REVIEW

Deep Brain Stimulation: Current and Future Clinical Applications

MARK K. LYONS, MD

Deep brain stimulation (DBS) has developed during the past 20 years as a remarkable treatment option for several different disorders. Advances in technology and surgical techniques have essentially replaced ablative procedures for most of these conditions. Stimulation of the ventralis intermedius nucleus of the thalamus has clearly been shown to markedly improve tremor control in patients with essential tremor and tremor related to Parkinson disease. Symptoms of bradykinesia, tremor, gait disturbance, and rigidity can be significantly improved in patients with Parkinson disease. Because of these improvements, a decrease in medication can be instrumental in reducing the disabling features of dyskinesias in such patients. Primary dystonia has been shown to respond well to DBS of the globus pallidus internus. The success of these procedures has led to application of these techniques to multiple other debilitating conditions such as neuropsychiatric disorders, intractable pain, epilepsy, camptocormia, headache, restless legs syndrome, and Alzheimer disease. The literature analysis was performed using a MEDLINE search from 1980 through 2010 with the term *deep brain stimulation*, and several double-blind and larger case series were chosen for inclusion in this review. The exact mechanism of DBS is not fully understood. This review summarizes many of the current and potential future clinical applications of this technology.

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AD = Alzheimer disease; AN = anterior nucleus; CM = centromedian; DBS = deep brain stimulation; ET = essential tremor; GPi = globus pallidus internus; GTS = Gilles de la Tourette syndrome; IPG = implantable pulse generator; MCS = minimally conscious state; NAc = nucleus accumbens; NBIA = neurodegeneration with brain iron accumulation; OCD = obsessive-compulsive disorder; PAG = periaqueductal gray; PD = Parkinson disease; PVG = periventricular gray; PVS = persistent vegetative state; RLS = restless legs syndrome; STN = subthalamic nucleus; SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

The spectrum of disease to which deep brain stimulation (DBS) surgery has been applied during the past decade continues to expand. Since the initial observation of tremor control with stimulation of the thalamus, investigators have been exploring options to expand stimulation to a variety of disorders and diseases. Trials to elicit the mechanisms of action of DBS are ongoing. Meanwhile, clinical investigators continue studying the effects of DBS in these disorders and defining optimal targets. For some conditions, such as essential tremor and Parkinson disease (PD), well-established studies have confirmed the positive effects of DBS. For other conditions, such as neuropsychiatric disorders, epilepsy, and pain, long-term results and universally agreed on optimal targets are less well defined. The history of psychosurgery is a cautionary tale to all those who want to apply stimulation procedures to progressive and debilitating diseases.

For this review, the pertinent MEDLINE literature from 1980 through 2010 was analyzed using the search term *deep brain stimulation* with a focus on the best-designed randomized double-blind trials and case series. Several of the current clinical applications of DBS and potential future development are highlighted. Functional imaging and neuroelectrophysiological data will be essential to the development of targets, trials, and unbiased assessment of clinical response. For the newer applications of DBS, more well-controlled prospective clinical trials are necessary to accurately assess the efficacy and, most importantly, the safety of DBS. The major conditions and deep brain nuclei targeted for DBS are summarized in Table 1.

The surgical procedure of DBS is generally performed with the patient awake and use of a stereotactic localizing system. Midline anatomical structures, such as the anterior and posterior commissures, are often used as reliable landmarks for target planning. After local anesthesia of the scalp, a bur hole is made in the skull. Identification of the deep nuclei is based on a combination of magnetic resonance imaging or computed tomography, stereotactic atlases, and microelectrode recordings. Although not essential, microelectrode recordings allow for stimulation of the target area and can aid in placement of the permanent electrode (Figure 1). After electrode placement, lead extensions and the pulse generator are surgically implanted (Figure 2). The device is programmed via a transdermal programming unit that allows for innumerable therapeutic options (Figure 3). In addition, the programming feature permits ongoing adjustments given the dynamic nature of the central nervous system and progression of disease. The major risks of DBS are hemorrhage; transient confusion; infection; and fracture, misplacement, or migration of the lead. The mean morbidity rate for DBS surgery is 3% to 4%.[1] During the past 2 decades, these risks have continued to decline as experience has grown due to more than 75,000 procedures performed.

From the Department of Neurological Surgery, Mayo Clinic Hospital, Phoenix, AZ.

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Address reprint requests and correspondence to Mark K. Lyons, MD, Department of Neurological Surgery, Mayo Clinic Hospital, 5777 E Mayo Blvd, Phoenix, AZ 85054 (lyons.mark2@mayo.edu).

