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Deep Brain Stimulation for Neurologic and Neuropsychiatric Disorders

Review

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In the 1960s, ablative stereotactic surgery was employed for a variety of movement disorders and psychiatric conditions. Although largely abandoned in the 1970s because of highly effective drugs, such as levodopa for Parkinson's disease (PD), and a reaction against psychosurgery, the field has undergone a virtual renaissance, guided by a better understanding of brain circuitry and the circuit abnormalities underlying movement disorders such as PD and neuropsychiatric conditions, such as obsessive compulsive disorder. High-frequency electrical deep brain stimulation (DBS) of specific targets, introduced in the early 1990s for tremor, has gained widespread acceptance because of its less invasive, reversible, and adjustable features and is now utilized for an increasing number of brain disorders. This review summarizes the rationale behind DBS and the use of this technique for a variety of movement disorders and neuropsychiatric diseases.

Introduction

Stereotactic surgery for movement disorders, especially ablative approaches for Parkinson's disease (PD) and tremor, was commonplace in the 1950s and 1960s, along with psychosurgery, i.e., interventions to treat abnormal and even violent behavior with focal lesions of different brain regions. Stereotactic surgery greatly decreased for movement disorders with the introduction of levodopa for PD in the 1960s, and psychosurgery came under severe criticism and was abandoned in the 1970s. However, it soon became clear that patients on levodopa and other antiparkinsonian drugs often develop significant drug-induced complications, such as involuntary movements (dyskinesias), motor fluctuations, hallucinations, and psychosis, which limit the usefulness of these drugs.

These findings, combined with a better understanding of the pathophysiologic basis of movement disorders and neuropsychiatric conditions, rekindled interest in the earlier surgical approaches. With significantly improved techniques, surgeons first revisited the use of ablative procedures. More recently, however, electrical deep brain stimulation (DBS) has largely replaced ablation, because it is less invasive, reversible, and adjustable. In this review, we will survey the rationale and current use of this neuromodulation technique in a variety of movement disorders and neuropsychiatric diseases.

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In DBS procedures, stimulation electrodes are chronically implanted into specific brain regions, and continuous electrical high-frequency stimulation is delivered via an implanted, externally programmable pulse generator, similar to a cardiac pacemaker. The use of this technique for movement disorders was pioneered in the 1980s by Benabid, who first stimulated the thalamus for essential tremor (ET) and tremor seen in PD. The subthalamic nucleus (STN) was subsequently targeted for PD, following the finding that STN lesions dramatically reversed the motor signs of Parkinsonism in experimental animals. Although FDA approval has been given only for ET and PD, the use of DBS has been extended to other neurologic diseases and is now also being studied for psychiatric disorders. The exact mechanism of action of DBS remains uncertain, but the use of this technique has brought dramatic and lasting benefits to patients with an increasing number of disorders.

Basal Ganglia and Cerebellar Circuits

The reintroduction of surgical procedures like DBS was guided by the growing understanding of the circuitry of the basal ganglia and cerebellum, which were shown to be components of larger brain circuits, and by the realization that anatomically identifiable pathology in these circuits could account for many of the motor, cognitive, emotional, and motivational disturbances seen in movement disorders, such as PD of dystonia, and some of the neuropsychiatric disorders, such as Tourette's syndrome (TS) or obsessive compulsive disorder (OCD). Modern models of these circuits, introduced in the 1980s based on physiologic and anatomical studies, postulated that basal ganglia, thalamus, and cortex are components of segregated, largely closed, reentrant loop structures, which originate in specific cortical areas, traverse the basal ganglia and thalamus in nonoverlapping regions, and then return to their respective (frontal) areas of origin (Alexander et al., 1986). The different circuits are commonly designated as "motor," oculomotor," "prefrontal," and "limbic" (Figure 1). While these terms do not adequately capture the complexity of the functions subserved by these circuits, we will continue their use in this review for simplicity. It is thought that all of the basal ganglia-thalamocortical circuits are built following a similar general anatomical scheme, which is shown in Figure 2. The figure also shows the cerebello-thalamocortical system that functions (largely) in parallel to the circuits traversing the basal ganglia. DBS and other focal neurosurgical interventions appear to work through selective effects on these cortico-subcortical circuits. Common and experimental DBS targets are indicated with asterisks in Figure 2.

