MOVEMENT DISORDERS, SUCH as Parkinson’s disease, tremor, and dystonia, are among the most common neurological conditions and affect millions of patients. Although medications are the mainstay of therapy for movement disorders, neurosurgery has played an important role in their management for the past 50 years. Surgery is now a viable and safe option for patients with medically intractable Parkinson’s disease, essential tremor, and dystonia. In this article, we provide a review of the history, neurocircuitry, indication, technical aspects, outcomes, complications, and emerging neurosurgical approaches for the treatment of movement disorders.

KEY WORDS: Deep brain stimulation, Dystonia, Essential tremor, Globus pallidus pars interna, Movement disorders, Parkinson’s disease, Stereotaxis, Subthalamic nucleus, Ventralis intermedius nucleus

Historical Perspective

Various surgical approaches, such as resection, lesioning, stimulation, and others, have been used to treat patients with movement disorders. Craniotomies were performed for the resection of the motor cortex (68), cerebral peduncles (381, 382), and a variety of subcortical lesioning procedures (326). Irving Cooper (72a) first reported the effects of ligation of the choroidal artery for Parkinson’s disease (PD) in 1953. Six patients were treated with eight ligations, which resulted in significant alleviation of rest tremor, rigidity, and contralateral cogwheeling. It was not until the introduction of stereotaxis by Spiegel et al. (328) in 1947, and later by Leksell (206) in 1949, that a more accurate, less invasive, and more consistent placement of lesions in various subcortical locations became feasible.

The development of stereotaxy led to a variety of lesioning procedures of the basal ganglia and the thalamus for the treatment of rigidity and tremor in the 1950s and 1960s. Various surgical techniques, lesion locations, lesion sizes, and outcomes were reported (77, 256, 327, 392). The motor thalamus and the pallidal targets lying in the ventral and posterior portions of the globus pallidus internus (GPI) as well as the pallidal projections were considered to be the most effective targets. However, it was the advent of l-dopa in the mid-1960s and its significant clinical benefits that led to a dramatic decrease in surgery for PD. For the next 20 years, surgery for movement disorders was predominantly limited to thalamotomy (8, 115–117, 149, 167, 254, 275, 343) for the treatment of tremor and pallidotomy and thalamotomy for dystonia (224, 341, 371, 383). PD surgery was rarely performed during this time. It was not until the late 1980s that there was a reemergence of interest in the neurosurgical treatment for PD due to the increasing realization of the limitations of PD medications and the side effects of l-dopa. This led to a resurgence of lesioning surgeries such as pallidotomies for PD. The initial Leksell (336) target of pallidal lesions for treatment of PD was modified and repopularized by Laitinen et al. (196, 197). Original analytical descriptions of thalamic nuclei and circuitry by Hassler (142), Hassler et al. (143), and Macchi and Jones (230) and basal ganglia circuitry by Delong et al. (81, 82) also served as a foundational substrate for newer targets for therapeutic interventions using stereotactic techniques.

The ability of electrical impulses to modify functional outcome in certain brain regions was identified almost 200 years ago, in 1809, by Rolando (98). Aldini had previously attempted to stimulate the brains of executed criminals immediately after death by applying current from voltaic piles (98). The use of electrical stimulation to understand and map the function of the human brain and its circuitry became commonplace in the 20th century (4, 64, 65, 291). Early explorations by Hassler et al. revealed that acute low-frequency stimulation during stereotactic exploration for ablation of...
the pallidum could augment tremor, whereas high-frequency stimulation at 25 to 100 Hz had the opposite effect (143). These observations paved the way for the future development of chronic electrical stimulation therapies for the management of movement disorders.

The first systematic use of chronic deep brain stimulation (DBS) for the treatment of movement disorders is attributed to Bechtereva et al. (22) in Russia. Beginning in 1967, they reported benefits with chronic DBS of the thalamus, striatum, and pallidum. But it was not until the 1980s that Brice and McLellan (54), Blond and Siegfried (52), Siegfried and Shulman (319), and Benabid et al. (34, 36) published reports of the use of chronic electrical stimulation or DBS for the treatment of movement disorders, thus ushering in a new era of functional neurosurgery for movement disorders.