ARTICLE HIGHLIGHTS

- Deep brain stimulation surgery is a safe and effective treatment for many disorders
- Correct preoperative diagnosis is essential
- Microelectrode recording and nuclear mapping are helpful, but not essential, for optimal electrode placement
- Multiple deep brain nuclei targets and diseases are currently being investigated
- Multiple programmable options allow for adaptation to the electrophysiologic changes that develop in the neuronal circuitry in these patients

PARKINSON DISEASE

Parkinson disease is thought to affect at least 100 persons in every 100,000. The cardinal symptoms of tremor, bradykinesia, postural instability, and rigor result in substantial disability for patients with PD. During the course of the disease, up to 50% of patients will have symptoms refractory to medication and will experience drug-induced dyskinesias. Overactivity of the globus pallidus internus (GPi) and the subthalamic nucleus (STN) is believed to be part of the pathophysiologic mechanism of PD. In 1994, Benabid et al[2] and Siegfried and Lippitz[3] reported successful treatment of patients with PD who underwent DBS of the STN and of the GPi, respectively. Since those reports, thousands of patients with PD have undergone successful DBS surgery worldwide.

Multiple series have reported on the long-term efficacy of DBS for PD. The motor symptoms of PD respond well to bilateral DBS of the STN[4-7] and bilateral DBS of the GPi.[8,9] Weaver et al[10] conducted a large meta-analysis and found that, although response was better for motor symptoms in patients who underwent STN DBS vs those who underwent GPi DBS, the difference was not statistically significant. In many patients, medication-induced dyskinesias can be as debilitating as symptoms experienced when they are not taking medication. Both STN DBS and GPi DBS can result in reduction of dyskinesias.[5-9] Because GPi is thought to act directly on L-dopa–induced dyskinesias, neurostimulation is more independent of medication reduction,[11] whereas medication reduction is necessary to decrease dyskinesias in patients undergoing STN DBS.[5] One study reported significant reductions in dyskinesias with bi-

TABLE 1. **Major Conditions Currently Being Treated With Deep Brain Stimulation**

Condition	Most common deep nuclear targets	Status (United States)
Parkinson disease	STN, GPi	FDA approved
Essential tremor	Thalamus (Vim)	FDA approved
Dystonia	GPi, Thalamus (Vim)	FDA approved
Spasmodic dysphonia	Thalamus (Vim)	Being studied
Orthostatic tremor	Thalamus (Vim)	Being studied
Meige syndrome	GPi, Thalamus (Vim)	Being studied
Cluster headache	Hypothalamus	Being studied
SUNCT	Hypothalamus	Being studied
Trigeminal neuropathy	Hypothalamus	Being studied
Trigeminal neuralgia	Hypothalamus	Being studied
Chronic paroxysmal hemicrania	Hypothalamus	Being studied
Chronic pain	Thalamus (VPL/VPM,Vc), PAG/PVG	Being studied
Tourette syndrome	GPi, thalamus (CM/pf)	Being studied
Aggressive behavior	Hypothalamus	Being studied
Depression	Cingulum,VS, STN, GPi, ITP, NAc, ALIC, LH	Being studied
Obsessive-compulsive disorder	ALIC, NAc, VC/VS, ITP	Being studied
Epilepsy	Thalamus (CM/pf, AN), ICN, STN, hippocampus	Being studied
Camptocormia	GPi, STN	Being studied
Restless legs syndrome	STN	Being studied
Obesity/addictions	NAc	Being studied
Disorder of consciousness	Thalamus (CM/pf)	Being studied
Alzheimer disease	Fornix/hypothalamus	Being studied

ALIC = anterior limb internal capsule; AN = anterior nucleus; CM/pf = centromedian/parafascicularis; FDA = US Food and Drug Administration; GPi = globus pallidus internus; ICN = inferior nucleus caudate; ITP = inferior thalamic peduncle; LH = lateral habenula; NAc = nucleus accumbens; PAG/PVG = periaqueductal gray/periventricular gray; STN = subthalamic nucleus; SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; Vc = ventralis caudalis; VC/VS = ventral capsule/ventral striatum; Vim = ventrolateral intermedius; VPL/VPM = ventral posterolateral/ventro-posteromedial; VS = ventral striatum.

