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Deep Brain Stimulation for Highly Refractory Depression

Darin D. Dougherty[1,2], *Alik S. Widge*[1,2], *Benjamin D. Greenberg*[3,4]

[1]Massachusetts General Hospital, Boston, MA, United States; [2]Harvard Medical School, Boston, MA, United States; [3]Butler Hospital and Alpert Medical School of Brown University, Providence, RI, United States; [4]Providence VA Medical Center, Providence, RI, United States

OUTLINE

INTRODUCTION

"Depression" connotes a group of conditions imposing a serious public health burden (Fava et al., 2016). The lifetime prevalence of unipolar major depressive disorder (MDD) has been estimated at 10%–20%, with rates significantly higher for women than for men (Kessler and Bromet, 2013). Most (50%–85%) patients have recurrent depressive episodes. Depression can cause profound disability in addition to marked distress. Impairment in marital, parental, social, vocational, and academic functioning can be pervasive. Depression, in fact, ranked as the leading cause of adult disability in developed countries in the Global Burden of Disease

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Study (Murray et al., 2013). Death from suicide is a major complication (Joukamaa et al., 2001). Also, the presence of depression markedly worsens the morbidity and mortality of many comorbid medical diseases. For example, when depression and cardiovascular disorders coexist, mortality increases (Frasure-Smith and Lespérance, 2006).

As in clinical practice, depression is usually treated as a categorical construct in research. However, current definitions allow considerable heterogeneity of presenting symptoms within the category of MDD. Depressive syndromes can also be described along continuous symptom dimensions. When depression severity questionnaire items are factor analyzed, a variety of dimensional structures result. Some of this is undoubtedly due to differences among the scales used, as well as symptom heterogeneity within the groups of depressed patients studied. Some major dimensions that emerged after factor analyses are depressed mood (a bias toward negative emotion); anhedonia (loss of pleasurable experiences); amotivation (impaired goal-directed behavior); impaired sense of energy or vitality; somatic or "neurovegetative" symptoms (disturbances in psychomotor activity, sleep, feeding, and body weight); depressive cognitions (pessimistic thoughts, feelings of guilt, low self-esteem, and suicidal ideation); cognitive impairments; and anxiety. These factor-analyzed dimensions may be reflected by abnormalities in differential brain networks (Drysdale et al., 2016).

As for psychiatric illnesses more generally, understanding of the pathogenesis of depressive conditions remains elusive. It appears that many genetic and environmental factors are relevant at the group level. At the individual level, interactive models of genetic and environmental susceptibilities have been proposed (Berton et al., 2006; Caspi et al., 2003; Cohen-Woods et al., 2013; Jabbi et al., 2008; Nestler et al., 2002). Hypotheses about pathophysiology, as opposed to pathogenesis, may be somewhat better developed. Research into associations between brain networks and depressive phenomenology has a relatively long history. Over two decades ago ideas were put forward that disruption in normal reinforcement contingencies due to cortical–limbic–thalamic–striatal dysfunction might contribute to affective components of neuropsychiatric conditions (Swerdlow and Koob, 1987). Cortico–basal circuits implicated in modulation of mood as well as reward signals have figured prominently in more recent neuroanatomical models based largely on functional neuroimaging (Hamilton et al., 2012; Rive et al., 2013). Recent reviews (Greenberg et al., 2010a,b; Widge et al., 2015) described how this circuitry may relate to symptom improvement after lesion procedures that, though derived largely empirically, target different nodes within these networks of interest.

TREATMENT OF DEPRESSION

Pharmacotherapies

The early antidepressants iproniazid and imipramine were first developed for tuberculosis and psychosis, respectively. Their antidepressant effects were discovered serendipitously; patients treated for those other illnesses had reduced depressive symptoms. The insight that these and related agents affected monoamine neurotransmission allowed the field to "improve on serendipity." Thus drugs such as selective serotonin reuptake inhibitors were developed, and eventually became first-line antidepressants due to their better tolerability and reduced lethality in overdose. However, the earlier classes of antidepressants remain in use as second- or third-line medications in refractory cases. More than 20 antidepressants are commonly used. The drugs are usually grouped by their chemical classes or pharmacological actions, such as tricyclics and tetracyclics; serotonin reuptake inhibitors, which include the more selective medications; monoamine oxidase inhibitors; and those affecting other or combinations of biogenic amine systems. Medications from different classes are frequently combined, particularly in refractory cases.

Treatment of Refractory Patients

While efficacy of antidepressants is well demonstrated, they benefit many but not all patients. A key point to emphasize at the outset is that there are a number of different degrees of refractoriness or "treatment resistance." It is instructive to review classifications of levels of poor responses to treatment (e.g., Trevino et al., 2014). The important methodological point here is that entry criteria for studies of "resistant patients" may vary substantially. This applies to trials of any potential antidepressant treatment, including neurosurgical therapies. Thus differences in the degree of refractoriness, along with other characteristics of study patients, may be expected to affect efficacy rates of any given trial. This can complicate attempts to compare outcomes from different studies. It appears beyond dispute that affected individuals who have an inadequate response to all the treatments discussed below—medications, psychotherapies, and electroconvulsive therapy (ECT)—currently have little prospect of sustained recovery. But how specific differences in refractory or resistance criteria might affect outcomes remains poorly understood.

By any measure, the limits of conventional treatments remain a serious problem. The STAR*D trial, a stepwise treatment protocol involving thousands of patients with major depressive disorder, highlights

this issue. Actually a relatively small proportion of patients experience remission with their first antidepressant trial (Fava et al., 2006; Trivedi et al., 2006). Overall, antidepressant monotherapy may bring about and maintain remission in about half of patients (Rush et al., 2006). The most affected group remains refractory to all standard medication treatments for depression (McGrath et al., 2006; Nierenberg et al., 2006). A proportion of this group might improve after more aggressive "augmentation" trials where other classes of psychotropic medications are added to antidepressants. Augmenting agents include mood stabilizers (lithium or anticonvulsants), neuroleptics, thyroid hormone, and other medications. Use of certain dietary supplements or "nutraceuticals," including omega-3 fatty acids and S-adenosyl methionine, appears to be increasing (though systematic data is scant). The few agents approved for augmentation in refractory depression in the United States include the second-generation antipsychotic aripiprazole and the prescription "medical food" methylfolate.

Psychotherapies for depression, while considered first line in their own right, are very often used together with medications, especially in depressions of moderate or greater severity. Various forms of psychotherapy have been studied to different degrees. There is strong evidence for the efficacy of cognitive behavior therapy (and variants), interpersonal therapy, and family therapy for depression (e.g., Hans and Hiller, 2013). But, as noted above, many patients remain severely affected despite aggressive use of conventional treatments such as these.

