidepressant effects following chronic (6 months) SCC DBS in 4 of 6 TRD patients, with 3 patients achieving full remission (Mayberg et al. 2005). A number of these patients experienced acute, positive effects with intraoperative stimulation (such as a sense of calmness, increased alertness, and enhanced connectedness with others). No adverse effects of acute or chronic stimulation were described. Three patients developed infections requiring antibiotics; the DBS system was removed in 2 patients (both nonresponders) because of infection. This study was expanded to include a total of 20 patients followed for one year (Lozano et al. 2008). A 60% antidepressant response rate (defined as a $\geq$50% decrease in depression severity from baseline) was seen after 6 months of chronic DBS, and 55% of patients were responders at one year. Seventy-two percent of responders at 6 months were responders at one year, with 3 additional patients (all nonresponders at 6 months) achieving an antidepressant response at one year. Long-term follow-up, using an intent-to-treat analysis, found a 45% response rate and 15% remission rate after two years and a 60% response rate and 50% remission after three years of chronic stimulation (Kennedy et al. 2011). Adverse events included infection, 1 perioperative seizure (of unclear etiology), worsening mood/irritability unrelated to stimulation, and perioperative headache/incision pain. No adverse cognitive effects were identified, and improvements across several domains were observed (McNeely et al. 2008). Two probable suicides occurred in patients who had previously achieved response and/or remission and some degree of functional recovery. One occurred after three years of stimulation, and the other occurred after six years of stimulation. Both probable suicides were deemed unrelated to chronic stimulation or any change in stimulation parameters or other treatments.

Ventral capsule/ventral striatum. Earlier reports of VC/VS DBS for OCD consistently described significant antidepressant effects, independent of changes in OCD symptoms. Thus investigators hypothesized that VC/VS DBS may serve as an antidepressant treatment even in patients without comorbid OCD. A three-site pilot study found a 40% response rate following 6 months of open-label VC/VS DBS in 15 TRD patients, with a 53% response rate at last follow-up (an average of 24 ± 15 months after onset of stimulation, with a range of 6–51 months) (Malone et al. 2009). Acute stimulation was associated with both positive effects (improved mood, spontaneous smiling, decreased anxiety, and increased awareness/energy) and negative effects [autonomic symptoms (tachycardia, flushing), increased anxiety, perseverative speech, and involuntary facial movements]; the number of patients experiencing each was not described, though it is stated that these effects could be attenuated with a stimulation parameter change. Adverse events included 2 cases of hypomania/mixed-bipolar state, 5 cases of increased depression/suicidality, 1 case of perioperative pain, 1 device failure (DBS lead fracture), and 2 cases of syncope. Maintenance of response and recurrence rates are not described in the report.

Nucleus accumbens. The nucleus accumbens (NAcc) has been implicated in neural pathways related to reward processing and motivation (Humphries & Prescott 2010, Knutson et al. 2008, Sesack & Grace 2010). As such, Schlaepfer et al. (2008) hypothesized that DBS modulation of the NAcc may have specific effects on anhedonia, a core symptom of the depressive symptom that could effectively lead to an antidepressant treatment response in TRD. An initial report of three TRD patients receiving NAcc DBS described improvements in depression ratings and hedonic response with active stimulation that were reversed when stimulation was turned off (Schlaepfer et al. 2008). This cohort was expanded to 10 patients, and a 50% antidepressant response rate was seen following 12 months of chronic, active NAcc DBS (Bewernick et al. 2010). Acute positive effects were briefly described

but reported not to be predictive of a longer-term outcome. Adverse effects were generally similar to those seen with VC/VS DBS; one completed suicide occurred but was judged to be unrelated to chronic stimulation.

Inferior thalamic peduncle. A single case report described effects of 24 months of ITP DBS in a woman with TRD, borderline personality disorder, and bulimia (Jimenez et al. 2005). In general, notable and mostly sustained antidepressant effects were observed with chronic stimulation. A slight return of depressive symptoms was seen following double-blind discontinuation following eight months of active stimulation. Anxiety, fear, and significant adverse autonomic effects were noted with acute stimulation of certain contacts and resolved when stimulation ceased. A "pleasant sensation" (p. 589) with decreased anxiety was found with acute stimulation of other contacts. No adverse effects of chronic stimulation were described.