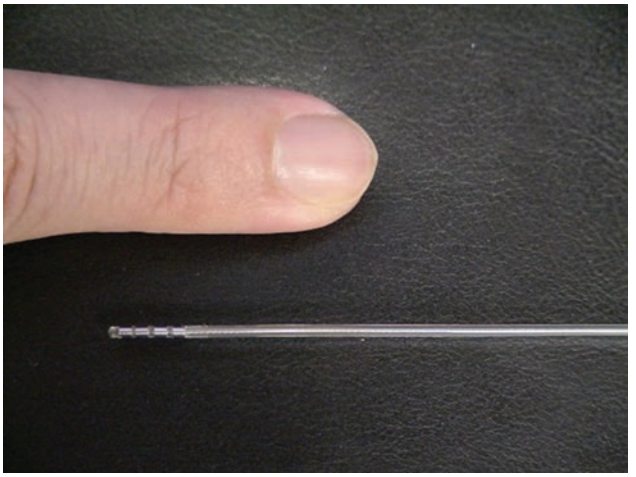

FIGURE 1. Permanent deep brain stimulation electrode. Note 4 contacts at distal end of lead, each 1.5 mm in length.

lateral GPi DBS.[10] Although there is some evidence that neurocognitive complications and programming adjustments with bilateral STN DBS are higher than with GPi DBS, many investigators continue to favor the STN over the GPi for PD.[12] The mechanism of the stimulation effect on PD is not fully understood but thought to likely be related to modulation of neuronal activity. The elegant work by Agnesi et al[13] using their wireless instantaneous neurotransmitter concentration system, which allows for in vivo measurements of real-time dopamine release, is an area ripe for ongoing and future research in DBS. Deep brain stimulation has become part of the standard treatment of advanced PD.

ESSENTIAL TREMOR

Essential tremor (ET) is the most common form of pathologic tremor. It most frequently affects the hands but can also involve the head, voice, tongue, and lower extremities. The prevalence of ET increases with age. Many patients will have a family history of ET consistent with a Mendelian dominant genetic pattern. Essential tremor can be effectively treated with propranolol and primidone, and alcohol can markedly diminish the tremor in many patients. Stereotactic thalamotomy has been largely replaced by thalamic DBS as the surgical treatment of choice. The thalamus is a large nucleus with several subnuclear divisions. Some centers still prefer radiosurgical ablative treatment for ET and have reported good long-term results.[14] The ventralis intermedius nucleus of the thalamus is the most widely agreed on target (Figure 4). Most series report 70% to 90% tremor control in patients undergoing thalamic DBS for ET.[15,16] Treatment of head and voice tremor with thalamic DBS is less effective, and generally these types of tremor require bilateral stimulation for optimal results.[16,17] Other investigators have recently suggested that the STN, zona incerta, or the prelemniscal radiation may be a more effective target in some patients.[18,19] Nonetheless, DBS for tremor control is effective and safe.

The association of upper extremity ET and several types of dystonias, including spasmodic dysphonia, has been reported. Schweinfurth et al[20] found a well-defined association between spasmodic dysphonia and ET with a 79% female preponderance. Spasmodic dysphonia with vocal tremor has been reported to respond to bilateral thalamic DBS.[21] Orthostatic tremor is the result of rhythmic muscle discharges of the lower extremities. Medical treatment is often ineffective and the condition disabling. Recently, orthostatic tremor was reported to be responsive to DBS.[22] However, further study is required because of the limited number of reports.

DYSTONIA

Primary Dystonia

Medical treatment of dystonia does not always produce adequate symptom control and often leads to intolerable

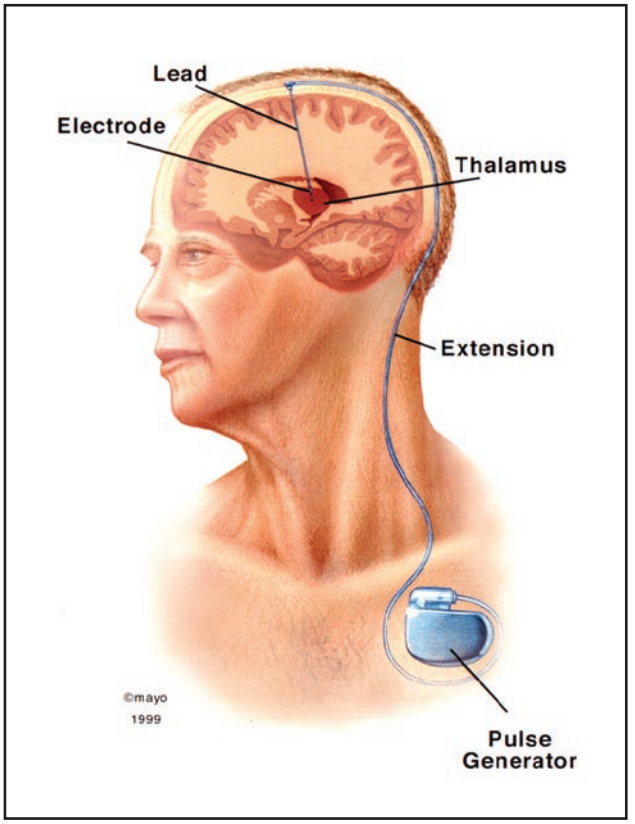

FIGURE 2. Drawing depicting the deep brain stimulation lead, lead extension, and infraclavicular location on implanted pulse generator.