DBS has similar efficacy as that reported with various lesioning procedures (e.g., pallidotomy, thalamotomy). However, the superior safety profile of DBS relative to lesioning procedures, particularly bilateral thalamotomy and pallidotomy, has made it the procedure of choice in countries where access to this technology is available.

DBS, with its inherent features of reversibility and adjustability, has gained popularity and emerged as the neurosurgical standard of care for movement disorders such as PD, dystonia, and essential tremor over the past 20 years (6, 9, 25, 32, 33, 37, 70, 101, 187, 193, 201, 202, 227, 252, 268, 274, 280, 293, 294, 343, 351, 357, 394). Since its inception, more than 40,000 DBS implants have been performed in more than 500 centers worldwide (28). In addition to the widespread use of DBS for movement disorders, a number of clinical investigations using DBS are under way to explore its safety and efficacy for conditions such as Tourette’s syndrome (14, 88, 111, 155, 243, 266, 322, 366), chronic pain (48, 69, 119, 188, 210, 295), and psychiatric disorders such as depression (60, 109, 238, 310, 314) and obsessive-compulsive disorder (OCD) (73, 121, 122, 190, 242, 386). Because DBS is the most commonly used neurosurgical procedure for the treatment of movement disorders, it is the major focus of this article.

Neural Circuitry of Movement Disorders

Traditionally, surgical procedures have targeted the known anatomic subcortical gray or white matter regions implicated in the circuitry and the pathophysiology of movement disorders. As discussed above, a long history of lesioning procedures for the treatment of movement disorders has provided a wealth of empirical evidence supporting the presumed underlying neurocircuitry associated with the aberrant motor symptoms. During the past two decades, technological advances in structural and functional brain imaging and physiological brain mapping, coupled with animal research, have further advanced our understanding of the underlying neurocircuitry of specific movement disorders, and led to additional refinement of the surgical targets.

The use of animal models has contributed significantly to a better understanding of the pathophysiology and underlying neurocircuitry of PD and other movement disorders (2, 29, 39, 41, 53, 56, 62, 83, 99, 120, 133, 135, 144, 152, 204, 205, 209, 223, 234, 239, 241, 246, 248, 249, 262, 273, 283, 292, 320, 325, 332, 340, 343, 385, 391). These data provided support for the concept of the cortico-striatal-pallidal-thalamic-cortical (CSPTC) circuits. Alexander et al. (7) hypothesized that a network of five parallel, segregated circuits exists that underlies a variety of functions. These circuits originate in various regions of the frontal lobes and then traverse through different nodes in the striatum, pallidum, and thalamus before returning to their cortical points of origin. One of these circuits underlies complex motor function and is implicated in the pathophysiology of PD.

The concept of a CSPTC motor circuit or loop implies that a number of the nodes involved in the circuit are potential targets for neuromodulation including neurosurgical procedures such as lesioning and DBS, somatic or stem cells, or gene therapy.

In the CSPTC circuitry model, the striatal structures, such as the caudate and putamen, serve as the input structures, whereas the GPi and substantia nigra pars reticulata (SNr) are the primary output structures. The motor circuit originates in the precentral motor regions (especially Brodmann areas 4 and 6). Information passing through the basal ganglia is organized anatomically though “direct” and “indirect” pathways within the CSPTC circuit (Fig. 1). Information in the direct pathway passes monosynaptically from the putamen to the output structures of the basal ganglia, the GPi, and the SNr. Information from the indirect pathway passes multisynaptically through the globus pallidus externa (GPe) and the subthalamic nucleus (STN) before terminating on the GPi/SNr. The information from both the direct and indirect pathways then projects to various thalamic relay nuclei, including the ventral oralis anterior (Voa) and ventral oralis posterior (Vop) nuclei (in Hassler’s nomenclature) (230). This information is then projected back to the frontal region of origin, thereby closing the circuit. The direct and indirect pathways appear to balance one another. The direct pathway is presumed to be responsible for the initiation of action and the indirect pathway for the braking of action or the ability to switch from one action to another.

Inhibitory γ-aminobutyric acid (GABA)ergic projections predominate in these pathways. Other than the excitatory glutamatergic projections from the cortex to the basal ganglia and the returning excitatory thalamocortical projections, the only projections within the deep subcortical brain structures that are excitatory are the glutamatergic projections coursing from the STN to the GPi/SNr. The most common surgical targeted regions in this circuit are the STN, the GPi, and their associated CSPTC motor circuit white matter inputs and outputs. There are other emerging targets in the CSPTC motor loop that are being further investigated, but, given the scope of this review, they will not be discussed.