Stria medullaris thalami (habenula). The habenula is a midbrain structure composed of several small nuclei (also called the habenular complex) that lies dorsal and caudal to the main body of the dorsal thalamus. The habenula is involved in the coordination of monoaminergic neurotransmission (primarily serotonergic and noradrenergic) and receives input from cortical and subcortical structures via the stria medullaris thalami. Given its neuroanatomy, and the clear role for monoaminergic neurotransmission in the pathophysiology of depression, Sartorius & Henn (2007) proposed that the habenula is as a potential target for DBS for TRD. A single case report described effects of DBS of the stria medullaris thalami in a woman with TRD who required biweekly ECT to prevent severe depressive relapse (although relapses occasionally occurred even with ECT at this frequency) (Sartorius et al. 2010). She was implanted during a period of full remission following ECT, treated with DBS at 5V, and experienced a severe relapse within 3 weeks following implantation. Stimulation intensity was progressively increased to 10.5V, and remission was again achieved. No acute stimulation effects were observed, and no adverse events were reported.

Other Disorders

Addiction. Human and animal studies have helped define the neural circuitry of addiction (Koob & Volkow 2010), indicating that focal neuromodulation within these systems may have clinical benefit. Case reports have associated nucleus accumbens DBS with benefits for nicotine addiction (Kuhn et al. 2009, Mantione et al. 2010) and alcoholism (Muller et al. 2009). It is not clear whether DBS acts by reducing the rewarding quality of the abused substance, perhaps by replacing the desire for the substance with stimulation [e.g., analogous to intracranial self-stimulation (Jacques 1979, Olds & Fobes 1981)] or by decreasing cue-associated reinstatement of addictive behavior, thereby reducing likelihood of relapse (Muller et al. 2009, Vassoler et al. 2008).

Alzheimer's disease. Alzheimer's disease (AD) is a neurodegenerative/neuropsychiatric disorder that affects 1%–2% of the U.S. population (Hebert et al. 2003). More than 10% of those over age 65 (Evans et al. 1989) suffer from AD. AD treatments are notably limited to behavioral interventions and acetylcholinesterase inhibitors and/or N-methyl-D-aspartic acid receptor antagonists that may slow but do not prevent further cognitive decline (Burns & Iliffe 2009). On the basis of a case report of memory enhancement with DBS of the fornix in a patient with obesity (Hamani et al. 2008), Laxton et al. (2010) performed a small open-label study of fornical/hypothalamic DBS in AD patients, which showed potential efficacy in patients stable on anticholinesterase medication(s) for at least six months. It is unknown whether this approach is superior to currently available medications. The potential mechanism of action of this approach is unclear, although the authors propose that activation of fornical axons leads to downstream activation of other

brain regions involved in memory (Laxton et al. 2010).

Tourette's syndrome. Tourette's syndrome (TS) is a neuropsychiatric disorder characterized by potentially disabling vocal and motor tics, with a prevalence of ~1% (Robertson 2008). TS is associated with a number of psychiatric comorbidities, including OCD (Swain et al. 2007). A subset of TS patients may have disabling symptoms despite standard medical treatment (including medications and behavioral intervention) (Mink 2009, Temel & Visser-Vandewalle 2004). Investigators have tried ablative neurosurgery in such patients with mixed success (Temel & Visser-Vandewalle 2004); among the various targets attempted, lesions of the centromedian-parafascicular complex of the thalamus have been most effective (Mink 2009). On the basis of results in related conditions (e.g., OCD and movement disorders), researchers have hypothesized that DBS of the GPi or VC/VS is also efficacious for treatment-refractory TS.

A number of case reports for thalamic DBS for TS have been published (Mink 2009). An open-label study of 18 patients showed initial positive results with follow-up of 3–18 months (Servello et al. 2008), and a 2-year assessment of this cohort identified significant decreases in tic severity, obsessive-compulsive symptoms, anxiety, and depression (Porta et al. 2009). Case reports also suggest potential efficacy of GPi and VC/VS DBS for severe TS patients (Mink 2009).