FIGURE 3. Transcutaneous programming unit.

adverse effects. Initially, ablative procedures of either the thalamus or the GPi demonstrated symptomatic improvement in patients with dystonia.[23] Several reports of DBS for intractable dystonia have targeted the ventral intermedius nucleus of the thalamus[24] and the GPi.[25-28] In general, responses have been favorable with both targets. Double-blind prospective trials of bilateral GPi DBS for primary dystonia have documented therapeutic response.[29] Although clinical trials comparing the targets have not yet been performed, the generally accepted target is currently the GPi. Results of DBS for secondary dystonias have been mixed.

Neurodegenerative Dystonias

Deep brain stimulation for other forms of dystonia, including posttraumatic, postanoxic, dystonia-plus syndromes, and tardive dystonias, has been reported in small series or case reports with generally favorable results.[25,27] Kurtis et al[30] found significant clinical and neurophysiological improvement in a patient who underwent bilateral GPi DBS for myoclonus-dystonia secondary to a mutation in the epsilon-sarcoglyan gene. Neurodegeneration with brain iron accumulation (NBIA) represents a rare group of neurodegenerative disorders characterized by iron accumulation in the brain. Severe generalized dystonia is a prominent symptom manifested by speech and swallowing difficulties as well as pain and gait and respiratory compromise. Timmermann et al[31] conducted a multicenter retrospective study in patients with dystonia secondary to NBIA treated with bilateral pallidal stimulation. Two-thirds of the patients had improvement in their dystonia severity score of 20% or more, and more than 30% had improvement in their disability impairment. This patient cohort confirmed that GPi DBS may be an effective treatment of NBIA-induced dystonia.

Meige Syndrome

Idiopathic cranial cervical dystonia is an adult-onset movement disorder that results in segmental dystonia. Blake, Wood, Brueghel, and Meige syndromes are other terms for this disorder, the most common of which is Meige syndrome.[32-40] Patients with Meige syndrome have blepharospasm, cervical dystonia, and facial oromandibular dystonia. In 5 of 7 cases of Meige syndrome, thalamic and/or basal ganglia lesions have been detected on single positron emission computed tomography and functional magnetic resonance imaging.[41] Although the underlying cause of Meige syndrome is unknown, it is primarily considered a variant of idiopathic torsion dystonia; however, autopsy reports have not provided specific details.[33,40] Stereotactic surgical ablation of the thalamus and the GPi has been associated with mixed results.[34,36] Recent reports have described the efficacy of GPi DBS in selected patients with Meige syndrome[32,34,38,39]; however, no definitive conclusions can yet be made regarding DBS for Meige syndrome, and further study is needed. Nonetheless, bilateral GPi DBS may be effective in patients with medically refractory Meige syndrome.

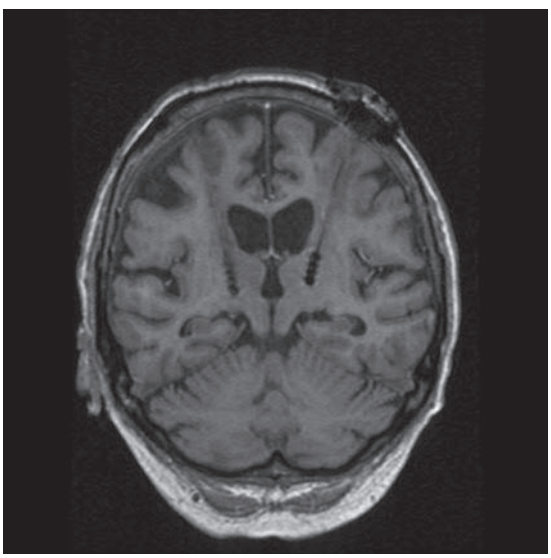

FIGURE 4. Coronal T2-weighted magnetic resonance image demonstrating bilateral electrode placement in the thalamus.

HEADACHE

Cluster Headache

Cluster headache is a rare condition that results in severe headaches occurring cyclically and can last for weeks or months at a time. In as many as 20% of patients, cluster headaches are considered medically refractory.[42] Positron emission tomography has identified focal increase in blood flow in the ipsilateral hypothalamus during a cluster headache attack.[43] In 2001, Leone et al[44] reported the first successful DBS of the posterior hypothalamus for the treatment of refractory cluster headache. Since then, more than 50 cases have been reported worldwide of hypothalamic DBS for cluster headache.[45-47] In a recent study of 10 patients who had undergone hypothalamic DBS for cluster headache, positron emission tomography showed both activation and deactivation in cerebral structures known to be activated during cluster headache attacks.[48] These findings suggest that, rather than inhibiting ipsilateral activity in the presumed generator, hypothalamic DBS may result in functional modulation of the pain neural matrix. Several other targets, including the periaqueductal gray (PAG) region, anterior hypothalamus, and subcommisural targets, are being studied for cluster headache.