Brain Stimulation Techniques

ECT remains a therapeutic gold standard after 75 years (e.g., see UK ECT Review Group, 2003). In ECT electrical current is delivered to the brain across the large electrical resistance of the scalp and skull. ECT can be associated with significant adverse effects, however, particularly memory loss, which can limit its acceptance. Moreover, ECT's therapeutic effects are transient in a large proportion of patients, and so continuation or "maintenance" treatment may be needed (Gagné et al., 2000). On the other hand, the recent development of an ECT technique using much briefer electrical pulses to induce convulsions reported a much lower rate of adverse effects on cognition, and is seeing expanded clinical use (Sackeim et al., 2000).

Various stimulation methods have been studied as potential treatments for depression. These device-based stimulation modalities can alter brain electrical activity directly or indirectly. Transcranial magnetic stimulation (TMS) magnetically induces electrical currents in brain tissue using an electromagnetic coil placed on the scalp, and was approved for the treatment of depression by the United States Food and Drug Administration (FDA) in 2008. Both a manufacturer-sponsored trial and an independent trial sponsored by the National Institutes of Health demonstrated efficacy (O'Reardon et al., 2007; George et al., 2010). As for ECT, variations in how TMS is delivered are beginning to be explored. These include magnetic seizure therapy, different magnetic pulse sequences, and markedly different designs of the electromagnetic coils themselves. Variations in coil design can result in advantages such as markedly lower requirements for electric current. Intriguing new TMS devices create magnetic field geometries that should allow effective stimulation deeper in the brain, and one such TMS approach was approved for the treatment of depression by the FDA in 2013 (Levkovitz et al., 2015). Transcranial direct-current stimulation and transcranial alternating-current stimulation, both of which involve inducing low-amplitude electrical current directly to the scalp, are currently under investigation for clinical use (Philip et al., 2017). Lastly, vagus nerve stimulation, approved by the FDA for the treatment of treatment-resistant depression in 2006, uses electrodes surgically wrapped around the left vagus nerve in the neck to activate its afferent projections to target nuclei and related neural circuits (see Chapter 42 in the present work).

In addition to the brain stimulation methods described above, neurosurgery remains an option for patients with otherwise untreatable and severe psychiatric illnesses, primarily depression and obsessive–compulsive disorder (OCD). Stereotactic ablative procedures like anterior cingulotomy and anterior capsulotomy continue in small-scale and/or research use in North America, Europe, and elsewhere. For MDD, symptom improvement has been reported in up to two-thirds of otherwise intractably ill patients after lesion procedures (Shields et al., 2008; Subramanian et al., 2016). Rates of persistent serious adverse effects have been generally modest at the most experienced expert centers. But this is not true when the volume of tissue lesioned has been large, particularly for some procedures such as thermocapsulotomy or high-dose multiple-target gamma knife procedures (e.g., Rück et al., 2008). An advantage of deep brain stimulation (DBS) compared to ablative neurosurgery is that the effects of stimulation itself are reversible, though long-term or even irreversible side-effects of brain lead implantation have occurred. Another key issue in assessing the risks and burdens of DBS versus lesion procedures is the need for patients to have access to highly specialized expert treatment centers, essentially in perpetuity. This model of care, with all its advantages, can impose important logistical and financial burdens on patients, who by virtue of long-term disability and psychosocial dysfunction may have few resources.

DEVELOPMENT OF DBS IN NEUROPSYCHIATRY

History

DBS for psychiatric illness, and specifically for depression, is not a new idea. But the devices are new, and there are now empirical findings from stereotactic lesion procedures and neuroimaging that have allowed theoretical models of depression neurocircuitry to advance dramatically since earlier attempts in the 20th century. In 1948 Pool (1954) used a silver electrode implanted in the caudate nucleus to try to treat a woman with depression and anorexia. Over subsequent decades, Heath, Sem-Jacobsen, and Delgado exemplified an earlier era of intracranial stimulation (see below).

Over the past 20 years the introduction and refinement of DBS for movement disorders have resulted in a renaissance in this branch of functional neurosurgery, and in the field more generally. In the United States DBS is approved for tremor and Parkinson's disease and, under a Humanitarian Device Exemption, for dystonia. Worldwide, DBS is or is becoming a standard of care for such patients.

These developments spurred renewed interest in the use of such procedures for the treatment of other refractory neurologic conditions. As of this writing, DBS remains investigational for primary psychiatric disorders. Investigational uses of DBS for neurologic illness include epilepsy, pain, cluster headaches, tardive dyskinesia, Gilles de la Tourette syndrome, brain injury, and persistent vegetative states. For OCD, a Humanitarian Device Exemption enables DBS use in medication/psychotherapy-refractory patients, with the understanding that clinical benefit is not proven.

DBS was conceived as a treatment for psychopathology in the 1940s, when caudate nucleus stimulation was tried for treatment of depression and anorexia. In work that began soon afterwards and was contemporary with Sem-Jacobsen's, Heath et al. stimulated the "septal region," an area including the ventral anterior capsule (VC) and ventral striatum (VS) that is just posterior to our current target. Heath chose it in part because tumors there and nearby in the forebrain had been related to psychiatric symptoms. Heath et al. selected 20 patients with heterogeneous symptoms including delusions, hallucinations, poverty of speech or near-mutism, depression, and compulsions, though all had a formal diagnosis of schizophrenia (Monroe and Heath, 1954a,b). Stimulation was limited to 1–3 days after electrode implantation, at an amplitude of 2–15 mA. Three of the 20 patients had "no objective signs" and a further two "could not be evaluated" during stimulation. The others had acute effects: "patients became more alert [13 of 15]; … had increased motor activity and spontaneous [speech] production; …[in] previously almost inaudible or expressionless [subjects], speech became louder and enunciation clearer and inflection more appropriate [in five who had been the least verbal]." One of these, "who had been almost mute, became talkative and later almost hypomanic." Three patients appeared acutely more tense, two less so (Monroe and Heath, 1954a,b).

Accompanying behavioral changes included improved social interaction and enhanced emotional expression. As observed by Monroe and Heath, DBS subjects demonstrated "ability to relate to other people, increased responsiveness to pleasure, gradual appearance of a sense of humor, and more overt expression of anxiety and ambivalence," as well as improved functioning, e.g., "Less negativism… everyday problems were approached more realistically and more interest was shown in ward activities." Eleven patients, described as generally "idle, seclusive, and withdrawn before operation, afterward participated actively in some or all of the ward activities." Improved emotional responsiveness in social settings was "even more dramatic." "Twelve patients showed significant improvement in their ability to relate to other people," one of the "outstanding aspects" of which was the "emergence of pleasurable feelings." Nine patients showed the "development of humor." Some of these effects apparently persisted after stimulation ceased, though for how long is not fully clear. Monroe and Heath believed that "patients who respond particularly well… [were those] whose main abnormalities seem to consist of flattened affect or disturbed motor behavior." The time course and persistence of therapeutic benefit after stimulation ceased is not entirely clear in this work, although effects apparently could be transient. Some lasting or emerging benefit might have been due to concerted multidisciplinary therapies also used in these patients, described as a "total push" approach—which had, however, also been tried before stimulation without improvement.