DBS for Movement Disorders

The rationale for using DBS in movement disorders is that these disorders arise at least in part from dysfunction within the basal ganglia-thalamocortical "motor" circuit. The motor circuit (Figures 1 and 2) originates from pre- and postcentral sensorimotor fields and involves the putamen (the motor portion of the striatum),

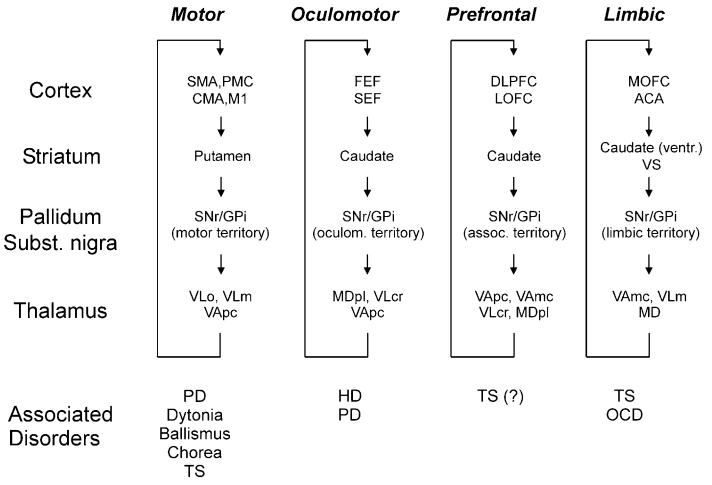

Figure 1. Circuit Anatomy of Cortex-Basal Ganglia-Thalamocortical Circuits

Intrinsic anatomy of the basal ganglia-thalamocortical circuitry. Abbreviations: ACA, anterior cingulate area; CM, centromedian nucleus of thalamus; CMA, cingulate motor area; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; HD, Huntington's disease; LOFC, lateral orbitofrontal cortex; M1, primary motor cortex; MDpl, mediodorsal nucleus of thalamus, pars lateralis; MOFC, medial orbitofrontal cortex; Pf, parafascicular nucleus of the thalamus; PMC, premotor cortex; SMA, supplementary motor area; SEF, supplementary eye field; VApc, ventral anterior nucleus of thalamus, pars parvocellularis; VAmc, ventral anterior nucleus of thalamus, pars magnocellularis; VLm, ventrolateral nucleus of thalamus, pars medialis; VLo, ventrolateral nucleus of thalamus, pars oralis; VLcr, ventrolateral nucleus of thalamus, pars caudalis, rostral division. See text for other abbreviations.

as well as motor portions of the external and internal pallidal segments (GPe and GPi, respectively), the STN, and the substantia nigra pars reticulata (SNr). GPi and SNr are the basal ganglia output nuclei, projecting to portions of the ventral anterior and ventrolateral nucleus of the thalamus (VA and VL, respectively). Thalamocortical projections from VA and VL to the frontal motor and premotor areas close the motor circuit.

Parkinson's Disease

PD is a progressive disorder with multiple etiologies, including genetic and environmental factors. The primary movement abnormalities in PD, collectively called parkinsonism, include slowness of movement (bradykinesia), tremor at rest, and muscular rigidity. These are due to degeneration of dopaminergic neurons in the SNc and their projections to the striatum, which secondarily result in striatal dopamine depletion (Figure 2). At least in the early stages of PD, the dopamine depletion preferentially affects the motor circuit. In the most common form of parkinsonism, sporadic PD, the motor signs are often accompanied by nonmotor features such as depression, anxiety, autonomic dysfunction, sleep disorders, and cognitive impairment. Although these may result in part from dopamine loss in nonmotor basal ganglia circuits, it is believed that additional (nondopaminergic) pathology throughout the brainstem and forebrain contributes as well (Braak et al., 2003).

