Deep brain stimulation for psychiatric disorders: where we are now

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Fossil records showing trephination in the Stone Age provide evidence that humans have sought to influence the mind through physical means since before the historical record. Attempts to treat psychiatric disease via neurosurgical means in the 20th century provided some intriguing initial results. However, the indiscriminate application of these treatments, lack of rigorous evaluation of the results, and the side effects of ablative, irreversible procedures resulted in a backlash against brain surgery for psychiatric disorders that continues to this day. With the advent of psychotropic medications, interest in invasive procedures for organic brain disease waned.

Diagnosis and classification of psychiatric diseases has improved, due to a better understanding of psychiatric pathophysiology and the development of disease and treatment biomarkers. Meanwhile, a significant percentage of patients remain refractory to multiple modes of treatment, and psychiatric disease remains the number one cause of disability in the world. These data, along with the safe and efficacious application of deep brain stimulation (DBS) for movement disorders, in principle a reversible process, is rekindling interest in the surgical treatment of psychiatric disorders with stimulation of deep brain sites involved in emotional and behavioral circuitry.

This review presents a brief history of psychosurgery and summarizes the development of DBS for psychiatric disease, reviewing the available evidence for the current application of DBS for disorders of the mind.

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IN *The Cure of Folly* (c. 1475–1480), Hieronymus Bosch depicts what is touted as the first great artistic representation of neurological surgery. The surgeon, wearing what resembles a dunce cap, operates on the cranium of his hapless patient, who exhorts him to “dig out the stones of my folly.”²⁴³ Subsequent work in the 15th and 16th centuries depicts surgeons cutting for stones in patients’ heads to cure mental illness, but whether this represented contemporary mental health practices or merely commentary on the plight of patients at the mercy of medical malfeasants remains debatable.^{145,243} Nevertheless, this

painting recapitulates the tensions underlying the increasing interest in neurosurgery for psychiatric illness today: the desire to affect human behavior and consciousness through physical action on the brain; the hope of treating or curing disabling illness by such action; the uncertainty regarding the underlying physiology, safety, and efficacy of such interventions; the willingness of the patient to undergo procedures with dubious benefit when no other effective treatment is available; and the popular perception of those performing and undergoing such procedures.

The cost of psychiatric illness justifies addressing these

ABBREVIATIONS ALIC = anterior limb of the internal capsule; AN = anorexia nervosa; BDI = Beck Depression Inventory; BMI = body mass index; CM-PF = centromedian-parafascicular thalamic complex; DBS = deep brain stimulation; ECT = electroconvulsive therapy; GAF = Global Assessment of Functioning; GP = globus pallidus; GPi = GP internus; HDRS = Hamilton Depression Rating Scale; ITP = inferior thalamic peduncle; LHb = lateral habenula; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; MFB = medial forebrain bundle; NAcc = nucleus accumbens; OCD = obsessive-compulsive disorder; PD = Parkinson disease; pHr = posterior hypothalamic region; PTSD = posttraumatic stress disorder; SCC = subcallosal cingulate cortex; STN = subthalamic nucleus; TRD = treatment-resistant depression; TS = Tourette syndrome; VC/VS = ventral capsule and ventral striatum; VTA = ventral tegmental area; YBOCS = Yale-Brown Obsessive-Compulsive Scale; YGTSS = Yale Global Tic Severity Score.

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difficult issues. Across the world, neuropsychiatric disease is the most important cause of disability, accounting for in excess of 37% of all healthy life-years lost to disability.¹⁶⁷ In fact, depression is the single leading cause of disability in both males and females,¹⁶⁷ affecting 10%–15% of the population.¹⁰ Notably, between 50% and 66% of treated patients do not respond fully to medical therapy alone, requiring additional psychosocial interventions, and between 10% and 30% of patients are resistant to multiple classes of treatment.¹⁰ In the US, more than one-quarter of the population at large has a mood, anxiety, or substance abuse problem.¹³¹ Faced with this disease burden, enthusiasm for a surgical treatment for psychiatric disease is understandable—if the procedures are safe and effective.

With the increasing recognition of the burden of psychiatric disease there is a concomitant increase in interest in the development of safe and efficacious surgical treatment of that subset of patients who remain refractory to medical treatment. Psychosurgery has endured popular backlash after indiscriminate application in the face of dubious efficacy in the first half of the 20th century. Compared with the imprecise destructive procedures of that era, DBS has the advantages of being precisely targeted, relatively minimally invasive, essentially reversible and nondestructive, and adjustable with respect to stimulation parameters. This article examines the growing body of evidence for the application of DBS technology in the treatment of psychiatric disease (Fig. 1).

A Brief History of Psychosurgery

Evidence of successful cranial surgery in the form of trephination predates recorded history.¹² Whether such procedures were performed in response to trauma, epilepsy, or mental illness is open to speculation.^{63,239} This practice persisted into the Medieval and possibly the Renaissance periods.¹⁶⁸

In the 19th century, the notion of functional localization in neuroanatomy was advanced by Franz Gall with the advent of phrenology. While ultimately discredited, this work formed the basis of the notion that discrete anatomical areas of the brain were responsible for various neurological functions.²³⁹ Physicians such as John Harlow,¹⁰² Pierre Paul Broca,³⁷ and Carl Wernicke²⁹⁵ described the association of patterns of brain lesions and behavior, forming the backdrop against which the underlying assumptions of early psychosurgery developed: pathological mental states, being associated with particular loci of cortex, could be treated by the removal of such loci, alleviating the patient's condition.

This theory was first put in practice in 1888 by Gottlieb Burckhardt in Switzerland, who performed the procedure in and reported on a series of patients undergoing cortical extirpation for the treatment of “primäre Verrücktheit”—a clinical entity equivalent to schizophrenia—consisting of aggression, delusions, and auditory hallucinations.¹⁸⁰ Patients received bilateral topectomies in the frontal, temporal, and parietal lobes; he reported success in one-half of patients thus treated, but without mention of aphasia or motor side effects. These results were greeted with skepticism and some degree of hostility.

FIG. 1. Schematic showing locations of common targets of DBS for psychiatric disease, with indications, in parasagittal, axial, and coronal sections. GPe = GP externus. Copyright Andrew J. Reikito. Published with permission.

In 1935, John Fulton and Charles Jacobsen presented a study on the behavioral changes exhibited by primates after surgically created frontal lobe lesions. Bilateral resection of frontal association cortex was noted to blunt emotional responses.⁷⁷ Six months later, Egas Moniz, a Portuguese neurologist, with the help of neurosurgeon Almeida Lima, began a clinical trial of prefrontal leukotomy for the treatment of anxiety, depression, and schizophrenia.¹⁹⁷ Despite lukewarm clinical results, the procedure became popular. In the US, Walter Freeman and James Watts championed the procedure, developing tools such as the “precision leucotome” and tailoring the lesion location based on patient symptoms.²³⁹ By 1949, more than 10,000 leukotomies had been performed in the US,²⁹⁸ rising to more than 60,000 by 1956.²³⁹

A major factor in the popularization of this procedure was the lack of alternative therapies for mental illness. Insulin coma therapy, metrazol shock therapy, and electroconvulsive therapy (ECT) were the major treatments for disabling mental illness in the early 1900s; “talking” therapies such as those endorsed by Sigmund Freud were beyond the ken of the more seriously ill.^{239,279} The burden of psychiatric illness in the 1930s and 1940s was tremendous, with nearly half a million Americans living in psychiatric institutions in 1937.¹⁸⁷ Yet, as early as 1949, the year Moniz was awarded the Nobel Prize for his work

on psychosurgery, skepticism regarding the efficacy and safety of the leukotomy procedure began to surface.^{91,106} Ultimately, it was not these concerns that led to the demise of the prefrontal leukotomy as accepted therapy, but rather the advent of chlorpromazine in 1953 that precipitated the decline in popularity of the frontal lobotomy.²³⁹ This decline was hastened by popular and cultural changes in the 1960s, evidenced by the portrayal of psychosurgery in novels such as *One Flew Over the Cuckoo's Nest*, resulting in the banning of psychiatric neurosurgery in states such as California and Oregon.