In our own experience to date, and that of others, ongoing DBS is required for persistent behavioral and emotional change. A potential exception to this, however, is the sustained benefit seen in two OCD patients after chronic stimulation. In these individuals, stimulation facilitated completion of courses of behavioral therapy (exposure and ritual prevention), which had been impossible for these patients before DBS treatment (Greenberg et al., 2006a). In this sense, lasting effects after DBS ceases might be possible. This intriguing possibility will require systematic study.

It is important to note that the early work, from the 1950s and later, predated modern research methods. Diagnostic and severity measures used did not meet current standards for reliability or construct validity, limiting interpretation. However, recorded observations of acute and subacute DBS effects (in patients diagnosed

with schizophrenia) have high face validity as manifestations of affective state. These include enhanced production, volume, and prosody of speech, greater affective range, social relatedness, sense of humor, and functioning, and increased level of activation or hypomania.

Affect and Mood Effects Observed During Depth Electrode Stimulation

Understanding where brain stimulation effects may converge at a systems level is now a reasonable goal. Observations of how DBS for movement disorders changes affect and mood continue to accumulate. They point to neural networks that might represent potential therapeutic targets for primary psychiatric illness. Taken together with early attempts with focal brain stimulation, they suggest that multiple stimulation sites may be useful for depression. In this context, considering efforts of an earlier era is worthwhile, with a view to integrating them with evolving anatomical models of pathophysiology.

In the early 1950s Sem-Jacobsen began recording effects of acute and chronic (several days) stimulation in 220 movement-disordered patients over more than two decades (Sem-Jacobsen, 1968). Most patients subsequently underwent lesion procedures for Parkinson's disease, but some were studied before ablative surgery. Stimulation of sites throughout the frontal lobes induced affective/mood changes, with apparent selectivity noted for stimulation of ventromedial brain areas. Positive effects ranging from mild relaxation and feelings of tranquility (most common) to marked euphoria were observed twice as often as negative mood effects. The latter ranged from mild tension and/or sadness (most common) to more pronounced sadness and overt sobbing necessitating stimulation cessation.

The same responses were elicited by unilateral stimulation on the right (at 327 sites) or left (316 sites), with no significant laterality differences (Sem-Jacobsen, 1968), suggesting stimulation of many different brain loci could induce positive and negative mood states. Further, effects of opposite affective valence (e.g., mild tension and sadness versus mild euphoria) were sometimes seen with stimulation of sites 5–10 mm apart in the same individual.

Modern DBS for movement-disordered patients has at times had dramatic effects on the affective state of patients. Case reports have described effects ranging from induction of depressive dysphoria, anhedonia, apathy, and blunted affect to hypomania, merriment, and involuntary laughter. These findings are extremely intriguing, especially given the possibility of mood effects when the subthalamic nucleus (STN) is stimulated to treat OCD. Case reports of DBS of the STN in two patients with severe Parkinson's disease who also had moderately severe OCD produced improvement in OCD symptoms by 2 weeks after the start of therapy. In one of the two patients, OCD improvement was seen despite little change in Parkinson symptoms. A controlled trial of STN stimulation for OCD itself by a collaborative group in France was published in 2008. Yale–Brown OCD Scale (YBOCS) scores decreased from 30 to 19 after 3 months of active stimulation in eight patients who received active DBS first. In contrast, in the sham group YBOCS severity declined from 31 at baseline to 26 after 3 months of sham stimulation. The YBOCS score was 24 at the end of 3 months of the subsequent active DBS period. There were 15 serious adverse effects, including hemorrhage and infection (Mallet et al., 2008).

DBS for Obsessive–Compulsive Disorder

Work using DBS for OCD, the first contemporary report of DBS for psychiatric illness, is described more fully in Chapter XX of the present work. The rationale for development of DBS for OCD in large part paralleled that for tremor, Parkinson's disease, and dystonia, where DBS was applied to structures where lesions had therapeutic effects. Case studies of severely ill, highly treatment-refractory OCD patients treated with DBS of the anterior limb of the internal capsule and/or the adjacent striatum were published beginning in 1999 (Nuttin et al., 1999, 2003; Anderson and Ahmed, 2003; Sturm et al., 2003; Aouizerate et al., 2004; Abelson et al., 2005). These reports support the therapeutic potential of DBS in this population, and suggest that DBS is generally well tolerated (Gabriëls et al., 2003).

For any surgery for psychiatric illness, a key issue is long-term outcome, as is true in established uses of DBS in movement disorders. Treatment decisions need to be based on the probability that therapeutic effects will be durable, while taking into account burdens imposed by potential adverse effects. A related issue is the need to determine the likely rate at which therapeutic effects will develop in multiple domains. This is in part necessary to give patients and family members a realistic idea of the potential unfolding of benefits when they occur. Based on our own experience and that of others with lesion procedures for OCD (Greenberg et al., 2003), even cases with ultimately positive outcomes take time to improve. Beneficial changes in symptom severity, functioning, and quality of life may develop gradually (and at different rates) in individuals who have had chronic and severely impairing illnesses that have disrupted not only the patients' functional capacities but also their family and social relationships. A related point is that a description of therapeutic outcomes that will be most meaningful to patients and families needs to go beyond symptom severity reductions and take into account functioning and quality of life.

In 2006 our research group reported on 10 OCD patients meeting stringent criteria for severity and treatment resistance who underwent DBS of a ventral internal capsule/ventral striatum (VC/VS) target (Greenberg et al., 2006a). This work followed and was based upon pioneering work by Nuttin et al. which began in 1998, which was itself influenced by earlier results of anterior capsulotomy for OCD. The OCD patients, who met rigorous criteria for diagnosis and failure to respond to multiple adequate conventional treatments, had quadripolar stimulating leads implanted bilaterally in the VC/VS. DBS was activated openly 3 weeks later. Mean YBOCS scores decreased significantly from baseline to 36 months ($P < .001$). Four patients had at least 35% threshold decrease in YBOCS severity at 36 months, and scores declined between 25% and 35% for two others, consistent with the categorical response definition commonly used in modern treatment trials for OCD. Mood and nonOCD anxiety symptoms improved in these patients, and there were improvements in self-care, independent living, and work, school, and social functioning. Surgical adverse effects included asymptomatic hemorrhage (n = 1), intraoperative seizure (n = 1), and superficial infection (n = 1). Psychiatric adverse effects included transient mood elevation, which met diagnostic criteria for a hypomanic episode, in 1 of the 10 patients.