Short-lasting Unilateral Neuralgiform Headache With Conjunctival Injection and Tearing

Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) is a rare primary headache disorder often refractory to treatment. Patients with SUNCT experience excruciating paroxysms of strictly unilateral orbitotemporal headache that persist for seconds to minutes and recur up to 200 times per day. Topiramate, lamotrigine, intravenous lidocaine, and gabapentin are the only medications that have been shown to have some effectiveness in isolated cases of SUNCT. On the basis of successful results for the treatment of cluster headache, Leone et al[44,45] developed a surgical option for patients with medically refractory SUNCT. The posterior inferior hypothalamus was targeted in part because functional magnetic resonance imaging demonstrated activation in this area during headache attacks, similar to that seen during cluster headache attacks.[43-49] Lyons et al[50] reported similar results in a patient with a history of SUNCT who underwent ipsilateral hypothalamic DBS. Although this procedure is not curative, it could be effective for medically resistant SUNCT.

Other Headache Syndromes

Franzini et al[51] reported their experience in targeting the posterior hypothalamus for trigeminal neuropathy and multiple sclerosis–induced trigeminal neuralgia. In patients with trigeminal neuropathy, DBS was ineffective; however, patients with refractory trigeminal neuralgia due to multiple sclerosis showed significant improvement in V1 distribution attacks. Moreover, Walcott et al[52] reported a single case of chronic paroxysmal hemicrania that responded to ipsilateral posterior hypothalamic DBS. Matharu et al[53] noted a similar observation in their patient. Thus, DBS may be effective for certain cases of refractory headache disorders.

CHRONIC PAIN

Treatment of a variety of pain syndromes using DBS initially focused on the sensory nucleus of the thalamus for neuropathic pain. The ventral posterolateral and ventroposteromedial nuclei were the most commonly targeted areas.[54] Subsequent trials found that chronic stimulation of the PAG region and periventricular gray (PVG) region at the level of the third ventricle was also effective.[55] The PAG/PVG region is generally targeted for nociceptive pain, whereas the ventral posterolateral and ventro-posteromedial thalamic subnuclear area have been used more often for neuropathic pain.[56] Several recent international studies have reported successful treatment of differing chronic pain syndromes with DBS. Hamani et al[57] performed DBS of the ventralis caudalis nucleus of the thalamus or PAG/PVG region in 21 patients with chronic pain, 13 of whom underwent permanent implantation; only 5 patients had long-term relief, and implantation was primarily in the thalamic subnuclei.[57] Conversely, Bittar et al[58] reported that PAG/PVG stimulation was more effective for phantom limb pain. Katayama et al[59] found that DBS of the posterior nucleus ovalis of the thalamus was much more effective for long-term relief of neuropathic pain after cerebrovascular accident compared with DBS of the ventralis caudalis nucleus of the thalamus or internal capsule.

NEUROPSYCHIATRIC DISORDERS

Tourette Syndrome

Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder that occurs most commonly in childhood and is characterized by phonic, vocal, and motor tics; pathophysiology is poorly understood. Among patients with GTS, severity of symptoms and responsiveness to treatment vary substantially. Nearly 1% of children worldwide reportedly have GTS.[60] Many of these children have psychological comorbidities, including obsessive-compulsive disorder (OCD), anxiety, depression, attention deficit disorder, and self-mutilation.[60] Most patients exhibit a self-limiting form of the disorder and, after the peak of tic severity during prepubescent years, note a significant decline in symptoms by the age of 20 years. In most patients, symptoms respond to

pharmacological treatment with alpha$_2$-adrenergic agonists or neuroleptics. Since the mid-1950s, ablative neurosurgical procedures have been used for patients with refractory GTS. The thalamus, limbic system, frontal lobes, and cerebellum have all been targeted. Results have generally been poor with serious complications.[61,62] Several recent series have reported on the effectiveness of DBS for GTS,[63-71] and most have described a decrease in or termination of behavioral symptoms.[63,66-71]

The first report of DBS for GTS by Vandewalle et al[65] targeted the centromedian (CM) and ventral oralis internus nuclei of the thalamus. Since then, other targets, including the thalamus, GPi, nucleus accumbens (NAc), and anterior limb of the internal capsule, have been used.[64,70,71] In a study by Servello et al[69] in 2008, 15 of the 18 patients who underwent bilateral thalamic DBS had symptomatic improvement. A prospective, randomized, double-blind study by Maciunas et al[67] demonstrated marked improvement in 3 of 5 adult patients who underwent thalamic DBS. In a controlled double-blind, randomized, crossover trial, Welter et al[68] implanted bilateral thalamic and GPi electrodes in 3 patients and reported significantly better outcomes with GPi stimulation. Although DBS surgery is considered to have a relatively low risk of morbidity and mortality, the optimal target has yet to be determined. Systematic study of this condition and the optimal target is necessary.

