Deep brain stimulation (DBS) at the interface of neurology and psychiatry

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Deep brain stimulation (DBS) is an emerging interventional therapy for well-screened patients with specific treatment-resistant neuropsychiatric diseases. Some neuropsychiatric conditions, such as Parkinson disease, have available and reasonable guideline and efficacy data, while other conditions, such as major depressive disorder and Tourette syndrome, have more limited, but promising results. This review summarizes both the efficacy and the neuroanatomical targets for DBS in four common neuropsychiatric conditions: Parkinson disease, Tourette syndrome, major depressive disorder, and obsessive-compulsive disorder. Based on emerging new research, we summarize novel approaches to optimization of stimulation for each neuropsychiatric disease and we review the potential positive and negative effects that may be observed following DBS. Finally, we summarize the likely future innovations in the field of electrical neural-network modulation.

Introduction

Deep brain stimulation (DBS) is a technique that consists of a surgically implanted lead that provides focal electrical neural-network modulation within a brain circuit or circuits of interest. Initially, modern DBS systems were developed to address dysfunctional circuits in patients diagnosed with treatment-resistant tremor or other movement disorders; recently, DBS's therapeutic role has expanded to several neuropsychiatric disorders. Neuropsychiatry is an evolving branch of medicine dealing with diseases in which the affected have symptoms that are both "neurologic" and "psychiatric" (1). The expansion of disease-specific indications has allowed scientists to move beyond traditional movement-related circuitry in order to address these relevant neuropsychiatric issues such as treatment-resistant mood and cognitive symptoms (2).

Diseases and indications with more concrete targets and straightforward outcomes, such as essential tremor, motoric symptoms of Parkinson disease (PD), and motor symptoms of dystonia, have been the most studied to date. The US FDA issued an approval for the use of DBS in essential tremor in 1997 and PD in 2002. A humanitarian device exemption (HDE) was granted for motoric symptoms of dystonia in 2003 (3). More complex cognitive and limbic targets, such as obsessive-compulsive disorder (OCD), depression, and Tourette syndrome (TS), have proven more difficult to study (2). The US FDA issued a HDE for obsessive compulsive disorder in 2009 (4). TS and depression both remain unapproved uses of DBS technology; however, many groups are implanting these patients under research protocols.

This review will focus on DBS in four neuropsychiatric syndromes: PD, TS, major depressive disorder (MDD), and OCD. Each disease has multiple brain targets (Figure 1), and each of the targets has been demonstrated as promising, albeit with reported unintended negative and positive effects. Following a brief review of the implantation/programming process, we will summarize the advances in optimized targeting and stimulation parameters. We will then discuss the four neuropsychiatric diseases, the currently utilized brain targets for each disease, and both the neuropsychiatric and motoric effects of the intervention. Finally, we will conclude with a description of other potential advances and pitfalls in this promising area (5).

DBS placement and programming

Preimplantation. Several variables should be considered prior to performing DBS surgery for a neuropsychiatric indication. Demonstration of treatment resistance (failure of both pharmacological and nonpharmacological interventions) is critical for all potential candidates (6, 7). The definitions for "treatment resistance" have been clearly defined for some (8–10), but not all neuropsychiatric conditions (11). There are DBS inclusion and exclusion criteria published for TS (12) and PD (13); however, there are less well-defined guidelines for depression and OCD (14). In the case of MDD and OCD, treatment resistance has been defined as the failure of standard of care interventions such as antidepressants and adjunctive medications (see STAR*D) (15), and psychotherapy (typically cognitive behavioral therapy [CBT]) as well as electroconvulsive therapy and/or transcranial magnetic stimulation in the case of MDD (16). Further, patients should be screened for comorbid psychiatric disease, as certain conditions predispose patients to worse DBS outcomes (17, 18). Moreover, clinicians should ensure that patients do not exhibit any clinically significant or unstable neurological medical illnesses and assess the patient for the capacity to understand the potential for harm as well as any therapeutic misconceptions.

Implantation. DBS implantation involves the use of stereotactic neurosurgical technique and modern imaging, which together allow for the treatment team to directly target a node in a dysfunctional circuit of interest. Next, microelectrode mapping (if performed) and intraoperative macro- or test stimulation occurs. In the case of PD, the tremor or rigidity and bradykinesia typically respond to intraoperative stimulation (19, 20), and this may aid in selecting the final target. In depression or OCD, for a few reported cases, intraoperative stimulation has been shown to result in subjective feelings of calmness, improved mood, and increased interest/motivation during macrostimulation in the sub-

as the electrode polarity, amplitude, pulse width, and frequency. The optimal DBS settings may depend on the disease, the targeted symptoms, and the neuroanatomical location of the stimulation field within the desired target (26). Research protocols have also been enhanced by programming "sham-DBS settings" to overcome the placebo effect of psychiatric outcomes within neurosurgery (27). Concomitant medication changes may also be required. The general lack of immediate feedback (i.e., clinical improvement in the office) in DBS programming for psychiatric diseases increases the level of difficulty and generally renders programming complex. Some of the challenge can be overcome through use of standardized self-rated and observer-rated instruments (26).