Long-term effects observed by our research group during open-label VC/VS DBS include worsened depression followed by a more gradual exacerbation of OCD symptoms at the point when DBS is interrupted by stimulator battery depletion. These observations are in accord with a hypothesis of overlapping neurocircuitry mediating at least some dimensions of depression and OCD. Another interesting observation from this OCD patient series is that two patients had sufficient improvement with VC/VS DBS to be able to engage in adjunct cognitive behavioral therapy. Later we found a similar overall picture of benefits and adverse effect burden in an expanded series including these 10 individuals and 16 others (Greenberg et al., 2010a). In this combined series it was easier to discern a "learning curve," in which patients in the second or third cohorts implanted did better over the long term than those enrolled when experience was more limited.

DBS of a target closely related to the VC/VS, the nucleus accumbens (NAcc), also appears promising (Denys et al., 2010). Sixteen patients had open-label DBS first. Exposure-based behavior therapy and pharmacotherapy were both ongoing (the case for almost all studies). Then there was a double-blind randomized cross-over to 2-week periods of active or sham DBS, followed by open DBS. In the initial open phase, 56% of patients responded. In the sham-controlled crossover (n = 14), symptoms were less intense during active versus sham DBS. The most prominent stimulation-related adverse effect was elevated mood/hypomania in half the patients, always judged nonserious. Other side-effects were a surgical wound infection (n = 1), forgetfulness (n = 5), and word-finding difficulties (n = 3). Objective testing (in other DBS studies in psychiatric illness) found no cognitive deterioration or improvement.

A controlled cross-over study tested DBS at a different target, the STN (Mallet et al., 2008), which is also within the general cortical–basal ganglia–thalamic circuitry implicated in OCD. Of 16 patients, half were randomized to active DBS and half to sham stimulation, after which each group crossed over to the other condition. There was a difference in favor of active treatment. Adverse events included intracerebral hemorrhage on device insertion (n = 1) leading to a permanent hand motor deficit, and infection leading to pulse generator removal (n = 2). One patient had hypomania and one had mania related to DBS, both reversible. Other putative DBS targets for OCD include the inferior thalamic peduncle and ventral caudate nucleus, each in small studies.

TECHNICAL ASPECTS OF DBS

Implantation

Since aspects of DBS technique are described in detail throughout this book, they are reviewed only briefly here. Implantation typically combines magnetic resonance imaging (MRI) and computed tomography imaging, computerized navigation, and often physiological mapping. Intracranial structures can be targeted with millimeter precision, with multicontact brain leads placed in subcortical nuclei or specific white-matter tracts, or spanning both kinds of structures. The subject is typically sedated but awake during the surgery. Intraoperative physiological mapping is routinely done for movement disorders, where targets are cell nuclei with characteristic physiological signatures, such as the globus pallidus interna, STN, or thalamic nuclei. Microelectrode and semimicroelectrode recordings attempt to define the boundaries of a given structure based on its known spontaneous and/or evoked electrical activity. Patients' responses to intraoperative macrostimulation may help guide the final positioning of the electrodes. The utility of such intraoperative stimulation for psychiatric disorders remains unclear at this point. In a second surgical phase (on the same or a subsequent day), the surgeon places the implantable neurostimulator or implantable pulse generator subdermally, usually in the upper chest. The stimulator(s) are then connected via extension wires tunneled under the skin (which requires general anesthesia) to the brain electrodes.

Stimulation Technique

The electrode used is typically referred to as a "lead." Each lead has multiple electrode contacts, which are the sites of stimulation. A commonly used lead is 1.27 mm in diameter. There are typically four or more platinum/iridium electrode contacts on each lead. Usually one lead is implanted on each side, allowing bilateral stimulation. Available DBS device systems are undergoing rapid technical refinements (Medtronic Inc., Minneapolis, MN, Advanced Neuromodulation Systems Inc., Plano, TX, St. Jude Medical, St. Paul, MN, or NeuroPace Inc., Mountain View, CA). Currently Medtronic, St. Jude, and NeuroPace have products approved for therapeutic brain stimulation in the United States. Only the Medtronic devices, however, are approved (under a Humanitarian Device Exemption) for a psychiatric indication.

The leads have independently programmable electrode contact sites, so the anatomical extent of stimulation is adjustable. By configuring positive or negative charges at different contacts along a lead, the shape and size of the stimulation field can be varied greatly. Chronic stimulation can thus be unipolar, bipolar, or multipolar, as each of the electrode contacts can be used as an anode or cathode (or may be set as inactive). The frequency, intensity, and pulse width are programmable for each lead, within safety limits that restrict the maximum density of the electrical charge induced. These limits are intended to prevent tissue damage due to excessive current. Stimulation parameters available include frequency ranges of 2–185 Hz, a voltage range of 0–10.5 V, and pulse widths ranging from 60 to 450 μs. High-frequency DBS is used most often for neurological conditions, a practice that has been followed for psychiatric indications. The stimulators are programmed via portable devices, which communicate with the implanted stimulators via telemetry. The patient holds the programming "wand" up to his/her chest-wall area over clothing while the programming clinician enters the desired stimulation parameters or interrogates the system for data regarding system integrity and battery status through a handheld or laptop computer. Stimulation can be delivered continuously or intermittently, cycling on and off during fixed time intervals. Patient self-programming devices are also available which allow patients to activate and deactivate the stimulator via handheld controllers, and to modify a subset of the stimulation parameters within given limits set by the programming clinician. Such patient controller devices are not typically used in the controlled phases of clinical trials, to protect the masked status of treatment for those periods.

Customizing Therapy

That DBS is adjustable provides an opportunity to optimize the therapy, but the large potential parameter space creates a challenge in doing so. In this sense, DBS is similar to repetitive TMS and vagus nerve stimulation in having a large number of potential combinations of stimulation parameters. As data has accumulated the task has gradually become easier, in that the range of parameter sets associated with improvement becomes increasingly better delineated. Further advances in DBS optimization will also be made possible by multidisciplinary work that defines the relevant anatomical networks in greater detail and precision. This work will also advance our understanding of the physiological and cellular bases of stimulation efficacy. Together the knowledge obtained will allow better targeting and improved stimulation parameter selection. DBS systems of the future may be able to self-adjust, altering the "dose" of therapy just as patients currently can do with their handheld programmers. The NeuroPace device does this for epilepsy, and new systems in preclinical development specifically target psychiatric disorders (Wheeler et al., 2015; Lo and Widge, 2017).