Although the relatively nonspecific prefrontal leukotomy was discredited, important neuroanatomical work by James Papez and Paul Maclean paved the way for survival of psychiatric neurosurgery by elucidating of the structures of the limbic lobe and the connections between the frontal lobes and subcortical structures.^{173,218} Surgeons such as William Scoville and Geoffrey Knight developed and advocated more focal lesioning to avoid indiscriminate destruction of brain tissue.¹³⁷ Additionally, the subsequent development of stereotactic techniques that allowed more precise, circumscribed lesions mitigated unwanted side effects of surgery.^{100,101,187} The anterior cingulotomy was described in 1952,²⁹⁷ and continues to be performed for obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and bipolar disorder, with more than 1000 cases reported without a death.^{156,220} Subcaudate tractotomy was described in 1964 as a treatment for similar indications by disrupting the connections between the frontal lobe and amygdala;¹³⁶ Lars Leksell and Jean Talairach described anterior capsulotomy for OCD;^{161,274} and the limbic leukotomy was reported in 1973, combining attributes of the subcaudate tractotomy and anterior cingulotomy.¹²⁷ Treatment response rates for each of these procedures ranges from 30% to 70%, with relatively minimal long-term side effects.^{160,220}

Concurrently, organizations such as the International Society for Psychiatric Surgery (ISPS) were emphasizing the need for conscientious data reporting and multidisciplinary cooperation between neurosurgeons, neurologists, and psychiatrists.¹⁶⁵ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research established circumstances under which psychosurgical procedures could be appropriately performed; in 1980, the first Diagnostic and Statistical Manual of Mental Disorders (DSM) codified the diagnosis of psychiatric disorders. Thus, the foundation for the contemporary application of procedures such as cingulotomy was established.^{165,187,220}

Common belief dictates that the use of long-term high-frequency stimulation of the brain was “invented” by Benabid in 1987 for the treatment of movement disorders. Certainly, this group was the first to study the therapeutic role of DBS systematically. However, the literature reveals that the use of long-term electrical stimulation at deep brain targets was explored as early as the 1950s.⁵¹ The reversibility of treatment effects was noted by Irving Cooper in the 1970s.²⁴¹ The fact remains, however, that the safety and efficacy of DBS as a therapeutic modality was established by its use in the treatment of movement disorders.^{25,54}

Several convergent lines of evidence were important

for the redevelopment of DBS as viable for the treatment of psychiatric disease. Functional and anatomical studies have recharacterized many psychiatric diseases as dysregulation of brain networks rather than simply shortages or overabundances of specific neurotransmitters. Simultaneously, observations of affective changes in response to DBS in targets such as the subthalamic nucleus (STN) have provided evidence for the psychomodulatory effect of long-term stimulation of limbic networks.²⁷⁵ Initial attempts to treat OCD with DBS targeted one of the traditional surgical targets for ablation, the anterior limb of the internal capsule (ALIC).²¹⁰ These studies have emphasized the interaction between basal ganglia, frontal cortex, and the limbic lobe, and have provided a physiological justification for several targets for neuromodulation.

For example, investigations into the mechanism of action of antidepressant medications revealed mediation of widespread but anatomically specific changes in brain metabolism corresponding to clinical response to treatment, providing potential targets for neuromodulation by DBS.^{128,189} Characterization of network changes via multiple modalities such as PET, fMRI, and diffusion tractography similarly elucidated possible sites for intervention in OCD.^{43,109,182,212,226} Metabolic and functional imaging studies demonstrate network abnormalities in patients with Tourette syndrome (TS),²²⁷ posttraumatic stress disorder (PTSD),¹¹² addiction,⁴⁶ and obesity.^{71,153} Trials investigating the modulation of these targets with DBS for the treatment of psychiatric disease have followed.

Depression

Background

Major depression is one of the most common psychiatric illnesses and, because of the high incidence, accounts for a relatively large loss of life and productivity.^{15,131,154} Many patients with MDD respond to pharmacotherapy and psychotherapy, but approximately 20% of patients continue to experience symptoms after years of maximal medical and psychiatric therapy.^{64,126,242} Advances in imaging technology have improved our understanding of the neurophysiological basis of depression, and we now know that specific brain regions and specific neural circuits are dysfunctional in severe depression. Areas such as the cingulate cortex, dorsomedial orbital cortex, and ventral striatum (VS) show pathological activity in depressive states, and this activity normalizes with treatment and resolution of depression.^{40,83,188} In cases of treatment-resistant depression (TRD), destructive neurosurgical interventions can be used on the dysfunctional areas. Destructive procedures such as cingulotomy, anterior capsulotomy, and limbic leukotomy help a subset of patients, but all treated patients risk long-term neurological deficiencies.⁹⁰ In the past decade, DBS has arisen as a way to modulate the dysfunctional regions and circuits in a reversible, nondestructive fashion. Several different areas within the limbic lobe have been targeted, including subcallosal cingulate cortex (SCC), nucleus accumbens (NAcc), and the medial forebrain bundle (MFB). To date, the success rates of DBS have been commensurate with those of destructive procedures, but the major benefit is that DBS is adjustable

and largely reversible. A summary of pertinent trials and results is presented in Table 1.

Response to stimulation is usually quantified with the Hamilton Depression Rating Scale (HDRS), although Global Assessment of Functioning (GAF), Beck Depression Inventory (BDI), and Montgomery-Asberg Depression Rating Scale (MADRS) are used as well. A “response” to therapy is commonly defined as a decrease of 50% or greater, and an HDRS score less than 8 is considered “remission.” In general, patients eligible for DBS trials start with an HDRS score between 25 and 40, and will have exhausted all other treatments, including cognitive-behavioral therapy, pharmacotherapy, and ECT. Most patients in trials have had multiple episodes of major depression that last several years. In these severely affected patients, for many the response to DBS begins as soon as weeks after the start of stimulation and, for some, has been sustained for years. Once a response is achieved, it is usually sustained for as long as stimulation continues. Both battery depletion and accidental disconnections have resulted in rapid regression and even suicidal crises.^{108,169}

In light of the promise of DBS and the early results from open-label trials, a number of groups are now moving forward with larger randomized and blinded trials to better establish the safety and efficacy of this treatment paradigm. Although a number of questions remain regarding the appropriate targeting and programming of DBS in the treatment of depression, the technique has clearly improved the lives of many patients.

Subcallosal Cingulate Cortex

Among the DBS targets for treatment of depression, the best studied is the SCC, also referred to as Brodmann area 25 (BA25) or subgenual cingulate (Cg25). Increased activity in this region has been linked to depression, and

normalization of activity correlates with clinical response to treatment.^{83,189,200,209} The first trial stimulation of this region was introduced in 2005,¹⁹⁰ and since that time other independent groups have found a similar therapeutic response from DBS.^{108,194,230} Other than complications associated with device implantation, including surgical site pain and infection, few stimulation-related adverse effects have been reported.^{108,190,194} This population has a high risk for suicide and suicide attempts, and so should be monitored closely.^{169,190,194} Neuropsychological testing has shown no persistent cognitive impairment as a result of stimulation at this target.¹⁹²

In a 2005 report on the initial group of 6 patients, some participants experienced intraoperative improvement in moods with electrode placement. Such an effect is similar to the microlesioning often seen in patients with Parkinson disease (PD), in whom placing the electrode leads to an immediate improvement in motor symptoms.⁴² At 6 and 12 months postimplantation, the response and remission rates were 60% and 35%, respectively.¹⁹⁰ In the following years another 14 patients were added to the cohort, and at the 3- to 6-year follow-up points, among the 14 patients still being followed, the response rate was 64%.¹⁷⁰ During the follow-up period, 3 patients had died: 2 from suicide and 1 from colon cancer.¹²⁹ Other reports show similar findings. A group in Spain implanted DBS electrodes in 8 patients with TRD, and the majority of patients showed significant improvement at 1 year, with 62.5% of patients responding and 50% in remission.²³¹ A group in Germany implanted electrodes in Brodmann area 25 in 6 patients with TRD, and reported 2 patients (33%) in remission by 9 months.¹⁹⁴ In a US trial of 10 patients with MDD and 7 patients with bipolar II disorder, at 2 years postimplantation 65% of patients had a clinical response, and 41% of patients were in remission.¹⁰⁸ A more intensive multisite

TABLE 1. Selected literature on DBS for depression

Authors & Year	No. of Pts	Study Type	Target	Results	Outcome Scale	Adverse Events
Mayberg et al., 2005; Lozano et al., 2008; Kennedy et al., 2011	20	Case series	SCC	64% response, 43% remission	HDRS	2 suicides
Puigdemont et al., 2015	5	Randomized, double-blind, sham-controlled	SCC	80% response	HDRS	
Puigdemont et al., 2012	8	Case series	SCC	62% response, 50% remission	HDRS	1 suicide attempt
Merkel et al., 2013	6	Randomized, double-blind	SCC	33% response	HDRS	
Holtzheimer et al., 2012	17	Open label, single-blind	SCC	65% response, 41% remission	HDRS	9 relapses w/ battery depletion
Lozano et al., 2012	21	Multisite case series	SCC	29% response	HDRS	1 suicide
Malone et al., 2009	15	Multisite case series	VC/VS	53% response, 40% remission	HDRS	
Dougherty et al., 2014	30	Randomized, double-blind, sham-controlled, multisite	VC/VS	23% response; no significant difference btwn sham & control arms	MADRS	
Bewernick et al., 2010, 2012	11	Case series	NACC	45% response, 9% remission	HDRS	1 suicide
Schlaepfer & Bewernick, 2013	7	Case series	MFB	86% response by MADRS; 29% response by HDRS	MADRS, HDRS	
Kiening & Sartorius, 2013	1	Case report	LHb	Remission	None	
Jiménez et al., 2005	1	Case report	ITP	Remission	HDRS	

Pts = patients.

trial across 3 hospitals in Canada reported a 57% response rate at 1 month and 29% at 1 year, although the authors point out that a greater number of patients experienced clinical improvement.¹⁶⁹

