Seeking New Solutions: Stimulation of Diseased Circuits in Depression and Other Neurobehavioral Disorders

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Five of the top 10 causes of disability worldwide are psychiatric and neurobehavioral disorders. Major depression alone is the number 1 cause of disability worldwide (> 120 million patients) in developed countries; alcoholism is number 4; bipolar disorder is number 6; schizophrenia is number 9; and obsessive-compulsive disorder (OCD) is number 10.[1] Total costs associated with severe mental illnesses exceed $300 billion per year in the United States, making them the third most costly medical conditions group.[2] Despite best efforts, ≥ 20% of patients with major depression can become treatment resistant with poor quality of life and limited social and occupational functioning. This disability results in enormous economic burden and requirement for sustained long-term care.[3] The suicide rate is as high as 15% in intractable depression.[4] For these highly disabled patients failing best medical therapy, a surgical option is a reasonable approach.

BACKGROUND

Progress in imaging in disclosing specific regions and nodes in the brain has resulted in an increased capability to pinpoint areas of the central nervous system involved in neuropsychiatric disorders and has advanced our understanding of the networks. Frontostriatal circuits, which connect the frontal cortex to subcortical structures, exist for limbic, cognitive, and motor processes in the brain.[5] Aberrations in the motor circuitry have long been implicated in Parkinson disease, a disorder successfully treated by deep brain stimulation (DBS) for > 2 decades. Imbalances in the network and associated nodes of the limbic and cognitive circuits are similarly implicated in such neuropsychiatric disorders as OCD, major depression, addiction, and others. In this context, it is reasonable to investigate neurosurgical interventions in specific nodes or hubs in these limbic and cognitive networks for patients with severe and intractable disability. These interventions include lesioning,[6] DBS,[7] and even gene therapy.[8]

Since about the mid-20th century, ablative approaches have been used to treat psychiatric disorders in treatment-refractory patients. These lesioning procedures include anterior cingulotomy,[9,10] anterior capsulotomy,[11] subcaudate tractotomy,[12] and limbic leucotomy[13] in the treatment of affective disorders.[14-17] In selected patients, these procedures can be effective. These lesions are now most commonly made by radiofrequency ablation or, in some cases, by stereotactic radiosurgery[18] but previously were often made by stereotactic implantation of radioactive isotopes. Improvements of 40% to 70% in carefully selected and highly resistant cases of OCD and treatment-resistant depression (TRD) have been reported.[18,19] The major drawbacks of these procedures are irreversibility of lesions and the lack of ability to titrate and adjust the therapy compared with DBS.

Functional neurosurgery has been undergoing a renaissance over the past 27 years. In the past decade, DBS has become an increasingly used and accepted option for patients with advanced and medically intractable Parkinson disease, essential tremor, and dystonia. Currently, there are > 80 000 DBS implants worldwide and a 27-year safety track record associated with the procedure.[20] In addition, DBS is an area of active scientific investigations, with multiple randomized, controlled trials demonstrating the safety and benefits of DBS.[20] The safety and efficacy of DBS for movement disorders have resulted in the exploration of new DBS targets and applications. In this context, DBS for the treatment of neurobehavioral conditions has been explored for the past decade with promising early results for those with severe and intractable OCD, TRD, and others. The most common DBS targets for OCD include the ventral capsule/ventral striatum (VC/VS) and nucleus accumbens (NAcc) region,[21-30] subthalamic nucleus,[31] and inferior thalamic peduncle.[32,33] In TRD, the most common targets are the VC/VS, NAcc,[29,30,34] and subgenual cingulate cortex.[35-37] Investigations of efficacy and safety of DBS for other psychiatric and behavioral disorders such as addiction to alcohol and opiates (NAcc),[38] aggressiveness (posterior hypothalamus),[39] and anorexia (VC/VS) are underway.[40,41]

The initial report of DBS for psychiatric disorders was published in 1999 for a patient with OCD.[22] Today, there are > 200 patients with such DBS implants.[42] The encouraging results from these initial studies led to the initiation of 2 randomized, controlled, blinded phase III trials of DBS for depression[43,44] and a Food and Drug Administration humanitarian device exemption approval of DBS for OCD. The DBS approach for neurobehavioral disorders has been guided by advances in our understanding of neural circuits implicated in anxiety, mood, and other emotional-behavioral

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states and the necessity to help the large number of patients with medication-refractory conditions. It is critical to have a multidisciplinary approach to identify candidates for DBS in psychiatric disorders. In general, patient selection mandates a dedicated psychiatric neurosurgery team consisting of a neurosurgeon, psychiatrist, psychologist, and other related specialists. Accurate diagnosis of the disease, sufficient severity and chronicity (> 5 years), personal and professional disability, unresponsiveness to multiple medication, and electroconvulsive therapy and psychotherapy failure are necessary before neurosurgical intervention can be considered.