Dopamine is one of the most powerful neurotransmitters influencing the motor CSPTC circuit. Dopamine can have either an excitatory or inhibitory role on striatal neurons, depending on the dopamine receptor subtype: D1 receptors are associated with an excitatory effect, whereas D2 receptors are inhibitory. In general, dopaminergic inputs to the striatum serve to reduce
basal ganglia output and subsequently disinhibit thalamocortical activity. Dopaminergic activity may also ultimately facilitate activity through the direct pathway over the indirect pathway, but this hypothesis is still under debate (110).

PD is a disorder characterized primarily by dopamine loss in the substantia nigra pars compacta, which results in the classic motor symptoms of PD, including tremor, rigidity, bradykinesia, gait difficulties, and postural changes. The reduced dopaminergic input associated with PD causes an increase in activity through the indirect rather than the direct pathway. This results in hyperactivity of the Gpi/SNr and subsequent inhibition of thalamocortical activation further downstream, which leads to reduced frontal cortical activity and the classic motor symptoms of PD (261, 263). The STN is one of the major driving forces behind the increased activity of the Gpi and SNr output nuclei. Given their unique role in the CSPTC motor circuit, the most common surgical targets are the STN, Gpi, and their associated CSPTC motor circuit white matter inputs and outputs. There are other emerging targets in the CSPTC motor loop which are being further investigated, but, given the scope of this review, they will not be discussed.

Recent advances in the pathophysiology of PD reveal that in addition to the abnormal frequency (hyper- or hypoactivity) between the structures of the CSPTC circuit, there is disordered neurophysiological rhythmic activities and patterns in these regions as well. Hashimoto et al. (141) assessed the effects of high-frequency (HF) STN DBS in the primate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of parkinsonism. HF DBS resulted in modifications in the pathological pattern of pallidal activity. Before stimulation, spontaneous pallidal activity was irregular, with varying intervals. Stimulation resulted in a higher frequency and regular pattern of spike activity, which correlated with improvements in parkinsonian signs. Further investigation on activity patterns has also been pursued by other groups. Synchronous low-frequency activity (in the β band) has been identified in the basal ganglia by Brown (55), Kühn et al. (189), Pogosyan et al. (287), and Trottenberg et al. (353) and correlated to bradykinesia. These results corroborate the recent view that the pathology of PD extends beyond abnormal frequencies and involves more complex interactions within the CSPTC circuit.

Although the pathophysiology of dystonia may be related to a disruption of the activity within the CSPTC circuit, the exact mechanisms are still uncertain. No gross morphological changes involving specific components of the CSPTC motor circuit or links to specific neurotransmitters have been consistently identified for dystonia. Electrophysiological studies indicate that the abnormality is not as simple as increased or decreased communication rates between the motor CSPTC loop components, but rather, a disruption of the communication pattern between two structures (370). Under this perspective, the effects of DBS could be mediated by a lesion-like effect that disrupts abnormal connectivity, similar to that which might occur after DBS for the treatment of PD. Thus far, the motor Gpi and ventral lateral (Voa/Vop) thalamus have been the primary surgical targets for dystonia.

The pathophysiology of essential tremor most likely involves components of the cerebellum, motor thalamus, and relevant frontal cortices, and, unlike PD and dystonia, it does not necessarily involve the CSPTC circuit. Essential tremor is probably related to frontocerebellar circuits in which axons from the cerebellum synapse on thalamic neurons that project to the cortex. Studies of patients with essential tremor who are undergoing positron emission tomography and functional magnetic resonance imaging (MRI) indicate hyperactivity of the cerebellum and thalamus (58, 387). These findings provide support to the well-established clinical knowledge that ablation of the cerebellar thalamus is highly effective in alleviating tremor. DBS of the ventralis intermediate nucleus (VIM) is demonstrated to be equally effective (275, 343) in alleviating tremor, and a recent study demonstrated that VIM DBS affects the excitability of the cerebellothalamocortical pathway (247).