Multiple groups are moving toward formalized trials, although sham-treatment periods in crossover and blinded trials have been limited because of concerns for patient welfare. For example, in one trial a 24-week sham-treatment period was stopped after 3 patients were recruited, because of a rapid regression to the depressive state with suicidal ideation.¹⁰⁸ Small studies, such as a recent double-blind, randomized, sham-controlled study in 5 patients, show definite response to DBS of the SCC in patients with TRD, with stimulation needed to maintain the response that was seen in 4 of 5 patients.²³¹ Despite the promising results, a number of questions remain unanswered, including the optimal electrode placement, optimal stimulation parameters, and patient selection criteria. The initial stimulation target was the gray/white matter junction adjacent to Brodmann area 25, but subsequent analyses of sites of efficacious treatment have argued that the nearby site Brodmann area 24, the associated SCC white matter tracts, or slightly more ventral sites may be more efficacious targets.^{97,108,230,236} Likewise, stimulation parameters are usually chosen based on empirical trials or optimal stimulation parameters used for other diseases, such as with PD.⁹⁴

The clinical outcome that should be optimized remains unclear: whether the immediate response to stimulation or the response after days or weeks. If a hyperacute response is seen in the operating room, more commonly the patient will improve over weeks to months.^{170,190} Conversely, all other antidepressant therapies reach their peak effect in weeks to months, so it is not unreasonable to expect that a similar time scale is necessary for DBS to reach its peak effect.^{83,189} Last, patient selection presents unique challenges in DBS for depression. Comorbidities such as anxiety and personality disorders are common in patients with MDD, and not all patients with TRD may have the same neurophysiological pathology susceptible to DBS in the SCC.

Ventral Capsule and Ventral Striatum

The ventral capsule and ventral striatum (VC/VS), also referred to as the ALIC, was initially a target for in the treatment of medically refractory OCD.¹⁶⁴ The idea for treatment of depression with DBS in the VC/VS came from reports of stimulation for OCD, where patients' depression and anxiety simultaneously improved.^{78,210} In an initial trial, 8 of 10 patients whose primary diagnosis of OCD had comorbid clinical depression, and from an average HDRS baseline of 21.1, by 36 months the average score had dropped to 15.4. More importantly, many patients had significant improvements in social functioning, including 6 who resumed work and/or school and 6 who had transitioned to independent living. During the course of the study, 6 patients had battery depletion or other unexpected interruption, which correlated with an acute return to depressed mood and a corresponding rise in HDRS from an average of 12.0 to 22.7.^{210,211}

Although these improvements in mood could have

been entirely secondary to change in circumstance from clinical improvement, evidence indicates that the neural pathology in OCD is concordant with that of depression.^{35,234,248} Since the initial reports, an open-label trial of VC/VS stimulation has been run with 15 patients.¹⁷⁹ At baseline, the patient cohort had an HDRS score of 33.1, which dropped to 17.5 at 6 months and to 14.3 at last follow-up. In looking at individual participants, 7 patients showed a response and 3 were in remission at 6 months postimplantation, and by the last follow-up 53.3% of patients were maintaining a response to treatment and 40% were in remission.¹⁷⁹ However, a larger, sham-controlled study of VC/VS stimulation did not show the same degree of positive results.⁵⁷ Thirty patients with TRD were recruited in a multisite trial that started with a 16-week period of either sham or active stimulation. Of those receiving active stimulation, 3 of 15 had a clinical response, but 2 of 15 had a clinical response from sham stimulation. The active-stimulation group did see a higher level of adverse effects from stimulation, including worsening depression, irritability, and mania. During the open-label phase, which included follow-up to a minimum of 24 months, only 6 of the 30 patients qualified as responders at 12 months, and that figure had only risen to 7 patients by 2 years.

Although these results appear discouraging, they should be examined in the context of other studies of DBS for TRD and the treatment of TRD in general, in that a 10% placebo effect is seen in surgery for depression.²⁴² Reported surgery-related complications included a small asymptomatic hemorrhage, intraoperative seizure, lead revision, and wound infection.^{57,89,179,211} Suicidality is also a major concern, with more than 10% of patients reported as attempting suicide in a larger study.⁵⁷ Stimulation-related adverse effects are seen most often with the ventral contacts closest to the VS, which are often the most efficacious for treatment as well.¹⁷⁹ Physiological effects of stimulation include tachycardia, nausea, changes in respiratory rate, and sweating; behavioral or psychological adverse effects include mania, hypomania, anxiety, panic, fear, worsening depression, unpleasant tastes or smells, and facial motor tics.^{89,179,215} In neuropsychological testing, 1 study reported a statistically significant but clinically questionable decline in some areas of cognitive performance, whereas other trials have noted an improvement in recall.^{57,89,179}

Nucleus Accumbens

The NAcc is a group of neurons located in the VS that has been closely linked to motivation and reward-seeking behavior.^{6,48} In humans, increased activity in this region is seen in association with reward-seeking behaviors: monetary reward, drugs of abuse, pleasurable music, and viewing attractive faces;^{9,31,34,58,122,139} decreased activity and dysfunction is seen in patients with depression, and so presents a reasonable target for focal neuromodulation.^{62,184,278} To date, only 1 group has focused on DBS of the NAcc for depression, although it should be noted that the electrode placement described in stimulation of VC/VS overlaps more ventral locations used for stimulation of the NAcc.^{28,179}

The initial trial of stimulation of the NAcc for TRD in-

volved 3 patients with severe depression. Each was refractory to repeated trials of psychotherapy, pharmacotherapy, and ECT. At the initiation of the trial, the average HDRS score for this group of patients was 33.7. Bilateral electrodes were placed in the VS, with the 2 deepest contacts targeted to the core and shell regions of the NAcc. The authors noted immediate changes in affect and improvement in mood and HDRS scores over the next several weeks, although for 1 patient the results were not sustained. After 1 week, the average HDRS score dropped to 19.7, and during a blinded period of sham stimulation, increased back to 29.3. The patients noted no euphoria from stimulation of the NAcc, and no adverse effects related to stimulation were noted.²⁵²

Based on these results, the authors initiated a larger, open-label trial of stimulation to the NAcc with first 10 and then 11 patients. The trial was initiated as a blinded, sham-controlled study, but the study design was changed after sudden resurgence of depressive symptoms during sham stimulation, as seen with other trials of DBS for depression.¹⁰⁸ This cohort of patients had similar characteristics, with the current depressive episode lasting an average of 10.8 years and an HDRS score of 32.5. The DBS electrodes were targeted as before to the core and shell subregions of the NAcc, and after 12 months of stimulation 5 patients were classified as responders and 3 patients were in remission. The patients who showed improvement with stimulation also had a reduction in anxiety, as measured with the Hamilton Anxiety Rating Scale.^{27,28} Comparing baseline to poststimulation PET imaging, patients showed decreased metabolic activity in the prefrontal cortex, subgenual cingulate cortex, and the thalamus, and they had increased activity in the precentral gyrus, which were consistent with changes seen in DBS of the SCC for depression.¹⁹⁰ Stimulation parameters were adjusted no more quickly than every 4 weeks, to account for a possible longer latency of antidepressant effect.

Although the patients did show acute improvement with stimulation, the acute response was not necessarily indicative of a long-term response.²⁷ Adverse effects from stimulation included flushing, anxiety, sweating, hypomania, agitation, and psychosis, with greater tension and restlessness noted at higher frequencies or pulse widths. Of note, one patient attempted suicide and another patient successfully committed suicide.^{27,28} With neuropsychiatric testing, the cohort of patients experienced a normalization of many of the previously below-average values, including attention, learning, memory, executive function, visual perception, and cognitive functioning. Deficiencies in these areas are often noted with depression, and the improvement may be marker of the resolving depression rather than an independent nootropic effect of stimulation in the NAcc.⁹²

Medial Forebrain Bundle

The success of DBS for TRD from not one but multiple different areas of stimulation has increased interest in stimulation of other neural pathways for a faster or more efficacious effect. The MFB is a white matter tract that mediates connectivity between many important cortical and subcortical regions, including the ventral tegmental area (VTA), NAcc, medial and lateral hypothalamus, lat-

eral and medial preoptic regions, and the bed nucleus of the stria terminalis.^{300,308}

Based on the connection between the VTA and NAcc from the superolateral MFB and the limited success of NAcc stimulation for depression,^{27,28} it was hypothesized that DBS of the superolateral MFB may be an equal or better target for treating depression.^{44,45} An open-label trial of DBS for TRD targeted the superolateral MFB in 7 patients, with stimulation sites selected based on diffusion tensor imaging and tractography.²⁵¹ Intraoperative stimulation produced acute and immediate effects, with the patients increasing visual and social contact with the clinical team. Similar responses were seen in the days and weeks after induction of stimulation; at 2 days after the start of stimulation, 6 of 7 patients were classified as responders, although this value dropped to 4 of 7 by 1 week. In this case, though, the authors defined clinical response and remission in terms of the MADRS rather than the more commonly used HDRS. Using the HDRS, only 2 of 7 patients would be considered to be responding, although both would also be considered in remission. This raises the question of whether MADRS or HDRS better represents the clinical improvement from DBS. Adverse effects of stimulation were predominantly oculomotor symptoms, including blurred vision, strabismus, and double vision.