Dopamine depletion in the basal ganglia induces prominent changes in neuronal activity within the motor circuit. Thus, neuronal activity in GPi and STN has been demonstrated to be increased in parkinsonian animals and humans, and abnormal oscillatory activity and increased synchrony of neuronal discharge has been observed throughout all elements of the motor circuit (recently reviewed in Gatev et al., 2006). While the link between specific basal ganglia discharge abnormalities and the behavioral manifestations of parkinsonism remains uncertain, it is likely that some or all signs of parkinsonism arise from the fact that the abnormally patterned basal ganglia output functionally disables related thalamic and cortical areas. Functional imaging studies have demonstrated that the changes in basal ganglia activity are associated with abnormal activation patterns in cortical motor (and other) areas both at rest and with movement. DBS within the motor portions of the STN or the GPi largely reverses these abnormalities.

DBS in GPi or STN. The most common indications for surgery in PD are intractable tremor or drug-induced motor fluctuations or dyskinesias. The best candidates for DBS treatment in PD are patients with levodopa-responsive parkinsonism who are free of significant dementia or psychiatric comorbidities. In contrast, patients with atypical parkinsonism or dementia benefit little, or not at all. Targets in the motor portion of GPi or STN are currently preferred for DBS in PD. DBS is most often performed bilaterally and simultaneously, but unilateral DBS can be highly effective for asymmetric cases. DBS in these areas alleviates parkinsonian motor signs, particularly during "off" periods, and reduces the often troublesome dyskinesias, dystonia, and motor fluctuations that result from drug administration (Anderson et al., 2005; Rodriguez-Oroz et al., 2004; Weaver

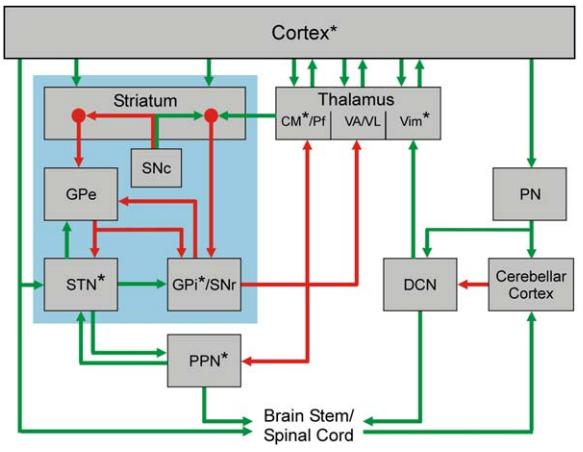

Figure 2. Intrinsic Anatomy of Cortico-Subcortical Circuits

Inhibitory (GABAergic) connections are shown as red arrows, and excitatory (glutamatergic) connections are shown as green arrows. The basal ganglia are shown in the blue rectangle. Common and experimental DBS targets are marked with asterisks. PN, pontine nuclei. For other abbreviations, see legend to Figure 1 and text.

et al., 2005). Both procedures have been shown to strongly improve the patient's quality of life, and both are more effective than medical management in the target population of patients with advanced PD (Deuschl et al., 2006; Halbig et al., 2005). In contrast to patients with GPi-DBS, those with STN-DBS are often able to substantially reduce their medications (Rodriguez-Oroz et al., 2004), which may, in part, account for the antidyskinetic effects of this procedure. Although there are no published blinded comparisons of the effects of GPi- and STN-DBS, the STN is currently preferred by most neurosurgeons because of its perceived greater antiparkinsonian effect. Controlled clinical trials comparing the two targets are nearing completion.