DBS FOR PRIMARILY DEPRESSIVE ILLNESS

Development of DBS for refractory depression has been supported by data from a number of related areas of research. Lesion procedures demonstrated the feasibility of focal brain interventions in both neurologic and psychiatric illness. Here it is of particular interest that the same lesion procedures (e.g., anterior capsulotomy, anterior cingulotomy, and subcaudate tractotomy) were associated with improvements in OCD and depression (or other conditions, including intractable pain). The VC/VS stimulation target for depression was initially based on anterior capsulotomy (used for OCD or depression). Notably, in many OCD cases mood and other affective symptoms (e.g., motivation, anhedonia, and resilience) were observed to improve faster than obsessions and compulsions, the "core" symptoms in OCD. Those observations in turn resonated with work on the anatomy and physiology of cortico-basal systems that underlie similar dimensions of behavior across species.

Thus observations that DBS at the same target appears to benefit patients with either OCD or depression are consistent with the decades-long experience from lesion procedures. Further, both lesions and DBS may have effects in common that cut across traditional categorical diagnostic boundaries. There is no compelling reason why this should not apply to other stimulation targets as well. As noted above, the potential for dramatic effects on mood, affect, and other dimensions of affective illness has been observed throughout the evolution of DBS treatment for neurologic conditions, suggesting that

stimulation sites related to those used in movement disorders may find application in psychiatry.

The other key impetus for application of DBS to depression has been functional neuroimaging. The overall literature is vast and so will not be summarized here, but a systematic series of studies by Mayberg et al. has led directly to the use of DBS targeting the subgenual region for depression (discussed below). Here it is very noteworthy that the same research group that pursued imaging-based models of depression neurocircuitry then translated those findings into a new therapeutic approach. It can be safely stated that the research-to-therapy paradigm exemplified by this work remains rare.

Results of research investigating DBS for primary depressive syndrome have been described for stimulation at several different neuroanatomical targets, as reviewed below. Randomized controlled trials, the scientific standard for antidepressant efficacy, are in various stages as of this writing.

Stimulation Targets for Depression

As in movement disorders, development of specific structural targets for DBS for psychiatric illness has derived in part from clinical outcomes observed following lesion procedures. A group of lesion procedures with overlapping targets within cortico-basalthalamic circuits (dorsal anterior cingulotomoy, anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy) have appeared effective in severe and resistant depression in multiple open studies, including large series (more than 1000 patients) for subcaudate tractotomy.

Subgenual Cingulate Cortex

Over the last two decades researchers armed with a body of functional neuroimaging research have targeted neuronal networks implicated in both the normal experience of sadness, in symptoms of depressive illness, and in responses to treatment. Using positron emission tomography (PET), the group observed a link between changes in metabolism in the subgenual cingulate cortex (SCC), including Brodmann area 25, and response to antidepressant medications. They then used DBS to target these networks in treatment-resistant depression (TRD) (Mayberg et al., 2005). Six patients with TRD were selected for notable but not extreme levels of treatment resistance and a relative lack of psychiatric comorbidity. Unblinded stimulation of white-matter tracts adjacent to the SCC was associated with rapid improvement, with substantial mean benefit at 1 week after stimulation initiation. Chronic DBS for up to 6 months was associated with sustained remission of depression in four of the six patients. While the first report of DBS for psychiatric illness was by Nuttin et al. in 1999 (for OCD), these results of SCC DBS for TRD were the first for depression. Since then, the results of numerous open-label trials of SCC DBS for TRD have reported response rates following 6–12 months of stimulation ranging from 29% (Lozano et al., 2012) to as high as 92% (Holtzheimer et al., 2012). On the heels of these exciting open-label results, St. Jude Medical (now Abbott) sponsored a multicenter prospective randomized trial of SCC DBS for TRD as a potential pivotal trial for FDA approval. Unfortunately, the study was discontinued after the results of an interim futility analysis (including 75 patients enrolled in the trial) predicted the probability of a successful study outcome to be no greater than 17.2% (Morishita et al., 2014).

Ventral Capsule/Ventral Striatum

Results from small-scale or case studies of severely ill treatment-resistant OCD patients treated with DBS of the anterior limb of the internal capsule and/or the adjacent striatum have supported the therapeutic potential of DBS in OCD. Onset of VC/VS stimulation was associated with the rapid onset of mood enhancing and antianxiety effects in OCD patients. Rapid worsening in these same clinical domains was noted with cessation of VC/VS stimulation. DBS-induced changes in mood and nonspecific anxiety symptoms seemed to precede observable changes in core OCD symptoms. In line with these observations in our OCD patient population, we undertook long-term studies of DBS at this same target in patients with severe and disabling primary major depression. The depressive syndromes of the patients who volunteered for VC/VS DBS were refractory to multiple adequate trials of antidepressant medications, to medication combinations from multiple classes and with augmenting agents, to standard psychotherapy, and to bilateral ECT. Results indicate clinically significant antidepressant responses in 8 of the 15 patients (53.3%) and remission in 6 of the 15 patients (40%) studied at last follow-up (as long as 48 months of stimulation) (Malone et al., 2009). As was the case with SCC DBS, a multicenter prospective randomized trial of VC/VS DBS for TRD as a potential pivotal trial for FDA approval was initiated, in this case sponsored by Medtronic. Here too, unfortunately, the results were discouraging. There was no significant difference in response rates between active (3 of 15 patients; 20%) and control (2 of 14 subjects; 14.3%) treatment arms during the 16-week blinded phase (Dougherty et al., 2015). However, one recent study placed the ventral tip of the DBS lead in the VC/VS (called by the alternative name, anterior limb of the internal capsule or ALIC, in the article) in TRD patients and stimulated patients open-label for up to a year (Bergfeld et al., 2016). Patients who consented were then randomized to a blinded cross-over discontinuation of their most effective clinical DBS settings. During this cross-over,

which enrolled 16 of 25 initially implanted patients, active DBS patients had a mean Montgomery–Asberg Depression Rating Scale score of 21.3, compared to 34.1 for patients receiving sham DBS. This difference was significant at $P < .001$.

Nucleus Accumbens

There have been three small open-label studies of NAcc DBS for TRD. It should be noted that despite the difference in terminology, the NAcc target and the VC/VS are close, if not identical. Regardless, the response rates for the two studies that reported them were in the mid-40% range following 12 months of stimulation, very similar to those seen in open-label VC/VS DBS studies for TRD (Bewernick et al., 2010, 2012).