Mechanism of Action

Neuronal effects. The development of DBS as an alternative for ablative neurosurgery posited that high-frequency DBS served as a "reversible lesion" by inhibiting the activity in the stimulated gray matter (Benabid et al. 1991, Benazzouz et al. 1995). Further research has clarified that the mechanisms of action for DBS are more complex, including elements of inhibition as well as axonal excitation (Iremonger et al. 2006, McIntyre et al. 2004). Thus, the neuronal effects of DBS will depend greatly on location and the mix of cell bodies and passing white matter fibers in the field of stimulation (and whether these are inhibitory, excitatory, or modulatory). The various parameters of stimulation will also impact the effects of DBS. For example, suppression of tremor with thalamic stimulation is generally not achieved with stimulation frequencies below 50 Hz, and an optimal effect is seen with frequencies greater than 100 Hz (Benabid et al. 1991). However, 60–130 Hz GPi stimulation may be similarly effective for dystonia (Alterman et al. 2007, Isaias et al. 2009, Moro et al. 2009). The efficacy of DBS may depend on the activity state of the region being impacted, as well as the ability of DBS to adequately modulate this. For example, presumably abnormal oscillatory activity in the STN and GPi has been implicated in the pathophysiology of PD (Brown et al. 2001, 2004; Hammond et al. 2007, Levy et al. 2002, Weinberger et al. 2006), and the therapeutic effects of DBS may depend on modulation of this activity (Brown et al. 2004, Kuhn et al. 2008). We do not know whether this represents a general mechanism of action for DBS in other disorders.

Animal studies are beginning to address the direct neuronal effects of DBS at targets used for psychiatric disorders. Hamani and colleagues (2010a,b) carried out a series of experiments using high-frequency stimulation of the prelimbic (PL)/infralimbic (IL) cortex in rats—a region homologous to the SCC target for DBS for TRD. Stimulation was associated with an antidepressant-like effect in the forced swim test (FST), an animal model for testing potential antidepressant treatments; 130 Hz stimulation was more effective than 20 Hz, and stimulation in the PL/IL boundary region was more effective than pure IL stimulation (Hamani et al. 2010a). However, lesions of this region did not show the same effects, and lesions of local gray matter (preserving passing white matter fibers) did not prevent the antidepressant-like effects of stimulation (Hamani et al. 2010b); these authors further showed that the antidepressant-like effects of PL/IL stimulation depended on an intact

serotonergic but not noradrenergic system (Hamani et al. 2010b). These results suggest that the effects of SCC DBS may be due to excitation of passing white matter fibers (possibly from brain stem monoaminergic nuclei) rather than local inhibitory effects. However, two other groups have described antidepressant-like effects of transient inactivation of rat IL cortex using the FST (Scopinho et al. 2010, Slattery et al. 2010).

Using the quinpirole model of OCD, high-frequency stimulation of the rat nucleus accumbens (both shell and core components) showed anticompulsive efficacy (Mundt et al. 2009). High-frequency but not low-frequency stimulation of the entopeduncular nucleus and globus pallidus (homologues of the human external and internal globus pallidus) showed anticompulsive effects in the signal attenuation model (Klavir et al. 2010). Both lesions and high-frequency stimulation of the rat STN have shown anticompulsive effects in both the quinpirole and signal attenuation OCD models (Klavir et al. 2009, Winter et al. 2008), suggesting that stimulation and lesions are functionally equivalent at this target.

System-level effects. Beyond the immediate neural effects of DBS, we presume that behavioral effects result from neural network activity modulation. In PD, overly synchronized oscillations within thalamo-cortico-striatal loops are associated with motor symptoms (Hammond et al. 2007), and DBS may work by modulating communication between these regions (Gradinaru et al. 2009, Hammond et al. 2007, Iremonger et al. 2006). Similarly, MDD and OCD (and most other psychiatric disorders) are viewed as network-level disorders in which behavioral abnormalities arise from dysfunction within a discrete network of interconnected brain regions (Freyer et al. 2010, Harrison et al. 2009, Mayberg 2009).