The major surgical risk of suffering significant surgical complications such as intracerebral hemorrhages is small (1%–2%). However, stimulation itself may also have side effects, including the induction of paresthesias, involuntary movements, or cognitive and mood changes. Many of these can be eliminated by adjusting the stimulation parameters. Interestingly, GPi- and STN-DBS differ in the incidence of cognitive and mood side effects. Cognitive side effects, specifically reduced lexical fluency and declines in executive functions (see, e.g., Parsons et al., 2006; Troster et al., 1997), are more often seen with STN-DBS than with GPi-DBS (Anderson et al., 2005). Postoperative mood problems are also more frequent after STN-DBS and include depression, mania, anxiety, and apathy (Temel et al., 2006). These side effects are likely caused by inadvertent stimulation of limbic circuit elements in portions of the nearby zona incerta, the ventral STN, or the SNr (e.g., Bejjani et al., 1999; Stefurak et al., 2003).

In both types of DBS procedures, the basal ganglia motor circuit is targeted, often through the use of intraoperative microelectrode mapping of neuronal responses to passive and active movements. In GPi, the motor territory is contained within the posterolateral part of the nucleus, while for STN-DBS, the anterodorsal border of the nucleus has been identified as the optimal DBS target. DBS at this location is likely to reach a larger proportion of the motor circuit within the much smaller STN than DBS within the GPi motor area. This may account for the perceived differences in effectiveness. Stimulation at the "ideal" STN-DBS target may spread to involve portions of the dorsally adjacent fields of Forel and the zona incerta (e.g., Yelnik et al., 2003).

Although it was initially believed that DBS, like lesioning, functionally inactivated the target, evidence now suggests more complex mechanisms of action. The electrophysiologic effects of GPi- or STN-DBS may depend on the distance of the stimulated elements from the electrode and may differ between the elements themselves. Modeling studies have shown that STN-DBS may inhibit the somata of STN cells through activation of local GABA release from GPe afferents, while directly activating STN axons (McIntyre et al., 2004). Stimulation in the STN has been demonstrated to evoke complex excitatory effects in the GPi, one of the primary recipients of STN efferents (Figure 2; e.g., Hashimoto et al., 2003), and may alter oscillatory resonance characteristics of the STN-GPi network (Brown et al., 2004). Stimulation of GPi may directly activate the axons of GPi cells. Both forms of DBS are likely to secondarily

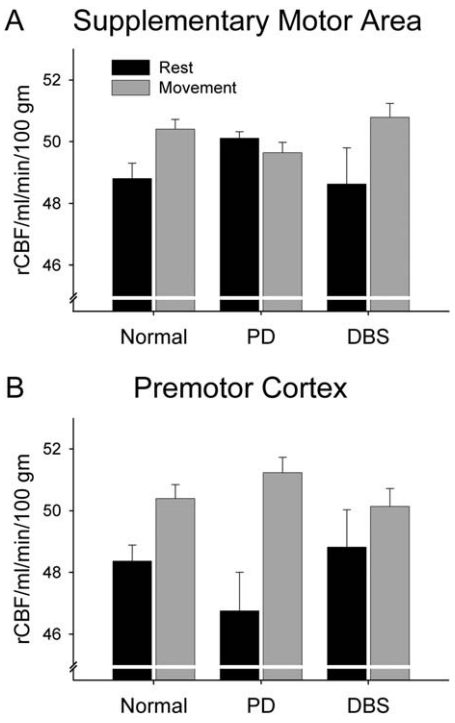

Figure 3. Effective DBS Normalizes Relative Cerebral Blood Flow Patterns in Cortical Motor Areas in PD Patients

Plots of relative cerebral blood flow (rCBF; shown as means ± SEM), measured with PET, in supplementary motor area (A) and prefrontal cortex (B) in normal controls (n = 13), and in PD patients (n = 6) with and without effective DBS. In all conditions, rCBF was measured at rest (black columns) and with standardized arm movements (gray columns). DBS normalized the activation of brain regions that were underactive (A) or overactive (B) in PD, relative to healthy controls. Data are from Grafton et al. (2006) and are used with permission.

alter firing patterns in the associated thalamocortical circuitry. In support of this idea, STN-DBS has been shown to normalize intracortical inhibitory mechanisms in transcranial magnetic stimulation studies (Pierantozzi et al., 2002), and functional imaging studies have shown that DBS induces widespread normalization of activity in frontal motor areas both at rest and with movement tasks (see Figure 3 and, e.g., Grafton et al., 2006).