Lateral Habenula and Inferior Thalamic Peduncle

Several smaller studies and case reports have demonstrated antidepressive effects of DBS in other sites in the brain, including the lateral habenula (LHb), inferior thalamic peduncle (ITP), and globus pallidus (GP). The ITP is a discrete fiber bundle connecting the nonspecific thalamic nuclei (midline, intralaminar, and paralamina) to the orbitofrontal cortex, and the ITP has been implicated in arousal, learning, and attention, and also in depression.^{115,175,250,288} Lesioning of this area and nearby ones has been used in humans to control TRD, and notably the subcaudate tractotomy, which includes the ITP, improves symptoms in depressive patients.^{134,287}

Bilateral DBS of the ITP was first demonstrated in 2005 in a case study of a woman with severe, treatment-refractory MDD comorbid with borderline personality disorder and bulimia.¹¹⁹ The patient had a baseline HDRS score of 33, and after starting stimulation this score dropped, corresponding to a rise in her GAF from 20 to 90. In the initial year after implantation, the patient experienced a moderate return of depressive symptoms when the stimulator was turned off for a double-blind testing period. After 3 years of stimulation, the patient chose to have the device explanted and did not have a relapse in depressive symptoms for the remainder of her follow-up.¹¹⁸ Side effects from stimulation of the ITP included anxiety, nystagmus, dyspnea, sweating, and tachycardia. Limited improvement has been noted in some areas of memory and cognitive function and no decline in function was noted on neuropsychological testing.^{118,119}

Stimulation of the LHb for TRD has been documented in a brief case report. The LHb has extensive connections to serotonergic, noradrenergic, and dopaminergic nuclei; hyperactivity in the LHb is seen in animal models of depression,²⁶⁴ and similar metabolic overactivity is seen in

the area in patients with depression.²³² Based on animal and human studies, Sartorius and colleagues implanted bilateral electrodes in the afferent fiber bundle approaching the LHb in 2 patients with TRD.^{133,246} The first patient's HDRS score decreased from 45 at baseline to less than 5 following stimulation, and the second patient was reported to have a greater than 50% decrease in HDRS. Interruption of the stimulation resulted in rapid relapse in depressive symptoms in both patients, which slowly abated after resumption of stimulation. The authors did not report the full range of stimulation parameters, but the first patient did require an increase in voltage from 5 V to 10.5 V to achieve full remission, which suggests that frequent battery replacements may be a complicating factor in long-term treatment. No adverse effects were reported.

Ethical Considerations

Limited data exist on the use of mood-enhancing stimulation in humans, and even less for areas known to be involved in motivation. In rats and other animal models, subjects will work for VTA self-stimulation in much the same way as for drugs of abuse such as cocaine.²⁶ The purposeful stimulation of cingulum, NAcc, and associated fiber tracts in humans may be justified as an experimental treatment for severe, chronic, and disabling depression, but this is nevertheless an area rife with potential ethical concerns. If DBS is approved for TRD, a concern would be the perceived overuse of the technique in a young and otherwise healthy population, who are already a substantial portion of the population on antidepressants. Another issue of consideration is the potential hedonic effect of stimulation. In animals, stimulation of the some of the same target areas used for TRD can produce behavioral effects similar to that of drugs of abuse; clinicians must be aware of the potential for abuse. Most medical systems use rigorous controls intended to prevent the misuse of this technology, but some countries may not be as closely monitored. There rises the potential for unorthodox, unethical, or abusive applications.

Steps have been taken to address the considerable ethical dilemmas involved in stimulation of the limbic system. Multiple authors have required consent from not just the patients, but also one or more caregivers, and have added a mandatory waiting period before consideration of DBS.²⁷ Guidelines are being established for use of stimulation for psychiatric indications, and these are all steps in the right direction.²⁵³ Before launching into greater use, the psychiatric and neurosurgical communities must spend additional time in open public discussion of the ethics, applications, and ramifications of the technique. Otherwise, the danger exists of repeating the events of the last century, when overuse and misuse of neurosurgery for psychiatric indications led to public backlash and the ban of such techniques in certain states (e.g., Oregon and California).

Obsessive-Compulsive Disorder

Background

Obsessive-compulsive disorder is a disabling psychiatric disease defined by repetitive, intrusive, and persistent thoughts combined with excessive and repetitive ritualistic

behaviors. It affects as much as 1%–2% of the general population and, because of the high prevalence and relatively high suicide rate, is a leading cause of disability.^{24,29,107,217} The majority of patients affected with OCD will improve with treatment, including pharmacotherapy (selective serotonin reuptake inhibitors, neuroleptics, and benzodiazepines) and cognitive-behavioral therapy, but as many as 10% of patients do not respond to these treatments.^{32,52} For these patients with treatment-refractory illness, a number of surgical and ablative options are available. Anterior capsulotomy and limbic leukotomy typically have a 50%–60% success rate, and the less frequently used subcaudate tractotomy and cingulotomy have slightly lower response rates.^{22,82,116}

Early attempts with DBS addressed the same targets used for ablation, specifically the ALIC.^{14,210,211} The patients in these preliminary studies were all disabled from severe OCD that had lasted for years or decades, were unresponsive to multiple and maximal pharmacological trials (including augmentation with clomipramine and a mood stabilizer such as lithium), and had little improvement from cognitive-behavioral therapy. Following preliminary trials with ALIC, the percent of patients responding improved as the target migrated slightly from the ALIC toward the VC/VS and NAcc.⁸⁸ Trials of DBS for OCD had similarly positive results with stimulation to the STN, ventral caudate, and ITP. Results of some of the more pertinent studies are summarized in Table 2.

The success of OCD treatment with stimulation at several different sites contributes to the hypothesis that the disease is a result of dysfunction in an entire corticostriatothalamocortical circuit, rather than a single site.^{93,249,296} Multiple studies of patients with OCD have most consistently noted hyperactivity in the orbitofrontal cortex, anterior cingulate cortex, and VS, but other metabolic abnormalities are seen in the amygdala, thalamus, cerebellum, prefrontal cortex, motor cortex, and parietal cortex.^{233,272,283} Similar to capsulotomy, DBS normalizes the hyperactivity in the orbitofrontal cortex, the VS, and the amygdala, and clinical improvement correlates with the decrease in metabolism in VS and other hyperactive regions.^{88,211,283}

Treatment-based improvements in OCD symptoms are quantified with the Yale-Brown Obsessive-Compulsive Scale (YBOCS), which has 20 points for obsessive symptoms and 20 points for compulsive symptoms, for a total score out of a possible 40 points.⁸⁶ Successful treatment of OCD is typically defined as a 35% reduction in the YBOCS score from baseline. Anterior capsulotomy, for instance, achieved a response in roughly half of patients.¹⁹⁶ Early experiments with DBS for OCD had responses in slightly less than half of patients, but with improved understanding of the circuit and targeting, approximately 60% of patients who receive DBS now respond to therapy, with a subset of those achieving minimal symptoms and YBOCS scores of less than 10. In a review of the literature on DBS for refractory OCD, the Congress of Neurological Surgeons found sufficient evidence to recommend the use of DBS for treatment-refractory OCD.⁹⁸ This procedure has been approved for treatment of OCD in Europe, and in the US a humanitarian device exemption was granted for the use of DBS in refractory OCD. It is important to keep

TABLE 2. Selected studies of DBS for OCD

Authors & Year	No. of Pts	Study Type	Target	Outcome	Rating Scale
Sturm et al., 2003	4	Case series	NAcc	Near total response in 3 of 4 pts	
Mallet et al., 2008	8	Randomized, cross-over, double-blind, multisite	STN	Mean 32% reduction in symptom severity; 30% increase in global function	YBOCS, GAF
Huff et al., 2010	10	Randomized, cross-over, double-blind, sham-controlled	NAcc	25% reduction in symptom severity in 50% of pts	YBOCS
Denys et al., 2010	16	Open label; randomized, cross-over, double-blind, sham-controlled; then open label	NAcc	Mean reduction of 46% during open phase; 25% reduction in symptom severity over sham stimulation	YBOCS
Greenberg et al., 2010	26	Case series	VC/VS	73% of pts responding w/ >25% decrease in severity	YBOCS
Jiménez et al., 2013	6	Case series	ITP	Mean reduction of severity score by 51%; functional score increased by average of 68%	YBOCS, GAF

in mind that a humanitarian device exemption is granted as a way to facilitate further research, but does not equate with FDA approval, and concerns have been expressed about the possible misuse of this exemption.⁶⁷ Any institution that wishes to use the treatment requires institutional review board approval, and all patients must indicate additional consent acknowledging that DBS for OCD is an experimental therapy without established efficacy.