NEUROCIRCUITRY OVERVIEW

The basic infrastructure of motor and sensory circuits consists of the cortical and subcortical systems with reciprocal feedbacks and numerous subcircuits that govern an interconnected network/system. Imaging has played a key role in our understanding of these complex networks from anatomic and functional standpoints.

BEHAVIORAL AND COGNITIVE NETWORKS/ CIRCUITS

Frontal lobe cortical and subcortical components are involved in mood, emotions, anxiety, motivation and drive, reward and punishment, behavioral self-awareness and regulation, decision making, memory, and cognition. Psychiatric disorders have commonalities in frontal lobe network dysfunction but manifest with various symptomatologies. This is consistent with the intricate complexity of psychobehavioral disorders and the presence of symptoms from 1 disease in another. For example, a person with OCD may also have anxiety. Frontostriatal circuits are functionally and topographically arranged, with limbic circuits placed ventromedially, motor function placed dorsolaterally, and cognitive control placed in between.[45] At certain nodes, these circuits interact, allowing the translation of emotional input into action, filtered by an intermediate cognitive control. Much neuroimaging research suggests an imbalance in the function of nodes in these circuits (hyporeactivity or hyperactivity of one or the other) that leads to disease. In the example of major depression, Mayberg et al[46] demonstrated via positron emission tomography studies that an increase in the blood flow to the subgenual cingulate cortex and a decrease in dorsolateral prefrontal cortex correlated with active depression and that this pattern reversed with resolution of symptoms.

The NAcc shell receives forebrain input primarily from the amygdala, hippocampus, and Brodmann cortical area 25. The NAcc core receives input from the entire orbitomedial prefrontal cortex. The dorsolateral prefrontal cortex projects to the VS, and the premotor and motor cortex projects to the dorsolateral striatum. Thus, the ventromedial part of NAcc, the shell, is linked to the limbic structures and the dorsolateral core is connected to the executive-cognitive areas.[45]

Rationale for using the VC/VS and subgenual cingulate cortex as targets for TRD and OCD is based on the highly interconnected nature of these targets to limbic and autonomic cortices and nuclei. These regions can be considered as a node or hub with connections to the lateral and medial prefrontal and orbitofrontal and cingulate cortexes, NAcc, ventral tegmental area, substantia nigra pars compacta, hypothalamus, and amygdala. The white matter tract connections of these targets that correlated with therapeutic response in TRD are those connections to the NAcc (part of the VS), amygdala, hypothalamus, and orbitofrontal cortex.[47]

SURGICAL PROCEDURE

The technique and sequence are similar to those for DBS for movement disorders.[48] High-resolution volumetric magnetic resonance imaging is used for planning, and a frame-based stereotactic system usually is used. Talairach coordinates for bilateral ventral anterior internal capsule/VS are 4 to 10 mm lateral to the anterior commissure-posterior commissure line, 3 to 5 mm ventral to the anterior commissure-posterior commissure line, and 1 to 3 mm anterior to the posterior border of the anterior commissure. Electrodes are implanted bilaterally in the VC/VS region mirroring each other, with the most ventral contact in NAcc in dorsoventral trajectory of the anterior limb of the internal capsule[29] (Figure). This is adjusted to avoid going through sulci and further modified to avoid subcortical vessels. During the placement, microelectrode recording, macrostimulation, and intraoperative neuropsychiatric testing are undertaken with the patient awake for that part of the procedure. Observations are made for improvement in mood and for side effects. Leads are connected to the standard bilateral internal pulse generators.

Postoperative care again continues to involve the multidisciplinary team approach. Psychiatrists usually manage patients before and after surgery and perform DBS adjustments and programming with concurrent optimization of medications and continuing behavioral therapy.

OUTCOMES FOR TRD

In an open-label study, 15 severe and treatment-refractory patients underwent DBS of the VC/VS.[29] Responder rates (50% reduction) on the Hamilton Depression Rating Scale and Montgomery-Åsberg Depression Rating Scale were 53.3% at the last follow-up (at least 6 months). Remission rates were 40% on the Hamilton Depression Rating Scale and 33.3% on the Montgomery-Åsberg Depression Rating Scale at the same last follow-up. The procedure was well tolerated with a safety profile comparable to that of movement disorders, and there were no new significant deficits in neuropsychological function. Currently, there is an active phase III randomized, controlled trial for this target.[43]

In a trial of DBS for depression at the subgenual cingulate region (Brodmann area 25 or Cg25), 6 studied patients had > 50% improvement.[49] This modality was again well tolerated and demonstrated a good safety profile. In another report of an open-label, sham/nonsham stimulation study of 12 patients undergoing DBS of Cg25 with treatment-resistant unipolar and bipolar depression, 92% of patients responded and 58% of patients were in remission