Other DBS Targets in PD. Similar to other tremor forms (see below), parkinsonian tremor can be effectively treated with thalamic DBS at the border between the thalamic nucleus ventralis oralis (Vop) and the nucleus ventralis intermedius (Vim) (Kumar et al., 2003; Ondo et al., 1998). Unfortunately, DBS at this location does not provide consistent benefits to parkinsonian signs other than tremor (Ondo et al., 1998) and is therefore appropriate for only a small minority of parkinsonian patients (Obeso et al., 1997).

Several small studies have also described beneficial results with extradural motor cortex stimulation (Pagni et al., 2005). The procedure appears to result in improved motor performance and reductions in dyskinesias and psychiatric symptoms, perhaps mostly because of reductions in medication requirements. A recent primate study has confirmed the antiparkinsonian effects of motor cortex stimulation (Drouot et al., 2004).

Stimulation of the pedunculopontine nucleus (PPN) in the brainstem has also been explored in PD. The PPN is a major target of GPi output and projects back to the STN as well as downstream (Figure 2; Mena-Segovia et al., 2004). Inactivation of the PPN has been shown to induce akinesia in animals (Kojima et al., 1997). Positive effects of low-frequency stimulation of the PPN have been described in MPTP-treated monkeys (Nandi et al., 2002b) and, recently, also in parkinsonian patients (Plaha and Gill, 2005).

As mentioned elsewhere in this review, stimulation of the region of the caudal ZI, just behind the STN, has significant effects on parkinsonian tremor, as well as rigidity and akinesia, reportedly rivaling those of STN-DBS (Kitagawa et al., 2005; Plaha et al., 2006). At this location, DBS may exert its antiparkinsonian activity through effects on ZI itself, but also on pallidofugal fibers to the thalamus, which pass through the stimulated area.

Dystonia

Dystonia is characterized by involuntary twisting movements, especially during attempted movement, as well as abnormal postures, muscular agonist/antagonist cocontraction, and "overflow" phenomena, where muscle activation spreads beyond that intended. Dystonia can occur in a primary form, i.e., without an identified structural or chemical abnormality, or as secondary dystonia, due to drugs, brain lesions, or other movement disorders, such as PD. Dystonia can also be classified into generalized and focal forms. Generalized dystonia usually starts in childhood, while focal dystonia occurs more commonly in adults, and may involve speech, eyelid closure, or neck or hand movements. While focal dystonias can often be managed with botulinum toxin injections, the medication treatments of generalized dystonia are less effective.

Neuroimaging studies in dystonic patients have demonstrated changes in portions of the motor circuit at both cortical and subcortical nodes (Carbon et al., 2004). Based on single-cell recording studies in patients, it appears that dystonia and PD are (grossly) similar with regard to many of the pattern changes in basal ganglia output. In contrast to PD, however, overall GPi output appears to be reduced (Starr et al., 2005). In cases of focal dystonia, there is electrophysiologic evidence for reduced cortical inhibition, and aberrant organization of somatosensory cortical maps (Hallett, 2004). These findings, together with the delayed effects of surgery (see below), support the concept that abnormal motor learning or excessive neuroplasticity may play a role in dystonia.

DBS Surgery for Dystonia. The insight that dystonia may arise from abnormalities in circuit elements shared by parkinsonism and the past experience with ablative procedures in dystonia have led to trials of GPi-DBS in cases of advanced intractable dystonia. Recent case reports suggest that STN-DBS may also be effective (Pastor-Gomez et al., 2003).