Some programming-related observations may be important predictors of chronic efficacy (21); however, no definitive immediate programming-related biomarkers have been validated. In neuropsychiatric diseases such as depression and OCD, satisfactory results can take as long as four to six months to achieve. Recent advances in target selection may reduce this latency to days in the case of depression (28). There is a risk of device malfunction (29), and in all cases, neurostimulator replacement may be necessary (30), provided the DBS patient outlives the device (i.e., typically two to five years for device replacement and seven to ten years for rechargeable batteries).

Novel methods of DBS optimization

DBS is evolving into a field of personalized medicine (31), with practitioners increasingly prescribing therapy for constellations of symptoms and making customized modifications to optimize symptoms (32). Because of the microstructural variability within an individual's brain connectivity (33), personalization of therapy will likely occur not only at the level of modifications for specific disease and general affected circuitry (34), but potentially even at the level of an individual's differences in specific neural connections (35). The use of diffusion tractography alongside traditional landmark-based targeting techniques for implantation of DBS electrodes may offer the level of imaging support necessary to start this personalized microstructural mapping (36). This technique could allow derivation of individual tractography maps that may aid in defining patterns of connectivity that could potentially optimize electrode placement and therefore individualize therapy (37). Optogenetics is another powerful technique for probing the pathways potentially responsible for neuropsychiatric disease while leaving the surrounding neural circuitry untouched (38). It has already been used to demonstrate that the therapeutic effects of DBS within the subthalamic nucleus (STN) for PD can be accounted for by stimulation of the afferent axons projecting to the STN (38).

Modifications of stimulation parameters, such as change in the geometry of the waveform, have been shown to have marked effects on charge and energy requirements (39). While fixed compliance voltage for constant-current stimulation has been shown to result in substantial energy loss, some of this energy can be recuperated if the compliance voltage can be adjusted in real time (40). The utilization of constant-current devices coupled with current steering programming strategies where multiple cathodes are used to modify the field can further optimize stimulation (41). Energy optimization can also be improved through the computation of an individual's axon fiber diameter to determine pulse width (40). Exploration of more target-specific electrodes could potentially optimize delivery through novel interactions with the circuitry of interest (42).
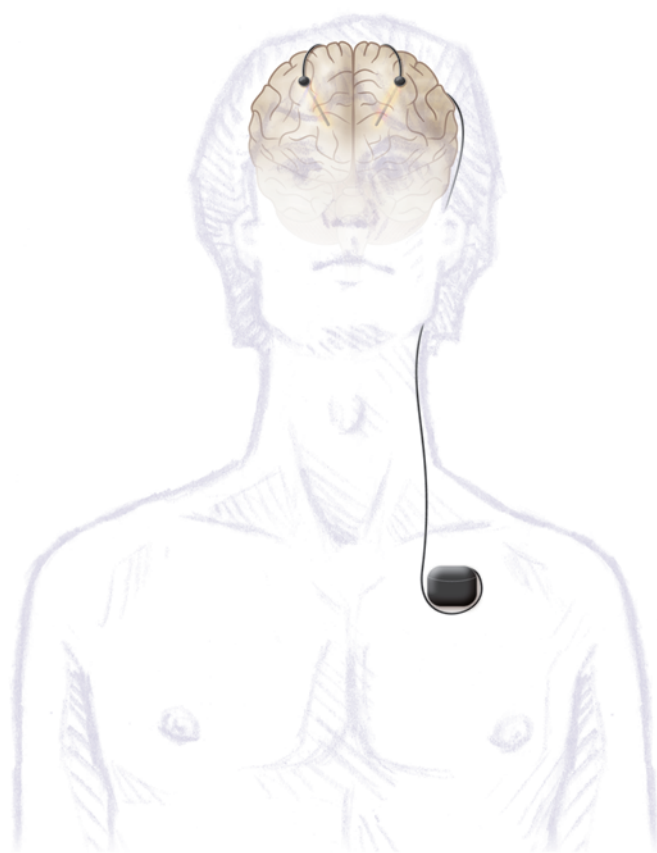

Figure 1
The modern version of the DBS system includes an electrode implanted into a deep brain target, which has been postulated to function as an important node that possesses the potential to modulate a dysfunctional brain circuit. The DBS lead is connected through an extension wire to an IPG (i.e., battery, neurostimulator), which is placed in the chest under the clavicle, or, less frequently, in the abdomen. The system is telemetrically programmed through the use of an external programming device to deliver pulses of electricity into the target region. These electrical pulses can modulate a circuit of interest to relieve disease symptoms. Schematic is not anatomically accurate.

callosal cingulate (SCC) target (21). Similarly, a contralateral smile and feelings of euphoria have been observed when stimulating in the ventral capsule/ventral striatum (VC/VS) (22). The presence of intraoperative stimulation effects such as the contralateral smile after stimulation in the ventral striatum has been demonstrated to predict eventual response to therapy (23). Once mapping is complete, a patient then receives a battery (implantable pulse generator [IPG]) placement within the next one to two weeks (24).