Anterior Limb of the Internal Capsule, VC/VS

The ALIC was previously used in the treatment of refractory OCD as a target for capsulotomy or Gamma Knife ablation. The first case series of DBS for OCD aimed for the same region, and reported improvement in 3 of 4 patients, although the improvement was not quantified.²¹⁰ In a follow-up report, 2 additional patients had been added to the cohort, and of the 6 patients, 4 of them responded to the treatment—they had a decrease in YBOCS greater than 35%.²¹¹ As has been seen with several trials of DBS for depression, the sham phase of the study had to be stopped early because of concerns for patient welfare with rapid regression of OCD and depressive symptoms. Two larger follow-up studies from independent institutes showed better numbers of patients responding. A combined study from Butler Hospital and Cleveland Clinic presented long-term data in 10 patients with severe, chronic OCD.⁸⁹ In this open-label study, the authors found that of the 8 patients followed to 36 months, 4 showed a clinical response, 2 other patients showed subthreshold response, and 5 of these patients were able to transition to independent living. A study at the University of Florida used a double-blind, staggered-onset design to compare sham versus active stimulation. Of the 6 patients who received implanted electrodes, 4 were classified as responders, and the other 2 “nonresponding” patients requested to keep the system in place because of a perceived benefit.²¹⁵ A recent small case series from Korea targeted the VC/VS with similar results; at 2 years postimplantation, 4 of 4 patients were classified as responders and 2 of 4 patients were in remission.²⁴⁰

To overcome the limitations from relatively small numbers of patients, a meta-analysis used the data from these first 3 independent studies to better show the trends in im-

provement after treatment.⁸⁸ From the combined patient data, the 26 patients had a baseline YBOCS score of 34, which dropped to 21 after 3 months of treatment and to 20.9 at 36 months of treatment. On the whole, these patients showed a clinical improvement in social functioning, with a pre- and posttreatment GAF of 34.8% and 59%, respectively. On the individual level, 61.5% of patients were responders by the last follow-up, and an additional 11.5% of patients had an improvement of at least a 25% decrease in YBOCS scores. From this meta-analysis, a trend in targeting was noted to correspond with improvement in patient outcomes. Patients appeared to have better outcomes as placements moved posterior and ventrally, and the stimulation settings almost always involved the more ventral leads, which are directly in or at the border of the NAcc. To reflect the change in targeting, this placement has been referred to as the VC/VS. One additional advantage of targeting this region has been similar clinical response with lower voltages and pulse widths, and thus longer times between battery changes.

Targeting VC/VS appears to improve outcomes, but a second part of the equation, the optimal stimulation parameters, remains an open question. Most studies have started with commonly used stimulation parameters and explored variations in frequency, pulse width, voltage, and contact combinations. No clear combination of settings has emerged as most efficacious, except that responses to stimulation almost always involve contact 0 or contact 1 (typically placed in or at the boundary of the NAcc). However, the improvement in functioning appears to occur over several weeks to months, so the correspondence (or lack thereof) between acute response and long-term improvement remains debated. One commonly noted response during the stimulation test has been the presence of acute mood improvement and a smile contralateral to stimulation, which appears to be predictive of long-term response.^{85,99,213} Contralateral smile is typically seen with stimulation in the deepest contacts, as are other adverse or unexpected effects on mood. Adverse effects are commonly seen at higher amplitude, larger pulse widths, or more ventral stimulation contacts, and the range of effects on mood include euphoria, giddiness, anxiety, panic, fear,

and acutely worsening depression. More severe adverse effects include occasional reports of hypomania and at least 1 case of mania that required hospitalization.^{85,99,215,260}

In patients with treatment-refractory OCD, a strong comorbidity exists with MDD, but whether the improvement in mood is a function of the stimulation or secondary to the improvement in primary OCD symptoms remains unclear; antidepressant effects have been seen independent of improvement in OCD function. However, suicidality and suicidal ideation have been seen with sudden DBS stops or battery depletion in patients treated for OCD or depression.^{1,85} Indeed, blinded studies on the effects of DBS have been limited because of concerns of worsening mood when attempting cross-over design. Despite the range of acute mood-related adverse effects, no consistent negative effects on cognitive or executive function have been reported from long-term stimulation.^{78,85,89,215} Non-mood-related adverse effects from stimulation include elevation of heart rate, flushing, seizure, and perception of heat.^{85,215} Surgical complications and adverse effects reported are typical for DBS placement, including infection, lead revision, headache, surgical site pain, and rare intraparenchymal hemorrhage.⁸⁸

Nucleus Accumbens

The NAcc is a discrete site in the VS that has been extensively tied to motivation and learning. The site is notable for its connections to other important limbic and motor regions, with efferent projections to the pallidum, striatum, thalamus, prefrontal cortex, and anterior cingulate cortex. The NAcc is best recognized because of the dopamine-containing projection from the VTA and the high concentration of D1- and D3-dopamine receptors in the NAcc.^{95,103} In studies conducted with animals, electrical stimulation of either the VTA or the NAcc is sufficient to affect motivational behavior, and animals will perform tasks for self-stimulation similar to what is seen with self-administration of drugs of abuse.²⁹⁹ Dysfunction of the VS is seen with OCD, and DBS for treatment-refractory OCD has gradually migrated to targets with significant overlap with the NAcc. Indeed, if an in-depth anatomical comparison is made between stimulation aimed at the VC/VS and at the NAcc, few differences can be seen in actual areas of stimulation.³⁰ However, the trajectories used and the contact placements do differ in some cases, so the NAcc will be discussed separately here.^{16,53}

The first reported cases of DBS specifically targeted to the NAcc for OCD were initially focused on unilateral stimulation.²⁷¹ The authors implanted electrodes bilaterally in 1 patient, but found that right-sided NAcc stimulation was as efficacious as bilateral stimulation, so for the following 3 patients they implanted unilaterally. Of these patients, 3 of 4 had reported resolution of OCD and anxiety by 24–30 months; the fourth patient had no benefit, which was attributed to a caudally and ventrally misplaced electrode. The authors did not quantify the degree of improvement, but did note that battery depletion led to rapid relapse of depressive symptoms, which was promptly resolved with replacement. A follow-up study in which unilateral implantation in the NAcc was used and a 3-month double-blind comparison found some improvement in patient outcomes,

but the clinical response was less than had been observed with other similar placements. Specifically, at 1 year only 1 patient qualified as responding to treatment, with a YBOCS score decrease greater than 35%, although 4 other patients had a decrease between 25% and 35%. During the cross-over period, these patients showed a moderate but significant decrease between baseline and stimulation, but no statistical difference was found between the stimulation and sham.¹¹¹ Despite the moderate improvements in OCD symptomatology, a significant improvement was seen in depressive symptoms, as measured with the BDI. In light of these modest gains, a systematic review by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons found insufficient evidence to recommend unilateral DBS for OCD.⁹⁸

Another study was published the same year that targeted the NAcc with bilateral implantation, and the authors reported that 9 of 16 patients responded with a YBOCS score decrease greater than 35%, and 3 others had a decrease greater than 20% but less than 35%.⁵³ The double-blind comparison had to be cut from 3 months to 2 weeks due to concerns for patient welfare and depressive relapse, and even then 2 patients refused to participate for fear of losing improvements. In the 2-week cross-over double-blind comparison, the authors found a significant difference (8.8 points) between sham and treatment conditions on the YBOCS, indicating clinical improvement from stimulation. The difference between these 2 studies may have been placement; in their work, Denys et al. noted that they specifically aimed to stimulate the NAcc at the border of the internal capsule and the bed nucleus of stria terminalis.^{53,111} Stimulation of the stria terminalis for OCD has not been extensively studied, but in a limited case series it was found to be comparably efficacious to NAcc stimulation.¹¹³ The specific target remains unclear, though, with another group targeting the junction between the NAcc and the caudate nucleus. These authors argue that the improvement in compulsive symptoms is actually secondary to caudate stimulation, whereas NAcc stimulation primarily mitigates the depressive symptoms.^{16,17,93} The data for this argument are based on small case studies, but many studies with ventral striatal stimulation note a consistent improvement in depressive symptoms that precedes the improvement in OCD symptoms, and stimulation-induced improvement in depression has occurred without improvement of obsessive and/or compulsive symptoms.⁵³

The adverse effects noted with implantation and stimulation are comparable to those seen with ALIC and VC/VS. Surgical site infections, pain, and headache are seen occasionally, and intraoperative and postoperative stimulation can elicit physiological and mood changes. The most common side effect of NAcc stimulation appears to be elevation of mood and hypomania, although subjective reports of word-finding difficulty and forgetfulness are also noted.^{53,111} Anxiety, agitation, and drowsiness were occasionally noted, and 1 patient had suicidal ideation, although the timing was inconsistent with changes in stimulation settings.¹¹¹

Subthalamic Nucleus

Interest in stimulation of the STN for OCD grew after

multiple case reports were published describing incidental OCD symptom relief following DBS implantation. The STN is a common target for the motor dysfunction seen in PD, but the area is involved in not just motor control, but also has cognitive and emotional functions. Based on cortical inputs, the region can be roughly subdivided into motor, associative, and limbic regions, with the anteromedial and ventromedial sections receiving more input from the limbic and associative areas, respectively.^{124,219} Stimulation of STN can result in reproducible alterations in mood,^{144,178} and recordings from the limbic and associative areas of the STN have revealed abnormalities in neuronal activity unique to OCD.^{223,293} Others have hypothesized that the STN is involved in integration of motor with limbic and associative functions, such as regulating impulse control and stop behaviors.^{19,61} Stimulation of the STN in humans has been reported to modulate other impulsive and compulsive behaviors, such as gambling, as well as resolving OCD personality traits.^{11,18}