Superolateral Branch of the Medial Forebrain Bundle

Due to its known role in reward and anhedonia, the superolateral branch of the medial forebrain bundle (slMFB) has been studied as a potential target for DBS for TRD. In an initial open-label trial of slMFB DBS in seven subjects with TRD, six subjects were responders, with many achieving rapid response within 1 week of stimulation. These results are cause for some excitement because the reported changes are rapid, within 1 week as opposed to months for other targets. However, this datais from a small open-label trial, and while controlled trials of slMFB DBS for TRD are under way (ClinicalTrials.gov identifier NCT02046330), there is no published data to date.

Lateral Habenula

There has been one published case report of DBS of the lateral habenula for the treatment of TRD where the patient experienced remission after 60 weeks of stimulation. While there is currently no other published data of lateral habenula DBS for TRD, a controlled trial is under way (ClinicalTrials.gov identifier NCT0198407).

Inferior Thalamic Peduncle

A case report presented at the World Stereotactic and Functional Neurosurgery Society meeting in Rome in 2005 described effects of bilateral DBS lead placement and stimulation in the inferior thalamic peduncle (ITP) in a woman with refractory depression (Jiménez et al., 2005). Stimulation at this target, via effects propagated by ITP fibers that continue rostrally in the ventral portion of the anterior limb of the internal capsule, would be expected to modulate projections of the dorsolateral prefrontal cortex, the orbitofrontal cortex (OFC), and the ventromedial striatum, as they extend to the dorsomedial and intralaminar thalamus. A substantial period of clinical benefit was observed following lead insertion itself before initiating stimulation of the ITP, perhaps reflecting a "microlesion" effect (mass effect of the perielectrode edema after implantation), a placebo response, or the natural waxing/waning course of the depressive illness itself. With subsequent chronic IPT stimulation, however, longer-term improvements were noted, particularly in association with relatively low stimulation intensities. This is of interest given that fibers coursing from rostral structures become more compact as they enter the ITP. Of note, since the 2005 report Jiménez et al. have published additional data involving six patients with OCD receiving ITP DBS, but still only the one case of a patient with depression receiving ITP DBS (Jiménez et al., 2013) Further exploration and follow-up will be necessary to establish whether this approach is both safe and beneficial.

ISSUES INDEPENDENT OF DBS TARGET

How does comorbidity affect long-term outcomes? Experience at centers with continuous work in psychiatric neurosurgery suggests that the psychopathology in most patients who might be referred for such interventions tends to be complicated. The complexity of individual patients is usually expressed diagnostically in two ways: a "primary" illness is identified, and other conditions are designated as "secondary" or comorbid. The terms are not mutually exclusive. Here it is helpful to bear in mind that the terms primary and secondary illness tend to be used differently in neurology, where a "primary" mechanism of disease implicates if not pathogenesis, at least central pathophysiologic processes mediating key features of a disorder. In contrast, descriptive psychopathology in psychiatry often designates a diagnosis as primary when its symptoms are what a patient finds most distressing and seeks treatment for, as opposed to resulting from some known pathogenetic event or process. In this tradition, which understandably arose in a field where the pathogeneses of illnesses were (and remain) unknown, disorders that appear later in the clinical course, or those judged to be less pressing clinical and psychosocial issues, can be viewed as secondary or often simply comorbid. While advances in psychiatric neuroscience might be gradually moving the field toward a position more familiar to neurologists, that is not the situation at present. Moreover, comorbidities can take several forms, including cooccurring illnesses considered as other diseases (e.g., panic disorder in a patient with depression); variation in personality structures at the extremes along dimensions of behavioral traits (personality disorders); or illnesses where marked disorder in motivated behaviors are most salient (e.g., addiction). How pathology in any of these spheres may affect the long-term risks and benefits of therapeutic DBS remains unknown.

Do Early Effects of Stimulation Have Prognostic Value?

The question of the predictive value of immediate or very early changes in behavior or physiology is a key issue. If such effects prove to be predictive, they might be very useful in lead placement and also during subsequent stimulation adjustment. At this point it is unclear whether effects demonstrated during intraoperative lead testing or early in the postimplantation course reliably predict long-term treatment success. However, as has been evidenced through many years of experience with psychotherapeutic, pharmacologic, and electroconvulsive treatments, dramatic or immediate shifts in affect are generally not reasonable therapeutic goals in psychiatric illness. This situation may be in contrast to observations of virtually immediate benefit during DBS for tremor. On the other hand, a slower tempo of therapeutic improvement appears to be the norm during DBS for dystonia. The most compelling treatments will be safe, effective, and sustainable over the long term.

Mechanism(s) of Action of DBS

Most likely, brain stimulation exerts its effects via a number of differing but interrelated mechanisms across system, neuronal, and genetic levels, each of which may come into play depending on the site of stimulation, the illness being treated, and the stimulation parameters used. A putative mechanism of antidepressant or antianxiety action of DBS is not known, but there is evidence supporting a number of potential mechanisms. High-frequency DBS (approximately 100 Hz or greater) has been proposed to modify neurotransmission, for example, via synaptic fatigue or "neural jamming" (the functional suppression of spontaneous neuronal signaling within the affected circuits) (Benabid et al., 2005a,b; Rauch et al., 2006; Dougherty et al., 2016). Either of a "functional lesion," mimicking the effect of ablative lesion procedures via a nondestructive mechanism. This is not an exact parallel, since the clinical effects of lesions and DBS in movement disorders do not always correspond. The limited data currently available from DBS therapy for psychiatric disorders suggests a time course for effect onset which is not consistent with that observed for therapeutic lesion procedures. For example, some therapeutic effects of stimulation appear more rapidly than those seen following lesions. Other proposed mechanisms of DBS action include direct inhibition of spike initiation at the level of the neuronal membrane via blockade of voltage-gated ion channels, and activation of GABA-ergic inhibitory terminals. A process known as stochastic resonance, in which stimulation actually enhances information flow within key neural pathways, may work to reduce symptoms by reducing chaotic information processing. It is possible that high-frequency electrical stimulation produces several of these effects simultaneously or sequentially within the brain, with the specific therapeutic effects depending on variables such as the spatial distributions of voltages and currents relative to the relevant group of neural elements. It is also possible that the effect of DBS on the functional state of a structure or pathway changes as the distance from the electrode increases.

Most likely, the clinical effects seen with DBS reflect the complex combination of inhibition and activation of cell bodies and axons, and depend on the orientation of the electrode, the cytoarchitecture of the structure being stimulated, and the quality (i.e., frequency, pulse width, and duration) of stimulation. Active research in clinical and preclinical laboratories is expected to help identify which of the proposed physiological mechanisms are most relevant to the clinical effects of DBS. Ongoing research efforts by our group and others include investigating the acute and long-term functional effects of DBS for OCD and MDD using PET imaging, as well as work examining potential predictors of response to DBS for OCD and MDD. Recent findings regarding the compatibility of DBS devices with certain MRI systems have opened additional avenues for research on neuroanatomical networks affected by DBS. MRI-based DBS research remains technically challenging, but will be superior to PET techniques for study designs that require reproducible scan conditions. Such investigations hold considerable promise for elucidating the therapeutic mechanism of action of DBS for psychiatric disorders. Other noninvasive techniques, such as electroencephalography, are also compatible with DBS and may offer important information about its mechanisms of action (Widge et al., 2016a,b).