DBS programming. DBS programming typically occurs approximately two to four weeks after DBS surgery, with the delay due to the lead placement itself causing a transient improvement in symptoms through a "microlesion effect" (25). Programming involves the use of a handheld machine that communicates wirelessly with the chest, or with the abdominal-based neurostimulator (i.e., battery source) (Figure 2). The objective of the initial programming session is to set and fine-tune stimulation parameters. There are several programming variables that must be set, such

Recent reports indicate that neural oscillations could potentially be used to guide DBS programming, particularly in the absence of noticeable changes in clinical symptoms. Several groups have been working to use these local field potentials to develop biomarkers of efficacy such that a closed loop system can be developed. The use of the β band for PD (43), the θ band for depression in thesubcallosal cingulate (44), and the γ band for TS (45) in the centromedian nucleus of the thalamus (CM) may prove to be useful. Several groups are currently using a closed-loop device to record and then stimulate on demand (46). The intent in all of these explorations is the development of a marker that can be adjusted in real time. This technology has already become available in epilepsy devices where the electrical signature is better characterized (47).

Neuropsychiatric disease and DBS targets

PD. PD is a neurodegenerative syndrome that affects motor and nonmotor thalamocortical circuitry within the parallel and segregated basal ganglia system. PD-related neurodegeneration results in characteristic changes in neuronal firing rates, firing patterns (48), and also in oscillatory brain-cell activity (43). Many of these changes are believed to manifest clinically as tremor, rigidity, bradykinesia, apathy, depression, and/or cognitive dysfunction (49). Several randomized clinical trials in PD have revealed efficacy in both unilateral and bilateral STN and/or globus pallidus pars internus (GPi) DBS. In many of the trials, results have directly compared outcomes of DBS and traditional medical management (see Table 1). In 2006, Deuschl and colleagues demonstrated that STN DBS was superior to medication management in advanced PD (50), results that were corroborated in the 2010 PD SURG trial (51) and in a younger, less advanced PD group in 2013 (52).

Because of the uncertainty of both the efficacy and the side effects from STN DBS and GPi DBS, several studies were conducted to compare GPi and STN. In 2009, the NIH COMPARE trial demonstrated no significant differences in mood or cognition when in the optimal DBS state, while simultaneously demonstrating equal motor outcomes in the two targets. Worsened verbal fluency was demonstrated, however, when the STN target was in one of three nonoptimal DBS states (53). In 2010, Follett also demonstrated that GPi and STN had equal motor efficacy at 24 months (54), but a follow-up study revealed more long-term cognitive problems in the STN group (55). STN is likely to be the preferred target for PD DBS if medication reduction is desired (56), while GPi is likely the best choice if dyskinesia and/or preexisting cognitive issues are present (refs. 32, 53, and 57; also see Table 1).

In order to more fully explain the mechanisms that underlie the therapeutic efficacy of DBS for PD, efforts to model the pathophysiologic mechanisms of PD will ideally link abnormal basal ganglia activity to the cardinal parkinsonian motor signs (58). Computational approaches have the potential to play an important role in exploring these mechanisms (58). Currently, clinicians are utilizing methods to reduce side effects, particularly mood and cognitive alterations, through the optimization of lead placement within the target (59). Future improvements may include customized modification of the electrode trajectory (60) and placement along with clinical stimulation parameter settings using a patient-specific model and atlas (PSA) (61–63). The use of temporally nonregular stimulation parameters may also allow for further honing of the therapy in an effort to increase battery life and to improve network delivery (64).
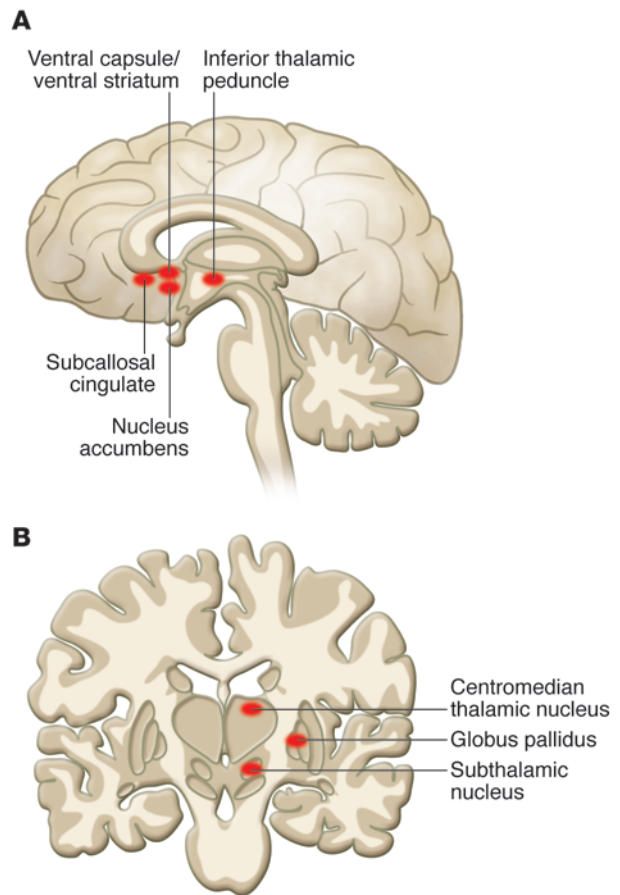