Aggressive Behavior

Impulsive and aggressive behavior unresponsive to maximal medical management can be extremely challenging. Lesional therapies involving the hypothalamus have been successful in improving behavior. Recently, investigators have reported on a small number of patients with severe aggressive and violent behavioral disorders who underwent posterior hypothalamic stimulation.[72-74] Bilateral medial hypothalamic stimulation in a young male with medically refractory aggressiveness and cognitive impairment resulted in sustained clinical improvement at 18-month follow-up.[72] Kuhn et al[73] demonstrated complete resolution of self-mutilation behavior in a 22-year-old woman after bilateral hypothalamic DBS. In their series of 6 patients who underwent hypothalamic DBS for violent and aggressive behavior, Franzini et al[74] noted that 5 of the patients experienced significant improvement. The initial anecdotal experience of DBS in patients with aggressive behavioral disorders is promising, but a substantial amount of work still needs to be done.

Depression

Major depression is the most common psychiatric disorder worldwide. Despite neuropharmocological agents, electroconvulsant therapies, and neuroablative procedures, depression in nearly 20% of patients is refractory to all interventions. In 2005, Mayberg et al[75] reported their experience in 6 patients with depression who underwent bilateral DBS of the subgenu of the corpus callosum. This target was selected on the basis of positron emission tomographic findings of a decrease in the subgenual cingulate activity in patients whose symptoms had initially responded favorably to treatments. At 6-month follow-up, 4 of their 6 patients had sustained improvement, as measured by the Hamilton Depression Rating Scale. In a study by Schlaepfer et al,[76] 3 patients who underwent bilateral DBS of the ventral striatum experienced improvement. Interestingly, after blinded withdrawal of stimulation, patient scores worsened, suggesting that the improvement was not due to placebo effect.

As with all DBS applications to psychosurgery, care must be taken to ensure adequate patient protection. The exhaustive analysis of the literature by Voon et al[77] regarding the neuropsychological effects of DBS in patients with PD is a cautionary tale of the importance of unintended adverse effects. Several different targets have been studied, and there appears to be overlap of these targets in Tourette syndrome, OCD, aggressive behavior, and depression. Information on the application of DBS techniques for these disorders is preliminary. The hope for potential "cure" of these devastating disorders among patients, the media, and health care professionals is substantial, and thus cautious interpretation of these early results is paramount for patient safety.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is a psychiatric disorder manifested by thoughts and impulses that produce anxiety and result in patients performing repetitive rituals. Treatment generally consists of cognitive behavioral intervention and serotonin reuptake inhibitors. Up to 40% of patients will have functional impairment that significantly affects their quality of life.[78] Neuroablative procedures, including cingulotomy and anterior capsulotomy, have been used during the past half century, with reports of 30% to 70% of patients responding.[78-80] Although the precise pathophysiologic mechanism of OCD is unknown, it appears that abnormal functioning of the cortico-striato-thalamo-cortical circuitry plays an important role.[81]

Several small series of DBS for OCD have been reported during the past 10 years, but an optimal target has yet to be be defined.[82-86] Improvement in symptoms is commonly assessed with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Mallet et al[86] and Fontaine et al[82] noted good responses targeting the STN. The anterior limb of the internal capsule was one of the original targets based on the

successful results from the original ablation techniques in anterior capsulotomy.[87] More recently, the ventral capsule in combination with the ventral striatum, which contains the NAc, has become a target of interest in several studies.[83,84] Long-term improvement in the Y-BOCS scores of 10 patients who underwent targeting of the right NAc was not apparent.[84] The inferior thalamic peduncle, which links the orbitofrontal cortex with the thalamus, has also been a target of recent interest in the treatment of OCD. This target has been used in only one study: Jiménez-Ponce et al[85] treated 5 patients with bilateral DBS for OCD. Although their study patients were not stringently controlled, the authors found reductions in the Y-BOCS scores of at least 35% in all patients. These preliminary studies indicate that DBS for severe, refractory OCD may be a promising treatment option. Clearly, the optimal target has yet to be defined, and further well-controlled studies are needed. Suicidal ideation and hypomania are potential serious complications in patients who have undergone DBS for OCD. Multidisciplinary treatment is essential for such patients.