Until a putative DBS mechanism of therapeutic action for psychiatric disorders can be demonstrated, available data from functional neuroimaging studies suggests hypotheses about activity in neural networks that may be associated with clinical OCD symptomatology. A considerable body of published imaging research findings implicates fronto-basal brain networks in mediating OCD symptoms and, possibly, in mediating the response to conventional OCD treatments. The most common findings in untreated OCD patients are increased glucose metabolism or blood flow in the medial cortex, the OFC and anterior cingulate gyrus, the caudate nucleus, and to a lesser extent the thalamus. These imply a pathophysiologic dysregulation in the basal ganglia/limbic striatal circuits that modulate neuronal activity in and between the OFC and the dorsomedial thalamus. The observed localized elevations in brain activity are, to varying degrees, accentuated during symptom provocation, and effective treatment of OCD with medications or behavior therapy tends to normalize activity in these same regions. One might speculate that modulation

of these circuits by DBS could exert therapeutic effects by reducing drive to engage in repetitive stereotyped behaviors and alleviating the negative emotional charge associated with such behaviors.

With regard to the neuroanatomy of MDD, several regions have been indirectly implicated. Sadness and depressive illness are both associated with decreased activity in dorsal neocortical regions and relatively increased activity in ventral limbic and paralimbic areas. Relative to that measured in healthy control subjects, MDD patients have shown increased regional cerebral blood flow and metabolism in the amygdala, OFC, and medial thalamus, while relative decreases have been observed for MDD patients in the dorsomedial/dorsal antero lateral PFC, subgenual ACC, and dorsal ACC (Mayberg, 2002). Though these mainly cross-sectional findings cannot distinguish primary processes relevant to pathogenesis from more "downstream" pathophysiologic consequences, dysregulation in these regions is thought to be related to the clinical syndrome characteristic of major depression (i.e., mood, motor, cognitive, vegetative symptoms), and as such may be involved in the mechanism of DBS antidepressant action. Other important regions implicated in the pathoetiology of depressive syndromes include the hippocampus, insula, and midbrain monoamine nuclei, as well as structural abnormalities such as reduction in volume or glia density. Future DBS research examining the impact of therapeutic stimulation on these structures, pathways, and regions in MDD populations will help clarify the biological basis of the disorder and inform our understanding of how the treatment produces relief from MDD symptoms.

Critically, this may also require a rethinking of our concept of "depression." Thought leaders throughout psychiatry have argued that our current syndromes are too heterogeneous, without one-to-one mappings between DSM diagnoses and neurobiologic mechanisms (Cuthbert and Insel, 2013). DBS, with its ability to affect minute structures and specific circuits, may only be effective for a subset of patients whose depressive symptoms are caused by a very specific mechanism. To identify that subset it may be more fruitful to study targets across diagnoses, i.e., to ask "what symptoms link to VC/VS pathology and do they improve with DBS?" instead of "is VC/VS DBS effective for MDD?" Early indications in experimental models are that this cross-diagnostic approach can identify circuit deficits and change those circuits' function (Widge et al., 2017).

ADVERSE EFFECTS

The complications of DBS can be separated into those related to the surgical procedure, to active stimulation, and to the device. Some adverse effects such as clinical deterioration observed in clinical trials of DBS therapy may of course also be related to the natural course of the underlying illness. The major risks of device implantation include seizure, intracerebral hemorrhage, and infection. Experience with DBS for movement disorders indicates that these adverse effects range from less than 1% per procedure for seizure to about 2%–3% for hemorrhage (with a mortality rate up to 1.6%) and 4%–9% for infection. The device-related complications include fracture of leads, disconnection, lead movement, and malfunction. These are becoming less common with increasing surgical expertise and evolution of device technology. In addition, there have been rare but very serious side-effects when patients with implanted DBS systems were exposed to therapeutic ultrasound or diathermy. Not surprisingly, when DBS is effective, subsequent battery depletion may result in symptom reemergence.

Adverse effects due to the actual stimulation are the most common type observed, but these are fully reversible with changes in stimulation parameters. Many stimulation-related effects have proven transient, even without changes in parameters. Stimulation-induced sensorimotor effects can include paresthesiae, muscle contraction, dysarthria, and diplopia. DBS has produced marked mood/affective changes in both movement-disordered patients (Landau and Perlmutter, 1999; Takeshita et al., 2005) and patients with psychiatric illness (Widge et al., 2016a). Side-effects in memory, impulsivity, and cognition have also been reported (Witt et al., 2004). As in movement-disorder populations, patients with primary neuropsychiatric illness may experience untoward effects, including changes in mood, suicidality, impulsivity, anxiety (e.g., panic), and other symptoms (e.g., obsessive thoughts or compulsive urges). Distinguishing adverse effects of stimulation from the symptomatology of the illness being treated may represent a challenge at times.

ETHICAL CONSIDERATIONS

As discussed, DBS is now a conventional therapeutic option for intractable movement disorders. The efficacy of the procedure is well established, although questions remain about the optimal stimulation targets and "dosing" techniques for movement disorders. While serious adverse events are possible, the overall side-effect burden is favorable for individuals who cannot benefit substantially from standard therapies. DBS has therefore become a useful therapeutic option in an otherwise untreatable group of patients who experience tremendous suffering and functional impairment.

Recent rapid growth in interest in DBS as a potential treatment for patients with severe neuropsychiatric illness is not surprising. Patients with TRD and those with

other severe disorders of mood, thought, and emotion regulation experience extreme distress and inability to participate in social and occupational life. Hopelessness and suicide are common outcomes for individuals who feel they have exhausted all available treatment options without relief. While there are strong parallels between the existing application of DBS for intractable neurological illness and its potential use in neuropsychiatry, there are also noteworthy differences. The most salient of these arises from historical experience in treatment for profoundly mentally ill persons. Special concern arising over the use of modern neurosurgical interventions for psychiatric illnesses is mainly the legacy of the widespread use of early destructive procedures, particularly frontal lobotomy, in the mid-20th century. Many patients underwent frontal-lobe surgery before adequate long-term safety data was obtained and without careful characterization of their primary disorder. Tragic consequences were reported, and remain a vivid reminder of the need for caution in this area. The current practice of psychiatric neurosurgery in place for DBS research trials is much more refined, restricted, and regulated. Candidates must meet stringent criteria for symptom severity and resistance to conventional multimodal therapies. DBS is an invasive procedure, and while it is nonablative in nature and theoretically reversible with interruption of stimulation, evidence supporting its use in psychiatric disorders is limited to the experiences observed for relatively small numbers of OCD and MDD patients worldwide. With modern practices, most patients who undergo DBS for psychiatric indications are pleased in retrospect with their choice, even if they personally received little clinical benefit from the neurostimulator (Klein et al., 2016; de Haan et al., 2015).