Figure 2
General schematic of DBS targets. (**A**) Sagittal view of DBS targets including VC/VS, STN, SCC, and ITP. (**B**) Coronal view of DBS targets including STN, GPi, and CM. Schematic is not anatomically accurate.

TS. TS is an early life–onset neuropsychiatric condition affecting approximately 1% of individuals worldwide. TS is characterized by multiple motor tics and one or more vocal tics that persist for more than a year. Approximately 90% of sufferers have comorbid disorders, including attention-deficit/hyperactivity disorder (ADHD), OCD, and self-injurious behaviors (SIB). In severe adult TS cases, DBS has been used in disabling settings when the patient is both medication and behavioral intervention resistant (65). There are multiple TS targets including the CM and substantia periventricularis (SPV) (66), the posteroventral (PV) GPi, the ventromedial (VM) GPi, the globus pallidus externus (GPe) (67), the STN (68), and the anterior limb of the internal capsule/nucleus accumbens (ALIC/NAc) region (69). We will discuss the two targets that have been the best characterized, and most utilized in clinical practice, the GPi (both the PV motor and VM nonmotor regions) and the CM. There are no large randomized controlled studies comparing TS targets available (69).

The largest study to date utilized the CM thalamus and demonstrated an average 52% reduction in Yale Global Tic Severity Scores (YGTSS) (65). The effect appeared to be reasonably durable: the long-term follow-up demonstrated 17 of 18 subjects had a 30% or greater reduction in their YGTSS (70). Of note, the CM target

Table 1
Summary of studies of PD DBS, both DBS versus medical management and GPi DBS versus STN DBS

Study	No. patients	Target	F/u	Outcome Positive effects	Outcome Negative effects
Deuschl 2006 (ref. 50)	156	STN	6 mo	Significant PD symptom improvement and decrease of levadopa use	Weight gain and worsening of dyskinesias
Okun 2012 (ref. 165)	168	STN	3 mo	Significant PD symptom improvement and decrease of levadopa use	Dysarthria, depression, fatigue
Schuepbach 2013 (ref. 52)	251	STN	24 mo	Significant PD symptom improvement and decrease of levadopa use	Impulse control worsening, depression, suicide attempt
Okun 2009 (ref. 53)	52	23 GPi, 22 STN	7 mo	Significant PD symptom improvement	Significant decrease in verbal fluency and increase in anger
Williams 2010 (ref. 51)	183	STN or GPi	12 mo	Significant PD symptom improvement	Psychosis, anxiety, suicide
Follett 2010 (ref. 54)	299	152 GPi, 147 STN	24 mo	Significant PD symptom improvement and decrease of levadopa use	Slight decrease in memory function, NS
Odekerken 2012 (ref. 166)	128	65 GPi, 63 STN	12 mo	Significant PD symptom improvement and decrease of levadopa use	Slight increase in dementia score, NS

F/u, follow-up.

appeared to have effects on OCD, depression, and anxiety symptoms, with an average reduction of 9 points on the Yale-Brown Obsessive Compulsive Scale (YBOCS) (42% reduction in the score), a reduction of 17 points on the Beck Depression Inventory (BDI) (55% reduction in the score), and an approximately 20-point reduction in the State-Trait Anxiety Inventory (STAI) (54% reduction in the score) (70). Two other smaller CM DBS studies demonstrated similar improvements (71, 72). For the GPi target, Martinez-Fernandez and colleagues demonstrated an average reduction of approximately 30% in the YGTSS (73). In a more recent study, 10 of 11 patients reported improvement in tic severity with an overall 48% reduction in motor tics and a 56.5% reduction in phonic tics at final follow-up. Six patients (54.5%) had a more than 50% reduction (ref. 74 and see Table 2). Additionally, the nonmotor target, NAc, has been explored for TS and surprisingly has demonstrated improvements in TS motor symptoms (69).