Animal and human studies have helped begin to elucidate the specific networks impacted by focal neuromodulation. Nucleus accumbens high-frequency stimulation in rats altered function and oscillatory power and coherence within a network involving the medial frontal cortex, the orbitofrontal cortex (OFC), and the mediodorsal thalamus (McCracken & Grace 2007, 2009). As above, the antidepressant-like effects of PL/IL DBS may depend on the integrity of passing white matter fibers, as well as an intact serotonergic system (Hamani et al. 2010b). A positron emission tomography (PET) study of six OCD patients showed that acute VC/VS DBS was associated with increased blood flow in the OFC, the anterior cingulate cortex, the basal ganglia, and the thalamus (Rauch et al. 2006); another PET study showed decreased OFC metabolism with chronic (3–6 weeks) VC/VS DBS for OCD in 2 of 3 patients (Abelson et al. 2005). Following 3 and 6 months of effective SCC DBS for TRD, investigators saw decreased blood flow at the SCC target, the medial prefrontal cortex, the OFC, the insula, and the midbrain; they saw increased blood flow in the mid-cingulate cortex and the dorsolateral prefrontal cortex. Lozano et al. (2008) saw similar changes in metabolism in the expanded cohort. The brain regions showing changes with DBS had been previously implicated in the neurobiology of depression and/or antidepressant treatment response (Mayberg 2009). With chronic NAcc DBS for TRD, decreased metabolism was seen in a number of cortical and subcortical brain regions implicated in the pathophysiology of depression (no areas of increased metabolism were identified) (Bewernick et al. 2010). A structural imaging study using diffusion tensor imaging tractography—an MRI imaging method and analytic approach that can delineate white matter tracts in vivo (Behrens et al. 2003, Johansen-Berg et al. 2005)—found that projections from the two major white matter targets for DBS for TRD (SCC and VC/VS) were largely divergent, but overlapped at several potentially important regions, including the medial prefrontal cortex, the amygdala/hippocampus, the nucleus accumbens, and the thalamus (Gutman et al. 2009). These regions may represent common remote regions impacted by DBS and necessary for its antidepressant effects.

SUMMARY AND FUTURE DIRECTIONS

Neurosurgical intervention for psychiatric disorders has a long history. However, earlier attempts were profoundly limited by the relative crudeness of available techniques and the neuroanatomical models employed. As both technical approaches and neuroanatomical models of mood, thought, and behavior have advanced, DBS has emerged as an intervention with the potential to ameliorate symptoms and restore function in patients with the most severe and treatment-refractory psychiatric disorders. Preliminary data on safety and efficacy of DBS at various targets for OCD and TRD are highly encouraging. However, these data are, by and large, open label and lack any control comparison. Although these patients are among the most difficult to treat, the possibility of a placebo effect cannot be discounted (Goetz et al. 2008). Therefore, these early data should be replicated in larger, placebo-controlled trials prior to widespread clinical acceptance.

As research progresses, a number of important issues will need to be addressed. First, the specific effects of various stimulation parameters at each target for each disorder should be carefully considered and tested. Current stimulation parameters in psychiatric disorders have been modeled after those used in movement disorders, which emerged from the earlier (mostly incorrect) understanding that DBS was simply a reversible lesion. The specific effects of frequency, pulse width, duty cycle (i.e., the ration of time on to time off), and stimulation intensity should be investigated at each putative target. The effects of unilateral versus bilateral stimulation should also be considered (Guinjoan et al. 2010, Hamani et al. 2010a). This work will be advanced by modeling approaches that incorporate anatomical data (Butson et al. 2006) as well as by animal studies. Second, the comparative safety and efficacy of the various targets for each disorder should be established, similar to efforts in movement disorders (Moro et al. 2010b). This research should also incorporate mechanism of action studies to help identify whether each approach is more appropriate for a specific subgroup of patients; such efforts will be greatly supported by academic, federal, and industry collaboration. Third, a careful consideration of the value of DBS versus ablation is needed. For some disorders, targets, and patient populations, ablation may be preferred over chronic stimulation (Gross 2008). Fourth, better animal models of psychiatric disorders are needed. Animal studies will be critical to refining stimulation targets and parameters. Studies of healthy and behaviorally normal animals may be useful in some cases, although studies in animal models of disease will be necessary, as well. However, there are currently no accepted models of treatment-resistant OCD or depression. To develop better models, it may be necessary to reframe more drastically how a particular psychiatric disorder is defined, especially in the case of treatment-resistant conditions (Holtzheimer & Mayberg 2011). Also, the interpretation of animal studies will need to consider the state of the animal being tested, e.g., awake and behaving versus anesthetized.

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