The concept of CSPTC circuits and other neurocircuits is critically important in functional neurosurgery with respect to providing guidance regarding targets and sites of intervention. These circuits are a model of a network of interconnected regions that is implicated in normal motor functioning and abnormal functioning associated with various disease processes. The surgically accessible components of this network are potential targets of intervention, which can include lesioning procedures, DBS, or other neurorestorative approaches involving somatic or stem cells and gene therapy.

**Mechanism of DBS Action**

The placement of stereotactic lesions and DBS reflect two different methods of neuromodulation. Whereas lesioning destroys a given volume of tissue, DBS exerts a reversible electrical field on the surrounding nervous tissue elements. The underlying mechanism of action of DBS remains a point of debate and active research. There appears to be a combination of inhibition of neurons, modulation of abnormal patterns of activity, and activation of axons. Initial observations suggested that HF stimulation caused inhibition of the cellu-

![FIGURE 1. A, cortico-striato-pallido-thalamo-cortical (CSPTC) neural circuitry in normal state. B, CSPTC in Parkinson's disease (PD). SNC, substantia nigra pars compacta; GPe, globus pallidus externus; STN, subthalamic nucleus; Gpi, globus pallidus internus; SNr, substantia nigra reticulata.](image_url)
Surgical Patient Selection Criteria

In general, patients must be able to tolerate the various components of surgery and have the cognitive skills and social support structure to comply with the demands of surgery and the postoperative care. For those undergoing DBS surgery, both the patient and the family members need to have a detailed understanding of reasonable outcomes, potential complications, and the multiple steps involved in the preoperative assessments, surgery, and perioperative and follow-up care. The patient needs to cooperate with follow-up programming and medication adjustments in the outpatient setting. Additionally, the patient and family should have realistic expectations about surgical outcome, and they should understand that the surgery will not cure the disease or stop its natural progression. Neurosurgery for movement disorders can provide improvements in disabling motor symptoms and motor function. It is important to provide accurate information to the patient and family members regarding those symptoms that are likely to respond to surgery versus those that are not.

Patients should be in stable overall health with respect to cardiac, pulmonary, and systemic conditions such as hypertension, diabetes, and cancer. Patients who require anticoagulants, such as warfarin or antiplatelet medication, must be able to tolerate complete withdrawal from these medications before surgery. Consultation with other medical specialists may be required before proceeding with surgery.

In recent years, there has been increasing recognition of the neurobehavioral changes associated with PD and other movement disorders, including cognitive, mood, and personality changes. Neuropsychological assessment is recommended as part of the preoperative assessment to determine candidacy for neurosurgical intervention for the treatment of movement disorders. The neuropsychological assessment should include assessment of cognition, neuropsychiatric symptoms, social support, and goals for surgery. Patients with severe cognitive dysfunction or frontal dysexecutive syndrome may still undergo surgery, but these individuals should have a strong social support structure and receive extra counseling, along with family members, regarding the potential for increased risks for cognitive impairment and confusion post-surgery. Psychiatric conditions such as anxiety, depression, and mania must be identified and medically optimized by a specialist preoperatively. Neurosurgical intervention in patients with delusional psychosis or severe personality disorder, such as borderline personality disorder, is generally not recommended.

PD: Selection Criteria

PD is a progressive neurodegenerative disorder resulting in prominent motor abnormalities such as bradykinesia (slowness of movement), rigidity (muscle stiffness), tremor, and gait and postural instabilities. In PD, there is progressive degeneration of dopaminergic neurons. Administration of l-dopa and