There are many unanswered questions in TS DBS. Does the altered connectivity in TS (75) explain the apparent improvements in motor tics after stimulation of a "limbic" target (NAc DBS) (76)? Which subcomponent of the GPi should be targeted (73)? Advances in the treatment of TS could involve a head-to-head comparison of major targets (such as the GPi versus CM versus NAc) in order to determine not only which of the targets has the greatest efficacy in reducing motor tics, but additionally which one has the greatest efficacy in reducing the comorbid psychiatric symptoms (77). Only one study has attempted to answer this question, and it demonstrated superiority of GPi with a small number of patients (78). Future studies should determine ideal stimulation conditions (should continuous stimulation be used for a paroxysmal disorder?) (46) and characterize alterations in downstream neurotransmitter function (79). Future directions will most certainly include the use of closed-loop systems and may utilize a patient-controlled function, since tics are intermittent and the sufferer often has a premonitory urge (80). In the future, a TS patient may utilize multiple leads to treat different symptom clusters (81–83).

MDD. Depression is defined as a state of extreme sadness or melancholia that affects a person's activities in daily life as well as social functioning. Nearly one in five people experience an episode of major depression in their lifetime, and the World Health Organization declared major depression one of the four most disabling illnesses worldwide (84). Currently, antidepressants and/or psychotherapy are the mainstay of treatment, along with electroconvulsive therapy, which is reserved for treatment-resistant individuals. DBS is being utilized in a research setting for patients who do not respond to conventional therapies (see Table 4).

Four main targets exist for depression DBS: the VC/VS, the subcallosal cingulate (SCC) (brain area 25 [BA 25]), the NAc, and the medial forebrain bundle (MFB) (28), although the inferior thalamic peduncle (ITP) (85) and lateral habenula (86) are also potentially efficacious DBS targets. All four of the major DBS targets for depression have been studied for treatment-resistant individuals, and all have demonstrated positive results in small series, but there are no major randomized studies comparing these targets. For MDD, the response is defined as greater than or equal to a 50% reduction in the Hamilton Depression Rating Scale score (HDRS) or Montgomery-Asberg Depression Rating Scale (MADRS), while remission is a score of "nondepressed" on HDRS or MADRS.

The SCC has been demonstrated to be an important node in the mood regulation circuitry (87) and a novel neurosurgical target for depression (21). It carries the benefit of treating both unipolar and bipolar depression (88) while appearing not to have the risk of mania seen with other depression targets (89). For SCC, an initial response rate (24–26 weeks) of 41%–66% has been reported, while at two to six years, the response rates increased to 64%–92% with remission rates of 42%–58% (90). In a different pooled analysis from the same group, the initial response rate at six months was 46.4% (16, 88, 91, 92). Mood, interest, psychic anxiety, middle insomnia, and suicidality are affected by this intervention and are therefore primary contributors to the HDRS score improvement (91). The Mayberg group has demonstrated that they can isolate the exact white matter projections that interface with the active contacts of those in remission through the use of tractography methods. This method has shown that the SCC target is effective when it contacts tracts that cause downstream changes in the midline thalamus, ventral pallidum, and medial frontal cortex (93). The long-term response rate for SCC DBS was approximately 60% (94). In addition to appropriate electrode placement, programming parameters within this node have not been fully explored (95) and optimized (96). Future trials, such as the ongoing multi-

Table 2

Summary of studies of TS DBS including CM DBS and GPi DBS

Study	No. patients	Target	F/u	Outcome summary
Porta 2012 (ref. 70)	18	CM	5–6 yr	Tics, OCD, depression, and anxiety significantly decreased
Ackermans 2011 (ref. 72)	6	CM	12 mo	Tics significantly decreased; OCD, depression, and anxiety decreased, but NS
Maciunas 2007 (ref. 71)	5	CM	3 mo	Tics, OCD, depression, and anxiety decreased
Cannon 2012 (ref. 74)	11	GPi	4–30 mo	10 out of 11 had decreased TS symptoms, but one did not tolerate DBS and two had increased anxiety
Fernandez 2011 (ref. 73)	5	GPi	3–24 mo	Tics and OCD decreased

site randomized control trial (BROADEN), may potentially utilize parameters described above to optimize treatment delivery.

The VC/VS target could potentially treat depression through its apparent mood effects in individuals who received this intervention for OCD. The response and remission rates of VC/VS at six months were 40% and 20%, respectively (97), and 71% and 35% at last follow-up (14–67 months) (98). The long-term response rate for VC/VS DBS was approximately 71% (98). A recent large study of VC/VS DBS conducted by the Medtronic company failed to show efficacy for this target; however, this could have been due to methodological limitations, especially in how the stimulation was delivered (99). One important methodological limitation in the study was that devices were programmed below the euphoria and hypomania threshold and patients could have been underdosed.