The first published case of STN stimulation alleviating symptoms in a patient with a formal diagnosis of OCD appeared in 2002.¹⁷⁶ Two patients with both PD and OCD had received standard bilateral STN implantation for PD, but with stimulation onset both patients experienced notable relief from OCD symptoms within 1 week. The changes in obsessions and compulsive behaviors appeared to be independent of the motor function; one patient had a large improvement in motor symptoms, whereas the other had relatively little improvement. When the effect on OCD symptoms was quantified, it was found that the patients had an 81% and an 83% decrease in YBOCS scores, corresponding to remission of their OCD. When the stimulation sites were examined, it was found that the active contacts were slightly anteromedial to the usual placement.¹⁷⁸ A second patient was also reported to have similar improvement in OCD symptoms with stimulation at slightly more medial and anterior contacts than are usually targeted. In this case, at 1-year follow-up, the patient had a decrease in YBOCS score from a baseline of 32 to a poststimulation score of 1.⁶⁹

Following these positive reports, a thorough, double-blind, cross-over study on the therapeutic effects of DBS of the STN on OCD was performed.¹⁷⁷ The authors recruited patients without PD but with a primary diagnosis of severe, chronic OCD who had not achieved relief from multiple trials of pharmacotherapy and cognitive-behavioral therapy. All received bilateral lead placement in the STN, with the target being 1 mm medial and 2 mm anterior to that typically used in PD. After a period of stimulation tuning, the patients were randomized to either a sham period or a stimulation period. During the 3-month trial period, the average YBOCS score for stimulation was 19 ± 8 , whereas the score for patients receiving sham treatment was 28 ± 7 . The scores for GAF were similarly indicative of a therapeutic effect, with an average score on stimulation of 56 ± 14 versus 43 ± 8 with sham treatment. On an individual level, 75% of patients showed a clinical response to stimulation.

Analysis of the therapeutic sites for stimulation found that the majority were in the anteromedial STN, and a much lower minority were in the zona incerta and internal capsule.¹⁷⁷ The rate of surgery-related adverse events was

similar to that seen with lead placement for PD: 1 hemorrhage that resulted in a minor but permanent palsy, and 2 infections that required explanting at least a portion of the system.¹⁴³ Stimulation-related adverse events were largely limited to transient motor or mood dysfunction that resolved with changes in stimulation parameters. Despite the positive results from this study, the mechanism of action by which stimulation in the STN improves OCD symptoms remains unclear. On functional imaging, the STN does not display unusual activity or metabolic changes in conjunction with OCD. Microelectrode recordings from the STN in patients with OCD have revealed bursting activity similar to that seen with PD, but the significance of this finding remains uncertain, because little is known about firing patterns in STN in healthy humans.^{223,293}

Inferior Thalamic Peduncle

The ITP is of interest for OCD because it connects the nonspecific thalamic nuclei with the orbitofrontal cortex, a region that is consistently hyperactive in patients with OCD.^{115,175,250,267} Attempts have been made to regulate orbitofrontal hyperactivity through lesioning of the ITP via subcaudate tractotomy, with some success.²⁶² The ITP has possible advantages over other current targets for DBS; it is anatomically and functionally distinct from the surrounding tissue, which may lower rates of misplacement and stimulation-induced adverse effects.

Six patients with treatment-refractory OCD received bilateral lead implants in the ITP and were followed for 1–4 years.^{118,120} Stimulation parameters were similar to those used in most other applications of DBS, with a frequency of 130 Hz, pulse width of 450 μ sec, and variable voltage and electrode contacts. The patients had a mean baseline YBOCS score of 35, which decreased to 17.5 with stimulation at 1 year. On the individual level, at 1 year all patients achieved a response, defined as a greater than 35% decrease in YBOCS score. The GAF scores were reported for 5 patients, and from a baseline of 20%, 5 patients eventually achieved a GAF of 60% or greater, with 2 patients as high as 80% (independent living). Battery depletion or dysfunction correlated with a rapid relapse in symptoms. No consistent detrimental effects were seen in neuropsychiatric testing, and no adverse effects were noted from target stimulation. Side effects of stimulation outside of the target included transient confusion, tachycardia, and hypertension. This cohort of patients had a relatively high number who had substance abuse comorbidities, and the trial was complicated by a death from cocaine overdose in 1 patient. In the patients with substance abuse comorbidities, stimulation did not appear to relieve or worsen their substance abuse, which is an open topic of interest with other DBS targets for OCD such as the NAcc.¹²⁰

Anorexia Nervosa

Anorexia nervosa (AN) will affect as many of 2% women in their lifetime, and is one of the most difficult psychiatric diseases to treat.¹⁰⁵ Acute treatment of AN focuses on medical stabilization of the cardiac, neurological, and musculoskeletal complications from prolonged starvation, and longer-term care goals are aimed at changing

behaviors. Selective serotonin reuptake inhibitors, neuroleptics, and cognitive-behavioral therapy are the primary treatment modalities, but despite optimal treatment, relapses are common. As many as 30% of patients show little or no improvement with treatment, and long-term mortality is as high as 15% from suicide or medical complications of starvation.³¹¹ In recent years, unique neural changes underlying AN have been delineated, suggesting that a distinct anatomical or physiological neuropathology is involved. For end-stage cases of AN, limbic leukotomy, thalamotomy, and anterior capsulotomy lead to improvement in some patients, but use of these procedures is limited by the potential for permanent side effects.^{23,198,309} In recent years a renewed interest in neurosurgical treatment of AN has arisen due to the success of DBS for OCD, because of the high comorbidity and similarity in patterns of behavior.^{13,283}

Exploration of DBS for anorexia is still in the earliest stages, with only a few reported case studies and small trials, and no standardized criteria for treatment have yet been established. Sites for stimulation have focused on the same targets used for depression and OCD, namely the NAcc, VC/VS, and SCC. Results are summarized in Table 3. In a single case report of stimulation in VC/VS for AN, the site of active stimulation was actually in the ventral caudate, but the patient was reported to have improved.¹⁹¹ In 2 patients in whom electrodes were implanted in the NAcc, stimulation was correlated with improvement in weight and attitudes toward food. The 2 patients had baseline body mass indexes (BMIs) of 13.3 and 12.9, and at 1-year follow-up their BMIs were increased to 18 in one and 20.8 in the other.²⁹² These 2 patients also had normalization of core temperature and heart rate, and decreased anxiety and depressive symptoms. A slightly larger study from China on stimulation in the NAcc focused on DBS in the NAcc in 4 female patients, who experienced an increase in average BMI from 11.9 to 19.6 in a multiyear follow-up.³⁰³ Despite the fact that all patients had the system explanted, they all were reported to have reached remission. However, these results should be approached with caution because the patients were all adolescents (16–17 years old), and none had a history of AN longer than 2.5 years. Given the natural history of this disease (three-quarters of adolescent AN resolves with standard treatment after 4–5 years), questions arise regarding the completeness of medical and psychiatric treatment before transitioning to neurosurgery.²⁶⁹

The second target that has been tested for DBS in AN has been the SCC. In a case report on DBS in the SCC, a patient with AN had a clear correlation between her depressive episodes and eating disorder relapses.¹¹⁴ The pa-

tient presented with a BMI of 19.7, and in the 2 years after electrode implantation in the SCC she had no reliable improvement in BMI, but did have a significant improvement in approach toward food, as measured with the Eating Attitudes Test (EAT_26).⁸⁰ A second, larger study on AN and DBS involved bilateral SCC electrode implantation in 6 patients with long-standing, treatment-refractory AN.¹⁶⁶ At 9-month follow-up, 3 of 6 patients were above their historical baseline BMI, but only 2 of those patients achieved a BMI greater than 18.5. Four of the patients had comorbid depression, and despite the moderate gains with their AN, these patients saw significant improvements in mood and anxiety. This study was limited by the relatively short follow-up (9 months after implantation). The authors rigorously reported adverse effects during the protocol, which notably included an air embolism during implantation and one instance of seizure during programming.