EPILEPSY

Epilepsy is one of the most prevalent and disabling disorders across all age groups. Nearly 1% of adults and up to 5% of children are diagnosed as having epilepsy; more than 30% of cases are refractory to treatment. A study in the early 1970s by Cooper et al[88] demonstrated significant seizure reduction in more than 50% of their patients with intractable epilepsy who had undergone cerebellar electrical stimulation; improvements in visual, verbal, and memory function were noted. Salcman et al[89] described 5 patients who underwent cerebellar cortical stimulation for intractable epilepsy. Histopathologic analysis performed at the time of electrode implantation revealed marked degeneration of the Purkinje cell layer in all patients; the authors concluded that neuronal damage in patients with epilepsy may be related to the cumulative effects of the frequency and chronicity of the disease. Davis and Emmonds[90] reported that most of their patients who had undergone cerebellar stimulation were either seizure-free or had significant reduction in seizure frequency during an average stimulation time frame of 8 years; in 65% of the patients, anticonvulsant medication requirements were reduced. However, a double-blind prospective clinical trial of cerebellar stimulation in 12 patients with various types of medically refractory epilepsy found no decrease in the severity or frequency of seizures.[91] In a double-blind trial of cerebellar stimulation in 5 patients with generalized seizures, Velasco et al[92] reported a 33% reduction in seizure frequency.

Most investigators studying cerebellar stimulation for seizure control place the electrodes via a bur hole approach. Despite postoperative imaging to confirm location, such placement may lead to variability of the exact structures being stimulated, and this may partially explain the variability in some of the reports. Larger double-blind trials with defined cohorts are necessary to fully evaluate the potential benefits of cerebellar stimulation for epilepsy.

The CM and the anterior nucleus (AN) of the thalamus have been proposed as targets for DBS treatment of epilepsy.[93-96] Andrade et al[96] described 8 patients with intractable seizures who underwent bilateral DBS of the AN (6 patients) or of the CM (2 patients) of the thalamus; 3 patients had a generalized seizure disorder, and 5 had partial complex seizures. During a follow-up period of 2 to 7 years, all patients experienced a reduction in seizures; however, the 2 patients who underwent CM DBS did not have a clear benefit in overall control of their seizures. Of the 6 patients who underwent AN DBS, 5 had a greater than 50% reduction in seizure frequency, although not with initial stimulator activation. These findings led the authors to postulate that seizure reduction may initially be due to the postsurgical microthalamotomy effect and that longer term improvement may be due to long-term stimulation. Placebo effect cannot be completely excluded when interpreting these findings. McIntrye et al[97] noted improvement in seizure frequency after discontinuation of stimulation.

The Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial, a double-blind trial of AN DBS for refractory seizures, has suggested that targeting the AN of the thalamus is effective for refractory epilepsy. On the basis of the recently published results of the SANTE trial, the European Union has approved this strategy for treating epilepsy; however, the US Food and Drug Administration has not granted approval in the United States.[98] The AN is a relatively large area, and the precise target within that subnucleus has yet to be clarified. Chkhenkeli et al[99] demonstrated improvement in seizure activity with low frequency stimulation of the inferior caudate nucleus. Although their study consisted of 57 patients, the severity of seizures and the evaluation protocols varied substantially, and several patients had undergone previous resective surgeries. A study of a small number of patients with refractory seizures reported benefit with STN stimulation.[100] The hippocampus has also been a target; its appeal is the potential for being a treatment for patients who have bilateral seizure activity for which bilateral temporal lobectomy is rarely an option. Initial results from Velasco et al[101] showed variable but consistent reductions in seizures in 85% of patients (N=15) undergoing hippocampal stimulation. In a long-term follow-up study, Boon et al[102] reported that their 10 patients did not experience significant improvement after unilateral hippocampal stimulation ipsilateral to the seizure focus.

A randomized, double-blind multicenter sham stimulation trial of the responsive neurostimulator is currently under way in the United States. The responsive neurostimulator system is an implanted device designed to detect abnormal activity in the brain and respond, similar to an implantable cardiac defibrillator, by delivering electrical stimulation to suppress development of seizure activity. Electrodes rest on the surface of the brain connected to the programmable neurostimulator, which is implanted in the skull. More randomized, double-blind, controlled multicenter trials are necessary to establish the future role of DBS in patients with epilepsy. However, this renewed interest will undoubtedly spawn further investigations into the potential of this treatment option.

CAMPTOCORMIA

Camptocormia, a posture abnormality, is characterized by involuntary truncal flexion induced by standing or sitting and has been found to be associated with other neurologic disorders, including idiopathic PD.[103,104] Nandi et al[103] reported a case of a young man who did not have PD but who underwent bilateral GPi DBS for disabling camptocormia secondary to adverse effects of neuroleptic medication. Micheli et al[104] targeted the GPi bilaterally in a patient with PD and camptocormia; at 14 months postoperatively, the patient had near-complete resolution of his truncal flexion deformity. In the largest series of PD patients with camptocormia who underwent DBS surgery, Sako et al[105] targeted the STN bilaterally; all 6 of their patients experienced substantial improvement in their camptocormia and motor symptoms. Reports of success with STN or GPi stimulation in controlling axial posturing in patients with camptocormia support the notion that the basal ganglia plays an important role in maintenance of posture. These reports suggest that bilateral stimulation benefits camptocormia in patients with PD.

RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) can affect up to 25% of the adult population, and the percentage of patients with PD who also have RLS may be even higher.[106] Although the pathophysiology is unknown, it might be related to impaired central dopaminergic transmission. Single photon emission computed tomography has revealed reduced striatal dopamine D2-receptor binding in patients with RLS; thus, central striatal dopaminergic dysfunction is a possibility.[107]

Functional magnetic resonance imaging has shown that activation of the thalamus is associated with RLS sensory symptoms.[108] The effect of striatal dopaminergic dysfunction on basal ganglia and thalamic neuronal activity in RLS is unknown. High-frequency STN stimulation results in increased substantia nigra pars compacta neuronal firing, without an appreciable increase in central dopamine levels.[109] Therefore, it is unlikely that STN DBS improves RLS through alteration of central dopamine levels. Stimulation may result in neuronal firing in the basal ganglia with effects on the thalamus and diencephalon-spinal dopamine pathway.

Reports on the effect of DBS surgery on RLS symptoms are limited. Kedia et al[110] noted emergence of RLS after bilateral STN DBS surgery for PD. Conversely, in a study by Driver-Dunckley et al[111] of 6 patients who underwent bilateral STN DBS for PD with concomitant RLS, 3 patients had complete resolution, and 3 had near-total resolution of their symptoms. Bilateral STN DBS surgery can improve RLS in patients with advanced PD. More prospective studies should be undertaken to elucidate further the possible mechanisms whereby DBS improves RLS symptoms.

OBESITY AND ADDICTIONS

Obesity is an increasingly important health problem, and DBS has been used in obese patients.[112-115] The lateral hypothalamus and ventromedial hypothalamus are the appetite and satiety centers of the brain, respectively. More recent efforts have been directed toward the reward center of the brain, the NAc.[112] Current reports of chronic stimulation of the NAc suggest that modulation of the reward sensation may affect dietary preferences. Additional analysis has concluded that DBS for obesity needs to achieve a success rate of 83% to be comparable to current bariatric surgical procedures.[113] Interestingly, however, obesity has developed in patients with PD who underwent STN DBS.[114] Other addictions, including smoking and alcoholism, have been reported to improve after NAc DBS.[116,117]

DISORDERS OF CONSCIOUSNESS

Traumatic brain injury, a leading cause of persistent vegetative state (PVS) or minimally conscious state (MCS), has been a recent, albeit sparse, area of study of the effects of DBS. Reports of brain stimulation for PVS/MCS have been published as early as 1950. In 2010, Yamamoto et al[118] described their experience in 21 traumatic and nontraumatic brain–injured patients who were in either a PVS or a MCS and who underwent DBS targeting primarily the thalamic CM parafascicularis complex. Eight to 19 months postoperatively, the authors noted improvement in cognitive functioning in 8 of the patients. The recent reviews by Sen et al[119] and Lancioni et al[120] concluded that DBS for PVS or MCS may be an effective and viable option for future research and clinical trials.

ALZHEIMER DISEASE

Alzheimer disease (AD) is a progressive degenerative disorder; however, recent data suggest that the disease may also represent a disorder of the integrated cortical and subcortical pathways.[121] Hamani et al[115] reported memory improvement in a patient who underwent fornix/hypothalamus DBS for obesity. These findings led Laxton et al[122] to develop a phase 1 trial of fornix/hypothalamus DBS in 6 patients with mild AD. The researchers used positron emission tomography to measure pre- and postoperative cerebral glucose utilization as an indicator of quantitative effects of DBS. Increased glucose metabolism was observed in the temporal and parietal cortical areas at 1 month in all patients and was sustained in most of the affected areas at 1-year follow-up.[122] Cognitive assessments suggested improvement or slowing of anticipated decline at 6 and 12 months after DBS. No conclusions regarding the efficacy of DBS in AD can yet be drawn from this phase 1 study. However, given the unrelenting and destructive nature of AD, any advances in treatment options should be explored.

CONCLUSION

Deep brain stimulation has provided substantial clinical improvement in patients with several different diseases and disorders. The understanding of how DBS works has advanced during the past 2 decades, but there is still much to be learned. Functional imaging studies and intraoperative electrophysiological monitoring have added greatly to the understanding of the effects of stimulation on the neurotransmitters and functional brain pathways. Ongoing trials and proposed studies to assess the safety and clinical efficacy of DBS in multiple diseases are being aggressively pursued at multiple international centers.

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