GPi-DBS has excellent effectiveness in cases of generalized dystonia (Coubes et al., 2004; Eltahawy et al., 2004; Vidailhet et al., 2005) but is less effective in secondary dystonia (e.g., Cif et al., 2003). Other emerging indications for GPi-DBS are cervical and tardive dystonia (e.g., Eltahawy et al., 2004; Loher et al., 2000; Trottenberg et al., 2005). For unclear reasons, the effects of GPi-DBS are usually delayed, often by weeks or months (Krauss et al., 2002). While it can be speculated that these delays involve anatomic or functional remodeling of neuronal interactions within the basal ganglia-thalamocortical circuitry, no specific information regarding this point is available. GPi-DBS for dystonia has few (if any) cognitive side effects (Pillon et al., 2006). GPi-DBS, administered to the motor portions of GPi, modulates activity in the basal ganglia-thalamocortical motor circuit. PET activation studies have shown that GPi-DBS reverses the over-activity of motor cortical areas present in dystonia (Detante et al., 2004), and electrophysiologic studies have demonstrated that GPi-DBS may enhance motor cortex excitability through modulation of thalamocortical projections (Kuhn et al., 2003).

Tremor

A variety of tremor types, other than the rest tremor of PD, are suitable for DBS, such as ET, cerebellar or intention tremor, and brainstem (Holmes) tremor. Tremor is also seen in the setting of other disorders, such as dystonia or multiple sclerosis. As mentioned before, tremor was the first movement disorder to be treated routinely with DBS, and it continues to be one of the major applications of this technique. DBS of the Vim nucleus of the thalamus, a part of the cerebello-thalamocortical system, appears to be effective for most forms of tremor (regardless of etiology). The choice of this DBS target was guided by the previous experience with Vim thalamotomy procedures. Thus far, there is no unifying pathophysiologic hypothesis that would explain the almost universal effectiveness of thalamic interventions in these varied tremor disorders. Only recently, other targets have emerged as possible alternatives.

Essential Tremor. ET, the most common movement disorder, is the prototypical action tremor, present with both movement and posture. Despite the availability of a number of effective medical treatments, the tremor remains poorly controlled in a substantial portion of ET patients. For these patients, surgery is a viable treatment alternative. The usefulness of Vim-DBS was serendipitously discovered while physicians were performing thalamotomies (Benabid et al., 1993). The optimal target for Vim-DBS for ET treatment has been identified as the border of Vim and Vop (Yamamoto et al., 2004). Numerous studies have confirmed that Vim-DBS reduces ET (Kumar et al., 2003; Ondo et al., 1998). The procedure benefits appendicular, vocal, and head tremor (e.g., Taha et al., 1999). It significantly improves the quality of life in ET patients (Fields et al., 2003) and remains beneficial over time (Rehncrona et al., 2003), although some tolerance may develop (Kumar et al., 2003).

Vim-DBS has now almost replaced thalamotomy as the surgical treatment of choice for ET, primarily because of its superior safety profile (Tasker, 1998). Although most side effects are mild (Ondo et al., 1998), persistent paresthesias and pain, and, in patients receiving bilaterally implants, dysarthria and balance difficulties, appear to be rather common (Pahwa et al., 2006). Vim-DBS has only minor effects on cognitive functioning with slight declines in verbal fluency (Fields et al., 2003).

The mechanisms that underlie the beneficial effects of Vim-DBS in ET are unclear. In agreement with the fact that Vim is part of the cerebello-thalamocortical circuitry

(Figure 2), recent imaging studies have shown that cerebral blood flow in motor cortex and cerebellum is altered by Vim-DBS (Ceballos-Baumann et al., 2001; Fukuda et al., 2004).

Besides Vim surgery, DBS of the caudal zona incerta region (discussed above, e.g., Kitagawa et al., 2000; Murata et al., 2003) has recently been shown to be highly efficacious in ET and other forms of tremor, especially those with a prominent proximal limb involvement. Recent case reports have suggested that DBS of the STN may also be effective in some cases of ET, specifically in cases in whom ET coexists with other movement disorders, such as PD (Stover et al., 2005).