Tourette Syndrome

Background

Tourette syndrome is defined by the presence of motor and vocal tics—rapid, repetitive, stereotyped movements or vocalizations—that manifest before the age of 18 years and last for more than 12 months in the absence of secondary causes.¹⁵⁷ Disease prevalence in children and adolescents has been estimated at 0.8%, although this figure drops to 0.05% in adults.¹³⁸ Symptoms typically present before puberty, with an average age at onset of 6.4 years, and a male predominance (4.4:1).^{20,237} The syndrome is often comorbid with other neuropsychiatric diseases such as OCD, attention deficit hyperactivity disorder, and other behavioral conditions.⁷⁶ Most patients have improvements in their tics during late adolescence and early adulthood, but a subset of patients continues to experience disabling tics that are refractory to behavioral therapy and pharmacotherapy.^{203,206}

Individuals with TS have demonstrated structural and functional abnormalities within the corticostriatocortical loop,^{261,302} although the primary site of abnormality remains controversial.⁶⁵ In fact, imaging studies in individuals with TS reveal widespread abnormalities in the size, connectivity, and microstructure of the caudate nucleus,^{158,222} thalamus,¹⁷⁴ sensorimotor and prefrontal cortex,²⁶⁸ cerebellum,²⁷⁷ corpus callosum,⁴¹ amygdala and hippocampus,²²¹ and limbic structures such as the amygdalae and NAcc.²⁰⁷ Electrophysiological studies implicate overexcitability and dysregulation of frontal-subcortical circuitry resulting in deficiencies in processing of stimuli.^{121,216,276,284} Histopathological and genomic studies provide evidence of structural alterations in the composition

TABLE 3. Selected studies of DBS for AN

Authors & Year	No. of Pts	Study Type	Target	Outcomes
McLaughlin et al., 2013	1	Case report	VC/VS	Healthy weight
Lipsman et al., 2013	6	Prospective, open label	SCC	50% w/ improvement in weight to near normal BMI
Wang et al., 2013	2	Case series	NAcc	Recovery of normal weight & menstruation
Wu et al., 2013	4	Case series	NAcc	Mean increase of 65% body weight; average postop BMI 19.6

of inhibitory γ -aminobutyric acidergic and cholinergic interneurons in the sensorimotor areas of the striatum and in the GP internus (GPi), suggesting an imbalance between inhibitor and excitatory regulation.^{125,162} Evidence for neurotransmitter dysfunction has been shown in dopaminergic,²⁶⁶ serotonergic,³⁰¹ cholinergic,³⁰⁶ glutamatergic,⁵ and intracellular second messenger transmission.²⁶⁵

With so many physiological and anatomical sites implicated in the pathophysiology of this disease, it may be no surprise that more than 7 different targets for DBS have been investigated in trials for the treatment of TS, which are summarized in a recent review by Schrock et al.²⁵⁴ The most common targets involve the centromedian-parafascicular thalamic complex (CM-PF) and the GPi. Selected studies are presented in Table 4, but see the aforementioned review for a comprehensive summary.

Centromedian-Parafascicular Thalamic Complex

The CM-PF is extensively connected to the basal ganglia, to sensory, motor, and premotor cortices, and to the anterior cingulate cortex, and it has been shown to be related to attentional processing. In particular, it is involved in the attentional shift to motivationally relevant stimuli.¹⁹⁵ Studies targeting the CM-PF for DBS extensively cite early work done by Hassler and Dieckmann, who reported control over obsessional symptoms with thalamic ablation in 1970.²³⁵ Based on this early work, successful control of tics with DBS at the CM-PF was reported in 1999,²⁸⁵ and more than 20 studies have subsequently reported successful treatment of TS with stimulation in the CM-PF and ventral tier of the thalamus.²⁵⁴ The majority of studies constitute Class IV evidence in the form of case reports^{2,4,21,159,263,289} or small case series,^{123,199,224,247,256} with many containing previously reported patients.^{149,183,225,257,290} Reported outcomes are variable, with 1 report of worsening tic behavior with stimulation,⁶⁰ and some series reporting 100% reduction in tic frequency.^{146,285} Three studies meet Class III evidentiary criteria, with a total of 16 patients who showed 50%,³ 44%,¹⁷² and 19%²¹⁴ mean improvement in Yale Global Tic Severity Score (YGTSS).

In addition to the usual adverse events associated with DBS implantation, reported complications include visual disturbances,²⁵⁶ decreased energy levels and sexual function,^{3,290} reduced verbal fluency,¹⁴⁶ an increased rate of wound healing and hardware complications, probably related to tic behavior,^{2,225,257} and 1 report of psychogenic complications eventually leading to death by starvation.⁶⁰

Globus Pallidus

Side effects of thalamic DBS for TS and evidence supporting the involvement of dopaminergic circuitry in the pathophysiology of tic development prompted exploration of stimulation at the GP for treatment of TS. A case report detailing the 47% reduction in YGTSS associated with stimulation at the GPi for TS was published in 2005.⁵⁵ Multiple case reports^{50,56,59,79,258} and small case series^{49,185} followed, with the largest series reporting a mean decrease in YGTSS of 50%.³⁹ The only Class III evidence supporting use of GPi in TS comes from 2 single-subject, blinded cross-over trials comparing stimulation at the CM-PF to that of the GPi in patients implanted at both sites. Both

patients exhibited approximately 65% reduction in tic severity with stimulation at either site.^{110,294} Adverse events related to stimulation included bradykinesia,⁵⁵ and reports of infective or hardware-related complications were similar to those seen in patients with thalamic stimulation.^{185,259}

Other targets investigated for DBS to treat TS include the ALIC/NAcc^{68,152,208,307} and STN.¹⁸⁵ Results range from a 20% worsening in tic severity³⁸ to near abolition of tic behavior.¹⁸⁶ Although outcomes have been favorable in most cases, most reports were uncontrolled and the outcomes measures varied between studies. Comorbidity with other neuropsychiatric disorders such as attention deficit hyperactivity disorder and OCD is common in patients with TS, further complicating treatment. To address some of this ongoing uncertainty, the Tourette Syndrome Association International Deep Brain Stimulation (DBS) Database and Registry Study Group issued updated recommendations for the treatment of TS with DBS in December 2014, highlighting the need for a multidisciplinary approach, emphasizing pre- and postoperative outcome measures, and proposing inclusion and exclusion criteria for DBS in patients with TS.²⁵⁴

Addiction and Substance Use Disorder

The term addiction is used loosely in modern society, generally to denote a pattern of persistent repetitive behaviors in the face of adverse consequences, whether medical, psychological, or societal. Commonly referenced addictions include substance abuse, gambling, and even Internet gaming, all of which are now listed as disorders in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders. The common element among these conditions is recurrent problematic behavior accompanied by a preoccupation with the behavior. Although substance abuse is often accompanied by a physical component, the persistent behaviors and preoccupations extend well after the physical withdrawal has faded, and craving and relapse rates are high even after detoxification.³³ Given this pattern, it is acknowledged that the development of addiction is not simply based on the acute impact of the substance or behavior,^{66,142} but instead represents disequilibrium in the reward system.²³⁸

Animal models and neuroimaging studies in humans have identified broad alterations in prefrontal, limbic, and cortical areas that are involved in addiction and maladaptive behavior,^{72,84,117} but the most consistent core regions appear to be involved in the dopaminergic connection between the VTA and the NAcc, which modulates learning, memory, and repetitive behaviors.¹⁴² Animal studies on the NAcc have shown that stimulation consistently attenuates and modulates learned behaviors related to alcohol, cocaine, and other habit-forming substances,^{87,135,286} and DBS in the NAcc has been successful in treating other disorders of repetitive behaviors.^{30,303} Thus significant interest exists in stimulation of these areas for the treatment of the behavioral component in addiction and substance abuse disorder. Ablative surgeries targeted at the NAcc have been used for several years in China with mixed results, but a relapse rate of 50% and ethical concerns now limit the use of destructive procedures in the treatment of addiction.^{163,304,305}

TABLE 4. Selected studies of DBS for TS

Authors & Year	No. of Pts	Study Type	Target	Outcome	Outcome Measure	Stimulation-Related Adverse Events
Maciunas et al., 2007	5	Prospective, randomized, double-blind, unilat vs bilat stimulation	CM-PF	Significant decrease in tic count & tic severity scores; mean 44% decrease in YGTSS	mRVRS, YGTSS, TSSL	1 episode, acute psychosis
Servello et al., 2008	18	Case series	CM-PF	All pts w/ significant decrease in tic severity; not otherwise quantified	YGTSS	None
Porta et al., 2009	15	Case series	CM-PF	Mean 52% reduction in tic severity; all pts w/ perceived improvement in social function	YGTSS, VAS	None
Ackermans et al., 2011	6	Double-blind, randomized, cross-over, sham controlled	CM-PF	Mean 37% reduction in tic severity during stimulation; long-term 50% reduction in severity	YGTSS	Decreased energy, visual disturbances
Okun et al., 2013	5	Prospective evaluation of scheduled vs continuous stimulation	CM-PF	Improvements did not meet goal of 50% reduction in tic severity; significant improvements were nonetheless noted	YGTSS	
Houeto et al., 2005	1	Prospective, double-blind, randomized stimulation at CM-PF vs GPi	CM-PF, GPi	70% reduction in tic severity at both sites	YGTSS	
Welter et al., 2008	3	Case series	GPi	Reduction in tic severity of 65%, 96%, & 74%	YGTSS	
Martínez-Fernández et al., 2011	5	Case series	GPi	Anteromedial GPi reduced tic severity more than posterolat electrodes (54% vs 37% reduction)	mRVRS	
Martínez-Torres et al., 2009	1	Case report	STN	Reduction of tic frequency by 89%	Count on 10-min video	
Kuhn et al., 2007 ¹⁵²	1	Case report	ALIC	41% reduction in severity	YGTSS	
Neuner et al., 2009	1	Case report	NAcc	86% reduction in severity at 3 yrs	YGTSS	

mRVRS = modified Rush video rating scale; TSSL = Tourette Syndrome Symptom List; VAS = visual analog scale.