PERSPECTIVE

Long-Term Follow-Up

For any surgical intervention for psychiatric illness, a key issue is long-term outcome. Treatment decisions, particularly when surgical intervention is required, need to be made based on the probability that therapeutic effects will be durable and the balance of the potential side-effect burden and efficacy is reasonable. Patients with severe, chronic, and highly resistant psychiatric illness typically require multiple treatment modalities to support their daily struggles and process of recovery. Particularly with DBS, frequent and long-term (i.e., over 5 or more years) follow-up visits are necessary to assess adequately the extent of clinical response across multiple symptomatic and functional domains. Particular attention should be placed on feelings of hopelessness that may arise in patients undertaking investigational treatments thought to represent "last-resort"measures. Suicide has been reported in patients placed on waiting lists for psychiatric neurosurgery and an OCD patient who actually experienced improvement in an investigational trial of DBS (Abelson et al., 2005).

Research Protocols for Investigational Treatment With DBS

An interdisciplinary group of collaborators who began to study the effectiveness and safety of DBS in psychiatric illness systematically in the late 1990s have set forth recommendations for psychiatrists and neurosurgeons contemplating use of DBS for psychiatric indications. Until FDA approval, treatment with DBS should be limited to that delivered in approved research protocols that are subjected to initial and ongoing review by an institutional review board (United States) or ethics committee. In the United States an additional review of IRB-approved DBS studies is required by the FDA via the Investigational Device Exemption mechanism. Careful psychiatric assessment with regard to diagnosis, illness severity, and suitability of a candidate for inclusion in a DBS protocol is essential. Procedures for establishing a history of resistance to standard therapies should include detailed consideration of the adequacy and quantity of past and ongoing psychosocial/behavioral, pharmacological, and somatic treatment approaches undertaken for each individual subject. It has also been proposed that potential candidates for psychiatric DBS undergo independent consideration by an interdisciplinary review committee with appropriate expertise, including bioethics. DBS research is optimally conducted at a specialized academic center with expertise in the treatment of patients with the neuropsychiatric condition being studied, and with a neurosurgical team experienced in DBS procedures. Recent experience with DBS in psychiatry has produced updated recommendations and guidelines for research teams (Fins et al., 2006). In anticipation of gradual expansion of research and clinical uses of DBS in psychiatry, issues of training and interdisciplinary collaborations are starting to be addressed (Greenberg et al., 2006b).

SUMMARY

DBS as an investigational treatment in neuropsychiatry has generated considerable interest. The pathophysiology of psychiatric conditions is poorly understood, leading to investigation of therapeutic effects at several different DBS targets. Although its mechanisms of therapeutic action are not completely understood, DBS can precisely target regions and circuits deep within the brain that are hypothesized to be centrally involved in

neuropsychiatric disorders. Relative to surgical lesion therapies, DBS offers the advantages of reversibility and adjustability, which might permit effectiveness to be enhanced or side-effects minimized. While results from pilot studies suggest DBS may offer a degree of hope for patients with severe and highly treatment-resistant neuropsychiatric illness, only one of three controlled trials to fully evaluate efficacy and safety has yielded positive results. The two trials (at SCC and VC/VS targets) that measured signal immediately after implantation ("front-end" trials) were negative, while the one trial (at VC/VS or ALIC target) that measured signal following blinded withdrawal after up to 1 year of open-label treatment (a "back-end" trial) was positive. Research to realize the potential of DBS in this domain requires a considerable commitment of resources and time across disciplines, including psychiatry, neurosurgery, neurology, neuropsychology, bioengineering, and bioethics. Limited evidence available at present suggests that, with the appropriate multidisciplinary work, cautious optimism about the role of DBS in psychiatric treatment is justified.

Future Directions

Despite the initial promise of DBS for the treatment of refractory psychiatric illness, results from all reported "front-end" controlled trials have been negative. Only the one reported clinical trial using a "back-end" design has been positive. There are several directions researchers can explore in hopes of mitigating these mixed results. First, this data suggests that, due to variance in time to initial response between patients, "back-end" trials may be a more viable approach for clinical trials investigating DBS for TRD going forward. Second, investigators can individually tailor the DBS target. With the exception of the slMFB trial (because imaging is required to locate the slMFB), the DBS targets have been at the same x,y,z coordinates for each target for all patients. However, because there is considerable anatomical variability in the locations of desired fibers of passage between individuals (Makris et al., 2016), the use of standard x,y,z coordinates for targeting will result in misplaced electrode location in a significant number of patients. Retrospective tractography studies in patients with TRD who have undergone SCC DBS suggests that only those patients whose DBS electrodes affected specific fibers went on to become responders (Riva-Posse et al., 2014), suggesting that prospective studies using individual imaging data preoperatively may help improve response rates. Third, it is entirely possible that some or all of the initial DBS targets studied for the treatment of TRD may not be effective, even if individually targeted or if studied using a "back-end" design. The field must be open to continuing to explore new targets. While we should remain cautious, given our experience of impressive open-label data not translating into positive controlled trials, the open-label data for the slMFB, for example, looks especially promising. Lastly, while open-loop DBS (DBS where the electrode is turned on and left on in a continuous manner) has been effective for movement disorders, closed-loop DBS (responsive DBS) may be necessary to treat more complex neuropsychiatric illnesses. Closed-loop DBS typically involves electrodes recording and monitoring neural activity in a brain region involved in the pathophysiology of the illness being treated. When this neural activity crosses some threshold (firing rate, amplitude, coherence, etc.) that has been predetermined to be tightly coupled to disease symptomatology, stimulation is delivered to this brain region or another brain region to suppress the neural activity and the associated symptomatology. In this manner, the stimulation is delivered only when needed rather than continuously. Studies of closed-loop DBS for Parkinson's disease suggest that stimulation linked to neural activity biomarkers of tremor may be more effective than indiscriminate continuous stimulation (Little et al., 2013). Initial research exploring approaches to utilizing closed-loop DBS for neuropsychiatric illness is under way (Widge et al., 2017). It is hoped that these approaches, with others, will result in continued growth of applications of brain stimulation technologies to treat patients with severe and treatment-refractory neuropsychiatric illness.

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