Surgery: The Team

Surgery for movement disorders is most optimally managed in the context of a multidisciplinary team. In addition to the neurosurgeon, this team should include a movement disorders neurologist, a neuropsychologist, a neurophysiologist, and physician extenders such as nurse practitioners and physician’s assistants. The movement disorders neurologist can help confirm an accurate diagnosis and rule out atypical parkinsonism or psychogenic movement disorders. The benefit of surgery for a particular movement disorder is largely dependent on accurate diagnosis, as it is the underlying pathophysiology and neurocircuitry of the specific movement disorder that is influenced by surgery. The movement disorders neurologist can also optimize medications for individuals who have not had adequate medication trials. Occasionally, medication adjustments by an expert can significantly improve the functioning of a patient such that he or she no longer requires surgery. The DBS programming can be performed by the neurosurgeon, neurologist, or physician extenders. As DBS programming results in changes in motor symptoms, there must be close attention to concomitant medication adjustments coupled with rehabilitation (e.g., physical and occupational therapies) to optimize an individual patient’s motor outcome.
synthetic dopamine agonists is the mainstay of medical treatment of PD. However, over time, patients experience a less favorable response to medications and may begin a cycle that includes increasing medication doses and multiple medications with disabling side effects. Dose escalations can be associated with motor fluctuations and troublesome dyskinesias (83, 251, 260). Despite major advances in the understanding of the pathophysiology of PD and improvements in pharmacological management, there are a substantial number of patients who are considered refractory to medical management. Such medically refractory patients with significant motor complications and disability can benefit from DBS of the STN or GPi. Neurosurgery has been shown to consistently benefit only patients with idiopathic PD. Atypical parkinsonism (supranuclear palsy, nigrostriatal degeneration, etc.) or other disorders with parkinsonian features have not been shown to respond favorably to surgery.

In general, surgery is most likely to benefit symptoms affecting the extremities rather than axial symptoms that involve posture, balance, gait, and speech. Surgical candidates typically have more than one of the following symptoms: severe tremors; off-medication-related rigidity, freezing, dystonia, and bradykinesia; on-medication-related dyskinesias; and significantly disabling on-off-medication motor fluctuations. One of the most important predictors of neurological surgical treatment response is the patient’s response to L-dopa. Patients who demonstrate a significant improvement in motor symptoms during L-dopa off-medication versus on-medication states are most likely to benefit from surgery. The only exception to this general rule involves tremor. Tremor is the only identified motor symptom that can improve with DBS regardless of response to off-on-medication testing. Consequently, a formal off-on test of L-dopa responsiveness can be very helpful in the selection of the best surgical candidates.

**Tremor: Selection Criteria**

Essential tremor is a benign condition (32, 173, 198, 222) that can be managed for many years with medications. In those patients who have disabling extremity tremor despite optimal medication management, surgery using the VIM target becomes an option. In general, patients with resting and distal postural tremor fare the best with surgery, followed by those with proximal postural tremor. Patients with intention/action tremor tend to benefit to a lesser degree. The more proximal and the action/intention features of tremor are the most difficult and challenging tremor characteristics to treat surgically (44, 85, 169). Head, neck, and lower-extremity tremors are also more difficult to treat than upper-extremity tremors. Tremors involving the head, neck, and axial regions usually require bilateral surgery.

**Dystonia: Selection Criteria**

DBS offers a therapeutically viable option for patients with severe, primary dystonia and also for a small subset of patients with secondary dystonia. The key to favorable responses after DBS in patients with dystonia is proper patient selection. Patients who are refractory to all conservative measures, including medication trials (anticholinergics, baclofen, benzodiazepines, or other muscle relaxants) and botulinum toxin injections are potential candidates.

Dystonia is a heterogenous condition with variable expression. It can be classified into primary or secondary dystonia according to etiology. Primary idiopathic dystonia refers to dystonia with no discernible etiologic factor responsible for its onset. Patients with primary idiopathic dystonia have normal imaging findings, cerebrospinal fluid composition, and laboratory test examinations. A subset of patients with primary dystonia have a DYT-1 mutation on chromosome 9q (12). Secondary dystonia refers to dystonia that is associated with a clearly preexisting, identifiable brain insult such as perinatal hypoxia, stroke, trauma, toxin exposure, or infectious sequelae. Tardive dystonia is another subset of dystonia that results from super-sensitivity of the postsynaptic dopamine striatal receptors due to long-term administration of dopamine receptor-blocking agents such as neuroleptics (105, 219, 395).

Dystonia can also be classified according to the affected body part. In focal dystonia, a single region of the body is affected, such as in blepharospasm (eyes), cervical dystonia/torticollis (neck), and spasmodic dysphonia or laryngeal dystonia (182). In segmental dystonia, two or more adjacent body parts are affected, such as cranial-cervical dystonia, crural dystonia, or brachial dystonia. Generalized dystonia refers to dystonia involving most body parts.