Tremor Associated with Multiple Sclerosis. Multiple sclerosis is frequently associated with severe intention tremor, most likely because of the predilection of demyelinating lesions for the cerebellar outflow tracts. Thalamic DBS has proven to be at least partially effective, especially in young patients with little comorbidity (Berk et al., 2002; Moringlane et al., 2004). A recent analysis of 75 published cases of DBS in multiple sclerosis came to the conclusion that the majority of patients benefited from the procedures, although complete cessation of tremor was rare (Wishart et al., 2003). As discussed above for ET, the caudal zona incerta target appears to be beneficial for the treatment of tremor associated with multiple sclerosis (Nandi et al., 2002a).

Holmes Tremor and Other Tremor Forms. Holmes tremor, resulting from brainstem lesions that affect cerebellar outflow, is a combined rest, postural, and intention tremor. Only a small number of cases of this tremor type have been treated with Vim-DBS (e.g., Romanelli et al., 2003), and these cases have had excellent results. Vim stimulation has also been used for other tremor forms, often due to rare diseases, such as phenylketonuria (Payne et al., 2005) or inherited cerebellar ataxia (Schramm et al., 2005).

DBS Use in Neuropsychiatric Disorders

The previous era of psychosurgery ended in the 1970s because of severe condemnation of the excessive and indiscriminate use of these procedures, their disappointing outcomes, and the lack of patient protection. It may seem surprising, then, that neurologists, neurosurgeons, and psychiatrists are again exploring surgical procedures for severe psychiatric disorders, such as OCD, TS, and depression. The acceptance of DBS is due to several facts, including (1) the failure of existing drugs to deal effectively with the psychiatric condition in a subset of patients, (2) the remarkable success of DBS procedures in treating movement disorders, (3) the relatively less invasive and reversible nature of DBS, (4) the greater public awareness of the enormous lifelong burden of these disorders on patients and their caregivers, and (5) the greater scrutiny and protection of patient rights. DBS procedures for neuropsychiatric conditions remain strictly experimental at this point.

Use of DBS in neuropsychiatric diseases is based on findings suggesting that these conditions are, at least partly, due to abnormalities within the nonmotor basal ganglia circuits, most prominently the limbic circuitry. As shown in Figure 1, the limbic circuit originates from the anterior cingulate and medial orbitofrontal cortices; engages the ventral striatum, the ventral and rostromedial GPi, and the rostrodorsal SNr; and continues to the paramedian portion of the mediodorsal nucleus of the thalamus, which projects back to the anterior cingulate cortex. Under physiologic conditions, this circuit may play a role in motivated behavior, and the modulation of emotional "tone," and may provide reinforcing stimuli to the ventral tegmental area and the SNc.

Obsessive Compulsive Disorder

OCD is a relatively common disorder, characterized by the presence of intrusive thoughts and compulsive behaviors and rituals. Selective serotonin reuptake inhibitors are highly effective in the majority of patients, but some severe cases are refractory and may benefit from surgical treatments. Neurosurgical treatments of OCD have been carried out for many years, using empirically defined targets, e.g., the anterior limb of the internal capsule (IC). Lesions such as anterior capsulotomy may benefit 35%–70% of these patients, but the irreversibility of lesions frequently deters patients from this treatment option.

Case reports and small case series have shown that the anterior limb of the IC is not only a lesioning target, but also a target for DBS (Nuttin et al., 2003). The benefits from the procedure are long lasting (Greenberg et al., 2006). In most treated patients, few side effects are seen. However, in a recent case report, a patient developed panic attacks with (presumed) ventral striatal (VS) stimulation (Shapira et al., 2006). DBS of other areas, such as the STN, is also currently being evaluated (Fontaine et al., 2004).

Functional imaging studies in OCD patients have demonstrated abnormalities in the activity of limbic basal ganglia-thalamocortical projection systems. Similar studies have suggested that anterior capsule stimulation works in OCD by influencing the activity in the nearby limbic VS (e.g., Nuttin et al., 2003). In fact, in one OCD patient treated with *direct* VS stimulation, long-lasting benefits were seen (Aouizerate et al., 2004). A recent PET imaging study has demonstrated that brain activity during DBS of the VS/IC target is enhanced predominately in limbic areas of cortex, basal ganglia, and thalamus (Rauch et al., 2006).