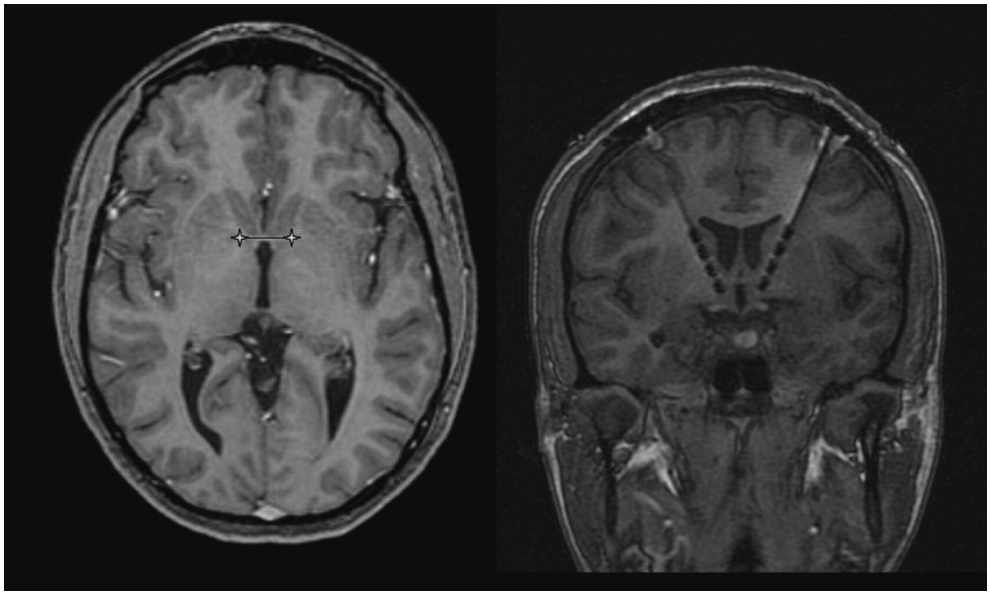

FIGURE. Axial magnetic resonance image on the left demonstrates bilateral target locations at the junction of internal capsule and anterior commissure, which corresponds to the nucleus accumbens (NAcc) region. Coronal image on the right shows contact zero in NAcc and dorsal contacts within ventral capsule/ventral striatum. Reprinted with permission from Malone et al.[29]

after 2 years of stimulation.[36] A multicenter study of the same target gave somewhat more modest results, with 29% of the 21 patients achieving responder status at 12 months and 62% of patients with $>40\%$ improvement in depressive symptoms.[37] For this target, there are also 2 current phase III clinical trials underway.[50,51] Another study will implant DBS at the VC/VS in addition to the subgenual cortex DBS.[44] Table 1 summarizes the outcomes of these studies.

There are smaller studies investigating DBS for TRD at other targets. Stimulation of the inferior thalamic peduncle yielded 100% response rate in 2 cases.[33] In stimulation of bilateral NAcc[28,30] in 13 patients, responder rates ranged from 50% to 100%.

In addition to DBS, certain groups have been exploring the use of cortical stimulation for TRD. This includes cortical epidural stimulation of the left dorsolateral prefrontal cortex (Brodmann areas 9 and 46). In a long-term open-label study, 6 patients had $\geq 40\%$ improvement on the outcome-depression scales, and five of those patients had $\geq 50\%$ improvement. Four of the 6 subjects achieved remission at some point during the study.[53]

OUTCOMES FOR OCD

Outcomes are generally measured by a reduction in Yale-Brown Obsessive-Compulsive Scale scores. Most of the experience comes from the stimulation of NAcc, VC/VS, and anterior limb of the internal capsule regions.

Denys and colleagues[54] reported 16 patients who received bilateral VC/VS DBS with a double-blind sham/nonsham stimulation. Yale-Brown Obsessive-Compulsive Scale scores were significantly improved between sham and nonsham stimulation, and 9 of 16 patients had a 72% decrease in Yale-Brown Obsessive-Compulsive Scale scores at the 8-month follow-up. Overall, the mean decrease in the scores for all patients was 46% at the same follow-up. Others have reported up to a 67% response rate at this target at 36 months of follow-up.[21,27]

Sturm and colleagues[25] stimulated 4 patients at the right NAcc, and three of those patients (75%) improved at the 30-month follow-up. Huff et al[55] reported a 50% response rate (5 of 10 patients) at 12 months after the DBS surgery at this target. Nuttin and colleagues[26] stimulated 6 patients at the bilateral anterior limb of the internal capsule with a 50% response rate at the 21-month follow-up. Other targets were