Although sparse, clinical data regarding the efficacy of NAcc stimulation exists in the literature in small case series. In 1 case study, a patient who was treated with bilateral NAcc stimulation for heroin addiction underwent explantation at 3 years postoperation, but remained abstinent from opioids to the last follow-up at 6 years.³¹⁰ A similar case involved a man with a 22-year history of treatment-resistant heroin abuse who was implanted with bilateral DBS electrodes in the NAcc. During stimulation testing, different combinations of contacts and settings brought about both increased and decreased craving for substances, and with optimized stimulation parameters the patient was able to achieve abstinence for more than 6 months.²⁸⁰ Other limited trials have also been conducted with DBS for alcohol and nicotine addiction. Two separate cases of patients with chronic, severe alcoholism who were treated with DBS in the NAcc reported abstinence at 1 year.^{148,150} In another study of 5 patients with chronic alcoholism, 2 patients remained abstinent for more than 4 years, and the remainder had significant reduction in alcohol consumption.²⁹¹ Several of the patients in the above series exhibited comorbid addiction to nicotine; these patients decreased their intake but none quit completely.³¹⁰ In a single case of DBS at the NAcc for OCD, cessation of nicotine abuse was reported,¹⁸¹ but a subsequent analysis of 10 patients who received DBS of the NAcc for OCD, TS, or anxiety found that only 3 patients achieved nicotine abstinence by 30 months.¹⁴⁷ These case reports and a couple of case series show the potential for treatment of substance abuse disorders with DBS of the NAcc, but randomized and blinded studies are lacking (Table 5).

Aggressive Behavior

Neurosurgery has been historically used for the management of aggressive behavior, although interest has waxed and waned. In the 1960s and 1970s, bilateral ablation of the amygdala was first used for treatment of epilepsy comorbid with aggression, but after early successes it became a common treatment for aggression. More than 1000 patients eventually received the procedure, with approximately 75% of these patients displaying no further aggressive behavior.^{171,201,204,205} Side effects of the procedure included reduced autonomic response to stressful cues, new-onset epilepsy, and hypersexual behavior, but overall these were limited to a small number of patients. Despite the high success rate of the surgery, subsequent public backlash against psychosurgery led to widely preferential use of pharmacological agents for behavioral control. More recently, though, increasing use of DBS has led to renewed interest in neurosurgical options for control of aggressive behavior, albeit in a reversible and adjustable fashion rather than a destructive one. A recent case

report describes the use of bilateral DBS in the basolateral amygdalae for intractable self-injurious behavior associated with mental retardation and autism.²⁷⁰ The patient, a 13-year-old boy, had failed multiple trials of pharmacotherapy and behavioral therapy, but by 26 months postimplantation his self-injurious behavior had been reduced, although it was not eliminated. Another patient with self-injurious behaviors, this time secondary to Lesch-Nyhan syndrome, experienced cessation of self-injury following DBS, although the stimulation was applied to the GPi for treatment of an unrelated movement disorder.²⁷³

Another site of interest in the treatment of aggressive behavior has been the posterior hypothalamic region (pHr), a region that shows strong interconnection with the amygdalae.²⁴⁵ As in the amygdala, lesions in the pHr have been used for the combination of epilepsy and aggressive behavior.^{244,255} Modern application of DBS to the pHr has mostly been for cases of mental retardation combined with severe aggression, and thus few results have been reported. In the first of 2 cases in the literature, a 22-year-old patient with mental retardation and aggression received bilateral low-frequency stimulation (15 Hz) to the pHr, and at 18-month follow-up the patient's behavior was significantly improved.¹⁰⁴ A second case involved a 22-year-old patient with severe, involuntary self-injurious behavior after a traumatic brain injury. At 4 months after the initiation of stimulation, the patient was reported to have complete cessation of the behavior.¹⁵¹ The largest reported cohort for pHr stimulation was of 7 patients, ages 20–68 years, with IQs between 20 and 40 and uncontrollable aggressive and violent behavior.^{73–75} After implantation of DBS electrodes in the pHr, 6 patients had cessation or significantly decreased outbursts of violent behavior. As is seen with other diseases, relapse of behavior occurred when the stimulation was interrupted or the battery became depleted (Table 6).

Posttraumatic Stress Disorder

Posttraumatic stress disorder is a psychiatric condition brought on by exposure to traumatic events, and produces cognitive, physical, and psychological disturbances accompanied by a broad range of symptoms, including hypervigilance, anxiety, aggressive behavior, sleep cycle disturbances, and intrusive thoughts.²⁸¹ It affects 6.8% of the US population and is most common among military personnel.^{130,132} Current best treatments include pharmacotherapy and psychotherapy, but even with combination therapy as many as 30% of patients remain debilitated by the condition.³⁶ Recent investigations into novel therapies for PTSD have identified changes in the CNS, specifically the amygdala, that occur in conjunction with the development of the condition. In patients with traumatic brain

TABLE 5. Selected studies of DBS for addiction

Authors & Year	No. of Pts	Study Type	Target	Outcome	Outcome Measure
Müller et al., 2009	3	Case series	NAcc	2 of 3 achieved abstinence at 1 yr	Alcohol consumption
Voges et al., 2013	5	Case series	NAcc	2 of 5 remained abstinent at 4 yrs; all reported reduced craving	Alcohol consumption
Zhou et al., 2011	1	Case report	NAcc	Abstinence for 6 yrs	Heroin use

TABLE 6. Selected studies of DBS for aggressive or self-injurious behavior

Authors & Year	No. of Pts	Study Type	Target	Indication	Outcome Measure
Sturm et al., 2012	1	Case report	Basolateral amygdala	Kanner's autism	Less injurious behavior at 24 mos
Franzini et al., 2005, 2007, 2013	7	Case series	pHr	Severe mental retardation	Reduced injurious behavior at 1 yr in 6 of 7 pts

injury, damage to the amygdala correlates with the development of PTSD.¹⁴¹ Direct stimulation to the amygdala can produce anger, and functional imaging studies have found increased activity of the amygdala in patients with PTSD.^{96,229} The increased activity of the amygdala is correlated with the degree of symptoms, and similarly, a decrease in amygdala activity corresponds to improvement and response to treatment.⁷⁰

The amygdala is a bilateral structure of the mesiotemporal lobe with important connections to the hypothalamus and brainstem, and is best recognized for its role in emotional expression and fear conditioning.^{8,193,228} However, it has numerous subregions that have been tied to other limbic and associative functions.^{7,47} Animal models of PTSD have shown that stimulation of the amygdala relieves abnormal behaviors.¹⁵⁵ Based on these cumulative results, the first trials of DBS in the amygdala were recently launched, although no results have been reported yet.¹⁴⁰ The amygdala represents a promising target for patients suffering from treatment-refractory PTSD, and outcomes of early trials will shed further light into the utility of DBS as a novel treatment.

Conclusions

The history of psychosurgery in the mid-20th century provides valuable lessons for the continuing development of brain surgery for behavioral disorders. Psychiatric disease remains the major source of disability in the world. There have been developments, however, that may help those involved in surgery for psychiatric disease avoid the mistakes of the past.

Diagnostic criteria for these disorders has improved. An increased understanding of the physiology underlying these disorders provides a firmer foundation for interventions, and in some cases may provide a biomarker for successful treatment. Advances in the ability to image the brain and subcortical structures should facilitate accurate and safe placement of electrodes at effective stimulation sites. Engineering improvements may increase the effectiveness of DBS by shaping stimulation fields, reducing hardware complications, and eventually allowing patient-responsive stimulation.

However, unbridled enthusiasm would run the risk of repeating the widespread overusage of imperfect techniques that led to the initial backlash against psychiatric surgery. As in DBS for movement disorders, the neuro-modulatory treatment of psychiatric illness should not be portrayed as a cure for these diseases. Management of patient expectations, as well as media portrayals of this treatment modality, must emphasize realistic outcomes rather than overly optimistic claims. Such premature optimism

regarding the potential treatment of memory disorders and disorders of consciousness via surgical means is already evident.⁸¹ Ethical dilemmas inherent in popularization of potential treatments for refractory disease cannot be emphasized enough.

The ability to place electrodes safely within the brain is not a moral mandate to do so; the knowledge of which stimulation sites are most efficacious for a particular disease is likewise not an ethical warrant for insertion. Careful preoperative evaluation by multidisciplinary teams and the use of rigorous outcome measures are necessary to prevent the type of indiscriminate and irresponsible application of these techniques by isolated practitioners such as Walter Freeman.

The continuing challenge inherent in neurosurgery for psychiatric disorders will be to balance the urge to offer promising (but in truth still investigational) operations for treatment-resistant disease, with the need for careful evaluation of underlying physiology and outcomes data. This balance can perhaps be captured in the words of psychosurgery's first practitioner, Gottlieb Burckhardt, who observed that "Doctors are different by nature. One kind adheres to the old principle: first, do no harm (*primum non nocere*); the other one says: it is better to do something than do nothing (*melius anceps remedium quam nullum*)."¹⁸⁰ The ideal and ethical doctor must do both.

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