Two depression targets, the NAc and the superolateral MFB (slMFB), are central components of the reward system, which has been shown to be dysfunctional in depression (100). The response and remission rates of NAc are 50% and 30%, respectively, at 12 months (101) and 45% and 9% at two years (102). A recent pilot study investigating the MFB target suggests that it may be part of the system for reward seeking with stimulation causing a state of positive affective excitement (103). For this small series, six out of seven patients attained the response criterion within days of stimulation activation. At last observation (12–33 weeks), six out of seven patients were responders and four were classified as remitters (see Table 4).

Depression is a heterogenous disorder that manifests with a variety of symptom constellations arising from several dysfunctional nodes (104) in one or several mood networks that is/are dysfunctional (105). DBS studies targeting the SCC (21), internal capsule (97), and the reward circuitry (28, 101) have shown efficacy in not only severe unipolar depression, but also in individuals with bipolar disorder that were in an extended depressive episode (88). It is also clear that efficacy will increase when programming settings (96), the lead position in relation to the relevant circuitry (106), and the exact microstructural targets of modulation (93) are optimized. Ultimately, the DBS target choice for an individual's depression may be selected using the nature of the depressive symptoms (91) coupled with the side-effect profile and relevant comorbidities (107).

Table 3

Summary of studies of OCD DBS including VC/VS DBS and STN DBS

Study	No. patients	Response rate	F/u	DBS target	Outcome summary
Huff 2010 (ref. 110)	10	8/10 (80%)	12 mo	Unil NAc	YBOCS, HDRS, and GAF significantly improved; HARS improved, but NS
Abelson 2005 (ref. 112)	4	2/4 (50%)	4–23 mo	Bil ant limb IC	YBOCS, HARS, HDRS, and GAF improved; no data about significance
Greenberg 2006 (ref. 113)	8	6/8 (75%)	36 mo	Bil VC/VS	YBOCS, HARS, HDRS, and GAF significantly improved
Goodman 2010 (ref. 167)	6	4/6 (66.67%)	12 mo	Bil VC/VS	YBOCS an HARS significantly improved
Denys 2010 (ref. 168)	16	9/16 (56.25%)	12 mo	Bil NAc	YBOCS, HARS and HDRS significantly improved
Jimenez-Ponce 2009 (ref. 114)	5	5/5 (100%)	12 mo	Bil inf thal	YBOCS, HARS, HDRS, and GAF significantly improved
Greenberg 2010 (ref. 107)	26	19/26 (73.1%)	36 mo	Bil VC/VS	YBOCS and GAF significantly improved
Chabardès 2012 (ref. 108)	4	4/4 (100%)	6 mo	Bil STN	YBOCS improved; no data about significance
Mallet 2008 (ref. 115)	16	14/16 (87.5%)	3 mo	Bil STN	YBOCS and GAF significantly improved; HDRS improved, but NS

Unil, unilateral; Bil, bilateral; ant limb IC, anterior limb of the internal capsule; inf thal, inferior thalamic peduncle; GAF, global assessment of function.

Table 4

Summary of studies of depression DBS including NAc, VC/VS DBS and SCC DBS

Study	F/u	HDRS	MADRS	GAF	Clinical global impression	HAMA
Bewernick 2012 (ref. 102)	24 mo	Improved significantly	Improved significantly	No data	No data	Improved significantly
Malone 2009/2010 (refs. 97 and 98)	12 mo	Improved significantly	Improved significantly	Improved significantly	No data	No data
Holtzheimer 2012 (ref. 88)	24 mo	Improved significantly	No data	Improved significantly	No data	No data
Lozano 2012 (ref. 92)	12 mo	Improved significantly	No data	No data	Improved significantly	No data
Lozano 2008 (ref. 16)	12 mo	Improved significantly	No data	No data	Improved significantly	No data

OCD. OCD affects 2%–3% of the population and is characterized by obsessions, which have been defined as recurrent unwanted ideas, images, or impulses, and compulsions, which have been defined as repetitive, stereotyped behaviors or mental acts that are often performed with the intention of neutralizing anxiety induced by obsessions. The variability of OCD symptoms mirrors its heterogeneity with respect to the response of the syndrome to conventional treatments such as CBT and medication. Following conventional treatment, 20%–40% of patients with OCD remain severely disabled. DBS has become an option for treatment-refractory OCD patients (108) initially through clinical studies, then through a HDE. To date, there is still a need for a large, randomized controlled trial to determine the effectiveness of DBS in OCD (109).