Primary, generalized dystonia of DYT-1-positive (184, 195, 201) or non-DYT-1 types, as well as patients with idiopathic cervical dystonia can obtain the best motor benefits with bilateral GPi DBS (363). Patients with juvenile-onset idiopathic dystonia whose age of onset is older than 5 years and who do not have multiple orthopedic deformities also have a good response to surgery (280). Appendicular symptoms (e.g., those affecting the limbs) appear to respond better than axial symptoms (201). With regard to focal dystonia, ideal surgical candidates are those with cervical dystonia (201, 331). The results of DBS for secondary dystonia are inconsistent. In general, DBS for secondary dystonia is less effective than for primary generalized dystonia, particularly in those patients with an identifiable structural brain abnormality. The only exception is tardive dystonia, which has been reported to respond well to surgery in a small number of patients (92, 331, 396).

**Surgical Targets**

The three most common targets for movement disorder surgery are the STN, GPi, and VIM thalamus. GPi and STN DBS improve PD symptoms (e.g., tremor, rigidity, and bradykinesia) and also reduce drug-induced dyskinesias. STN DBS also reduces the medication burden, thereby reducing medication-associated side effects (80, 59, 368). Both the STN and the GPi have corresponding associative (cognitive), limbic, and motor territories that require accurate surgical targeting of the motor component. Presently, the most commonly used target for DBS therapy to treat PD is the STN, followed by the GPi. The GPi is also the most commonly used target for dystonia (66, 100, 159,
185, 201, 280, 312, 331, 350, 351, 355, 396). The VIM target is the main target used for non-parkinsonian tremor. The VIM is very effective in alleviating PD-associated tremors, but is not effective in the treatment of other cardinal PD symptoms. (342, 343). Thus, VIM DBS surgery is rarely performed for PD treatment.

The STN Target

The STN was previously not considered a target because of the fear of causing hemiballismus. However, in 1990, Bergman et al. (42) showed that a lesion in the STN of a nonhuman primate model could reverse the symptoms of PD. This early work, coupled with the evolving concept of the flexibility (e.g., reversibility and adjustability) inherent in DBS for the treatment of movement disorders, resulted in Benabid et al. (34) and Pollak et al. (288) applying STN DBS for the treatment of PD initially in 1993, with report of a subsequent case series in 1995 (215). Since that time, STN DBS has become the most common target for DBS surgery for PD. Targeting the STN has been demonstrated to effectively treat the entire spectrum of advanced PD symptoms of tremor, rigidity, bradykinesia, motor fluctuations, and drug-induced dyskinesias, while also consistently reducing the need for dopaminergic medication postoperatively.

Anatomically, the STN (also called the corpus luysi) is an almond-shaped nucleus located on the inner surface of the peduncular portion of the internal capsule. The STN is surrounded by several key structures that need to be considered carefully (Fig. 2). This includes the anterior and laterally situated internal capsule, through which corticospinal and corticothalamic fibers pass. Anteromedially lie the fibers of Cranial Nerve III, the postero medial hypothalamus, and portions of the fields of Forel. The red nucleus, fibers with cerebellothalamic projections, and the prelemniscal radiations are situated postero medially. Dorsal to the STN is the zona incerta and Forel’s field H2 that separate it from the ventral border of the motor thalamus. The cerebral peduncle and the substantia nigra are situated ventral to the STN (Fig. 3, A–C).

The GPi Target

The GPi target is used for PD treatment less commonly than the STN. However, the GPi is currently the most common target for treating dystonia (364) despite reports of using thalamic (Voa, ventrolateral) (92) and subthalamic DBS targets (162, 373) for dystonia. The GPi DBS target is the posteroverentralateral GPi, which is the predominant motor territory of the nucleus (Fig. 4).

The globus pallidus is divided into two anatomic segments: internal (GPI) and external (GPe). Although these segments are separated by the medial medullary lamina, the pallidal neurons from each segment are similar and, for the most part, morphologically indistinguishable. The GPi is bound laterally and dorsally by the GPe. Medially, the GPi is bound by the internal capsule. Ventrally, it is close to the optic tracts (Fig. 5, A and B). The therapeutic sensorimotor territory of the GPi is ventral and posterior, and the somatotomy places the face and arm posterior and ventral, and the leg central and more dorsal (350). The striatal afferents terminate in the GPe, as do the afferents coming from the intralaminar nuclei of the thalamus and SN. Pallidal efferents pass through the major routes of pallidal outflow (the ansa lenticularis and lenticular fasciculus) primarily to the Vop nucleus of the thalamus, but they also interdigitate with the afferents to the VIM.