TABLE 1. Summary of Studies of Deep Brain Stimulation for Treatment-Resistant Depression[a]

Study	DBS Target	Patients, n	Outcomes Summary
Malone et al, 2009[29]	VC/VS	15	Remission rates were 40% on the HDRS and 33.3% on the MADRS at 6 mo
Bewernick et al, 2010[30]	Bilateral NAcc	10	50% Responder rate
Schlaepfer et al, 2008[28]	Bilateral NAcc	3	All 3 had improvement of anhedonia
Lozano et al, 2012[37]	Cg25	21	62% of the responder rate at 12 mo
Holtzheimer et al, 2012[36]	Cg25	12	92% of patients responded and 58% were in remission at 2 y
Mayberg et al, 2005[49]	Cg25	6	
Jiménez et al,[33,52] 2005 and 2007	ITP	2	Both patients improved

[a]DBS, deep brain stimulation; HDRS, Hamilton Depression Rating Scale; ITP, inferior thalamic peduncle; MADRS, Montgomery-Åsberg Depression Rating Scale; NAcc, nucleus accumbens; VC/VS, ventral capsule/ventral striatum.

TABLE 2. Summary of Major Studies of Deep Brain Stimulation for Obsessive-Compulsive Disorder[a]

Study	DBS Target	Patients, n	Outcomes Summary
Denys et al,[54] 2010	Bilateral VC/VS	16	46% Overall decreasing Y-BOCS score at 1 y
Greenberg et al,[21] 2006	Bilateral VC/VS	8	50% Response rate at 3 y
Goodman et al,[27] 2010	Bilateral VC/VS	6	66.7% Response rate at 1 y
Huff et al,[55] 2010	Right NAcc	10	50% Response rate 1 y
Sturm et al,[25] 2003	Right NAcc	4	3 Patients have sustained improvement at 30 mo
Nuttin et al,[26] 2008	Bilateral ALIC	6	50% Response rate at 21 mo
Aouizerate et al,[56] 2009	Ventral caudate	2	Both patients showed improvement
Jiménez et al,[33] 2007	ITP	1	Patient improved

[a]ALIC, anterior limb of the internal capsule; DBS, deep brain stimulation; ITP, inferior thalamic peduncle; NAcc, nucleus accumbens; VC/VS, ventral capsule/ventral striatum; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

the ventral caudate[56] in 2 patients, both of whom showed improvement, and the inferior thalamic peduncle[33] in 1 patient, who improved. Table 2 summarizes some of the studies of DBS for OCD.

INVESTIGATION TARGETING OTHER NEUROBEHAVIORAL DISORDERS AND PRELIMINARY OUTCOMES

The central role of the NAcc in reward circuitry makes it a possible target in treatment of addiction. A group in Germany has reported success with DBS at the NAcc for nicotine and alcohol addictions in several patients.[38,57,58] In addition, DBS of the NAcc/VC/VS region or subgenual cingulate cortex may aid in the management of anorexia nervosa.[41,59] Certain neurobehavioral disorders have commonality in symptoms that may implicate similar circuitry dysfunction across a number of disorders. Anorexic patients often have comorbid OCD or at least obsessional features,[60,61] suggesting that there may be similar functional pathologies. Some studies confirm altered reward processing in the VS and prefrontal cortex in anorexic patients.[62-67]

Similarly, the NAcc, amygdala, and ventromedial prefrontal cortex are commonly shown to have alterations in function in patients with posttraumatic stress disorder compared with healthy control subjects.[68-71] Neuromodulation of the frontostriatal circuitry or amygdala may be a potential option in the management of this disorder. So far, 1 animal study has suggested that high-frequency stimulation of the amygdala may alleviate symptoms of posttraumatic stress disorder.[72]

CONCLUSIONS

Neurobehavioral disorders have a complex and heterogeneous presentation. A number of nodes in these cortical and subcortical networks have been identified via imaging and other studies. These regions are being explored as targets for neurosurgical intervention in patients with severe and treatment-resistant disability. The most common indications with the longest-term safety and efficacy profile over the past decade have been the use of DBS of the VC/VS for treatment-resistant OCD and VC/VS and Cg25 DBS for TRD. Two randomized controlled trials of DBS for TRD are currently underway,[43,44] and additional long-term studies and outcomes are taking place. The use of cortical stimulation for TRD has also been promising and needs further evaluation. A number of targets are being explored in early pilot studies for addiction,[38,57,58] anorexia,[40] and other neurobehavioral disorders, and longer-term outcomes are necessary. Investigation of neuromodulation of cortical and subcortical targets in neurobehavioral disorders is an important area of research with a potential impact for severely disabled and treatment-resistant patients.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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