Several targets have been explored for OCD DBS including the NAc (110, 111), ALIC (112), VC/VS region (27, 107, 113), the ITP (114), and the STN (108, 115). An early study investigating ALIC as a potential target demonstrated a response rate of 50% in 4 patients (112). Two studies have examined unilateral (110) and bilateral (111) NAc DBS, reporting response rates of 80% (*n* = 10) and 56% (*n* = 16), respectively. The VC/VS region has been electrically interrogated to determine the downstream effects of such stimulation (116). For OCD, the VC/VS target has the most data and has been shown to have similar efficacy between groups with a 61.5% response (>35% reduction in YBOCS) (107) in a worldwide, pooled study. STN DBS for OCD has also been reported as a potential target. Two studies, with 16 and 5 subjects, respectively, demonstrated response rates of 87.5% (115) and 100% (108), where response was defined as greater than 25% improvement on the YBOCS in the Mallet study (115) which is lower than the usual response criteria (ref. 116 and see Table 3).

The next critical step in the advancement of this work is to hone in on the exact regions that are involved in the pathogenesis of OCD (117, 118). A combination of structural and functional imaging prior to and after implantation could potentially provide additional insight required to identify specific elements, which would allow for enhanced efficacy (119, 120). All of the DBS targets appear to exert their effects at least in part by altering activity in the orbital frontal cortex (OFC), anterior cingulate cortex (ACC), and striatum (121). OCD DBS alters neural firing patterns, information transmission, and coherence between different regions in the network (121). In the future, target selection may be guided by a combination of the major symptom

dimensions and by neuroanatomical subtypes discovered on detailed neuroimaging (122, 123). Optimization of lead position is evolving, and better results have been observed when ALIC and VC/VS electrodes were moved closer to the junction of the anterior capsule and the anterior commissure (107). Enrollment of more patients through trials instead of utilization of the HDE would allow further data collection (109).

Positive and negative effects of DBS

Positive neuropsychiatric effects from DBS of "motoric targets." Initial signals that DBS may be an intervention for psychiatric conditions came from changes that resulted from implanting in the motor circuitry (124). These unintended improvements have shaped later inquiries into new diseases and neuroanatomical targets (125, 126). Patients implanted in the GPi for PD and tardive dyskinesia have reported improvements in mood (127, 128), and patients with comorbid PD and OCD have also had improvements in anxiety with STN DBS (125, 129). Some TS patients implanted in the CM thalamus unexpectedly demonstrated reductions in OCD and depression symptoms (65). STN DBS for PD has been shown to improve alertness in some cohorts (130). Limbic improvements from intended motor targets may be the result of crossstimulation of nearby circuits, or alternatively, limbic-motor connections (125). The positive limbic and motoric benefits observed from a single DBS field may also be produced as a disease-specific effect (131) where microstructural differences in the basal ganglia and limbic circuits may allow for a traditionally "limbic" target to modulate motor circuitry (ref. 132; see Table 5).

Negative neuropsychiatric effects from DBS of "motoric targets." While motoric stimulation has shown some positive effects, several negative effects have also been identified. STN DBS may adversely affect cognitive and limbic circuitry in some cases (124). A case reported by Stefurak in 2003 illustrates the dissociation of mood and motor circuitry in STN DBS where a female patient with STN DBS would have voltage-dependent crying after turning on the stimulator and would stop when the stimulator was turned off (133). De novo impulse control disorder (134), mania (135), increased anger (136), worsening apathy (137), fatigue (138), cognitive decline (55), binge eating (139), worsening depression (124), de novo psychosis (124), and suicidality (140) all appear to be uncommon, but possible effects. While verbal fluency has been shown to be affected in STN DBS,