Tourette's Syndrome

TS is a familial, neurologic disorder characterized by childhood onset of motor and vocal tics. The tics are typically rapid, stereotyped movements with eye blinking and head and facial movements, as well as vocalizations such as throat clearing, coughing, grunting, or more complex behavioral acts and utterances. In addition, a high percentage of patients suffer from OCD, attention-deficit hyperactivity disorder, depression, and psychosocial difficulties, which are often more disabling than the tics. Symptoms typically peak in preadolescence and decline in the later teens for most patients. In many patients, the tic disorder is effectively treated with dopamine receptor antagonists, while the other components of TS may require antidepressant and other therapies. Based on imaging and other studies, TS appears to involve abnormalities in both the limbic and motor circuitry (see Figure 1), accounting for the complex constellation of nonmotor and motor signs.

In a small proportion of TS patients, severe symptoms persist into adulthood in spite of all therapeutic efforts. Recently, reports of single cases or small case series

have explored the use of DBS in such patients. Several targets have been used, including the midline intralaminar nuclei of the thalamus (Houeto et al., 2005; Temel and Visser-Vandewalle, 2004; Visser-Vandewalle et al., 2004), the motor and limbic portions of GPi (Houeto et al., 2005), and the anterior limb of the IC, close to the VS (Flaherty et al., 2005). The published reports describe that these procedures often result in >70% reductions in vocal or motor tics with disappearance of the sensory urge that often accompanies TS, even long-term. Before the use of these procedures can be recommended for routine treatment in TS patients, careful exploration of the various targets and the development of patient selection guidelines are mandatory (Mink, 2006).

Depression

Depression is one of the most common psychiatric disorders. Most patients are treated with drug therapy and behavioral therapies. Vagal nerve stimulation and electroconvulsive therapy may be tried in cases of depression that do not respond. A small proportion of patients nonetheless continue to suffer from severe intractable depression.

Interestingly, signs and symptoms of severe depression can be (reversibly) induced in PD patients undergoing DBS (e.g., Bejjani et al., 1999; Temel et al., 2006), likely because of inadvertent stimulation of limbic portions of the STN, the adjacent ZI, or SNr. The insight that focal brain stimulation can profoundly alter limbic function suggests that DBS of the limbic circuitry (at other targets) could be used to treat depression in patients who suffer from intractable forms of the disease.

Although earlier single case studies have reported that DBS of mesothalamic targets or of the inferior thalamic peduncle is effective against reactive depression in patients with chronic pain (Andy and Jurko, 1987), or treatment-resistant major depression (Jimenez et al., 2005), respectively, the precise target has not been well defined. In a recent study involving six patients with refractory depression, it has been shown that DBS of the white matter in the subgenual cingulate region (area 25) can produce very significant clinical benefits (Mayberg et al., 2005). This target was chosen after a series of neuroimaging studies showed that area 25 is overactive in depression (Mayberg et al., 1999). A region in the rostral cingulate gyrus has also been proposed as a possible target for DBS in depression (Sakas and Panourias, 2006).

Conclusions

The insight that the signs and symptoms of several major movement disorders and neuropsychiatric diseases are, at least in part, due to dysfunction within specific cortico-basal ganglia-thalamocortical circuits provides a basis for understanding the pathophysiologic basis of these disorders and has guided renewed trials of focal surgical interventions for patients with medication-resistant forms of these diseases. Because of its reversibility and adjustability, DBS has rapidly become the neurosurgical procedure of choice in these cases, largely replacing ablation. For movement disorders, it is proposed that DBS works by (nonspecifically) freeing thalamocortical and brainstem motor systems from abnormal and disruptive basal ganglia influences. The striking effectiveness of targeted focal surgical interventions such as DBS has lent further support for the existence of circuit disorders that result from pathology in specific cortical-subcortical and other networks. Although explorations of the pathophysiologic basis of complex neuropsychiatric disorders such as TS, OCD, and depression are just getting underway, preliminary results suggest that DBS may also benefit selected advanced medically refractory cases of these conditions.

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