Table 5
Positive/negative neuropsychiatric effects from motoric/limbic DBS

Study	Symptom	Effect	Comments
Kosel et al. 2007[A] (ref. 127)	Depression	Improvement	Case report with 1 patient
Damier et al. 2007[A] (ref. 128)	Depression	Improvement in 1 of 10	
Fontaine et al. 2004 (ref. 125)	OCD	improvement	Case report with 1 patient
Okun 2009 (ref. 53)	Happy mood	Increase	NS
	Sad mood	Decrease	NS
	Tense mood	Increase	NS
Graff-Radford 2010 (ref. 169)	Tense mood	Decrease	Significant
Moum 2012 (ref. 134)	ICD	Resolved in 2 and appeared de novo in 2	2 out of 6 patients for both
	DDS	no change	
	Both	no change	
Chopra 2012 (ref. 135)	Mania	Resolved	12 out of 14 patients
Kluger 2012 (ref. 138)	Fatigue	58% of patients	
Voon 2008 (ref. 140)	Suicidal ideation	0.45% (24/5311) after DBS	
	Suicide attempt	0.90% (48/5311) after DBS	
Zahodne 2011 (ref. 139)	Binge eating	Increased	
	Subthreshold BED	increased	
Burdick 2011 (ref. 136)	Anger	Increased after STN, GPi; decreased after VIM	
	Confusion	Increased after GPi, decreased after VIM	
Kirsch-Darrow 2011 (ref. 137)	Apathy	Increased in middle aged, not in older patients	
Kuhn 2007 (ref. 148)	Alcohol abuse	Cessation	Case report with 1 patient
Kuhn 2009 (ref. 170)	Smoking	Cessation	3 out of 10
Mantione 2010 (ref. 146)	Smoking, overeating	Cessation	Case report with 1 patient
Zhou 2011 (ref. 171)	Heroin abuse	Cessation	Case report with 1 patient
	Smoking	Decrease	
Valencia-Alfonso 2012 (ref. 172)	Heroin abuse	Cessation	Case report with 1 patient
Shapira 2006 (ref. 151)	panic	Reproducible with stimulation of ventral-most contacts	Case report with 1 patient
Haq 2010 (ref. 89)	OCD, mania	Present with specific DBS settings	Case report with 1 patient
Flaherty 2004 (ref. 173)	Mania	High voltage in dorsal-most contacts	Case report with 1 patient
	Depression, apathy	High voltage in ventral-most contacts	
Nuttlin 2002 (ref. 174)	Memory function	Decrease	1 out of 4
	Hypomania	Present with specific DBS settings	2 out of 4
	Fear	Present with specific DBS settings	

ICD, impulse control disorder; DDS, dopamine dysregulation syndrome; BED, binge eating disorder; VIM, ventral intermediate nucleus of the thalamus.

it appears that GPI DBS does not have as large an effect on fluency (141). In many cases these side effects are reversible (133) and may be stimulation related (142), resolving when the DBS is turned off (133). Some of these cases may be related to lead position and stimulation parameters. Some effects (e.g. verbal fluency) may be related to the surgery itself (i.e., microlesion effect). Optimization may lead to motor and nonmotor improvements (refs. 143, 144; see Table 5).

Positive neuropsychiatric effects from DBS of "limbic based targets." The NAc target was presumed to have an antianxiety effect, and because of improvements in OCD, it was hypothesized to have an independent antidepressant effect (102). Unintended improvements for other comorbid disorders have led to expansion of the potential neuropsychiatric DBS indications. Acute changes in memory were associated with unintended stimulation of the fornix in an intervention whose intent was to stimulate the lateral hypothalamus for obesity (126). DBS in the lateral hypothalamus was ineffective for obesity in that study, but utilization of novel programming techniques demonstrated efficacy in a later study (145). NAc DBS has also resulted in weight loss, and there are some reports of improvements in recreational drug use for patients receiving this treatment for OCD (ref. 146; see Table 5). The NAc is also a potential target for the treatment of addiction (147), and patients with comorbid OCD and addiction demonstrated reductions in addictive behaviors (148, 149). The addiction-like behaviors that have shown improvement include alcohol intake, nicotine dependence, and opiate use (149, 150).

Negative neuropsychiatric effects from DBS of "limbic targets." Mania is one of the most concerning negative neuropsychiatric effects resulting from DBS (89), but paradoxical worsening of anxiety and depression has also been reported (151). Feelings of suicidality can emerge; however, it is unclear whether these feeling are the result of the stimulation itself or of an augmentation of a preimplantation suicidality. Feelings of irritability and anger have been reported (53, 136, 152). Cognitive dysfunction at high amplitudes has been observed with BA 25 DBS along with the occurrence of paradoxical worsening of depressive symptoms (21). Limbic STN DBS for OCD has been associated with hypomania, anxiety, impulsiveness, depression symptoms, and obsessive-compulsive thoughts (ref. 152 and see Table 5).

Conclusion

DBS is a demonstrably effective tool for modulating dysfunctional brain circuits in a variety of conditions. As a therapy, it resides at an interface between functional neurosurgery, movement disorder neurology, and interventional psychiatry (153). DBS has not only been shown to improve several symptoms within a variety of neuropsychiatric disorders, but also to improve quality of life (154). We must remain cautious and careful as we expand DBS into neuropsychiatric diseases. Numerous articles have called for greater oversight of these technologies to prevent misuse (109). Ethical criteria for the use of DBS will be critical as the field moves forward (155, 156). The concern for an individual's decisional capacity (157) and therapeutic misconceptions (158) are important and relevant concerns. A call has been made for a registry for psychiatric DBS implantations (159) and for more forums dedicated to reducing poor outcomes in psychiatric DBS (160). The leaders in the field for these emerging technologies have authored guidelines, but more information on each target is needed (161). Additionally, a structured psychotherapeutic rehabilitation process post-DBS may be useful in addressing subsequent difficulties in reintegrating into society (i.e., TS DBS) (162). All of these efforts will help to improve and refine DBS therapy (163) and help us to avoid repeating the mistakes of the era of psychosurgery (164).

Acknowledgments

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