The VIM Target

The VIM is the common lesioning and DBS target used for the treatment of tremor (Fig. 3, B and C) (1, 6, 25, 33, 35–37, 63, 108, 113, 126, 164, 173, 174, 191, 221, 222, 226, 231, 267, 297, 377). In the somatotopic organization of the VIM nucleus face, responsive cells lie medially, followed by the upper extremity more lateral, and the lower extremity is the most lateral, situated closely to the internal capsule (Fig. 6). The VIM nucleus of the thalamus has neurons that fire in synchronous bursts with the tremor frequency and are called tremor cells (TCs). TCs are believed by some to act as tremorigenic pacemakers (178, 222). There is a significant confusion and controversy surrounding the nomenclature of the thalamic nuclei (178, 179). The DBS target for tremor control is the electrophysiologically defined VIM (178). This electrophysiologically defined motor thalamus (VIM) has TCs and kinesthetic cells, and it lies immediately anterior to the cutaneous receptive cells, which lie in the sensory thalamus (178). The somatosensory relay nucleus ventralis caudalis (VC) of the thalamus lies immediately posterior to VIM. The VC has specific neurons that respond to tactile stimulation in small, receptive fields. The Vop nucleus lies immediately anterior to the VIM. The internal capsule lies lateral to the VIM. The Vop receives affer-
ents from pallidal neurons (230) and the VIM receives affer-
ents from the cerebellar neurons (cerebellothalamic fibers).
There is some degree of overlap and interdigitation between
these two nuclei (230).

DBS Surgical Technique

In this section, we review the general principles and tech-
niques of DBS surgery, which is the most common surgical
treatment for movement disorders today. Although there is
general agreement about the efficacy of DBS for movement disorders, there is some variance in the protocols for placement of DBS leads (220, 272, 323, 358).

The surgical technique has its foundation in stereotactic principles. It has evolved from strong reliance on stereotactic atlases and incorporates advances in imaging and neurophysiological mapping techniques. At present, most neurosurgeons performing DBS use a variety of these approaches to localize the target of interest. These variations are a result of training patterns, surgeon preferences, and surgical practice logistics. There is no single correct approach, as long as outcomes are good and complications are kept to a minimum. The lack of randomized prospective studies comparing one approach to another is also a major barrier to advancement and standardization in this field.

The basic components of DBS implantation surgery involve stereotactic anatomic targeting, physiological target verification, DBS lead implantation, and implantable pulse generator (IPG) or power-source placement. The components of the surgery can all be done in one setting or in stages, depending on the group’s preference. We review these components, highlighting common practice patterns and acknowledging the variance of practices across centers.

Headframes and Acquisition of Stereotactic Coordinates

The least debated aspect of the surgery is the method chosen for acquisition of stereotactic coordinates. Currently, both frame-based and frameless techniques are commercially available for localization within the stereotactic space.

Frame-based Systems

The frame-based approach is the “gold standard” that has been used for many years with proven precision and reliability. A variety of headframes can be used, such as the Leksell (Elekta, Stockholm, Sweden), Cosman-Roberts-Wells (Radionics, Burlington, MA), Riechert-Mundinger (Fischer-Leibinger, Freiburg, Germany), and other commercially available systems. Based on a survey of North American centers that perform DBS surgeries, it appears that the Cosman-Roberts-Wells frame is the most commonly used, followed by the Leksell frame (Fig. 7) (271). The stereotactic accuracy of each frame has been well established (233), and these frame-based approaches represent the standard of care after decades of clinical use, consistency, and dependability. Placement of the headframe is achieved under local anesthesia. The frame should be placed parallel to a line extending from the lateral canthus to the tragus, to approximately parallel the anterior commissure-posterior commissure (AC-PC) line (Fig. 8).

Frameless Systems

The introduction of the frameless technique and device for DBS lead placement (90, 150) has provided an alternative approach that has been embraced by some groups. The frame-based fiducials have been replaced by small screws that are visible on computed tomography, which are secured to the patient’s cranium before the surgery (Fig. 9). The images obtained preoperatively are then loaded into a surgical navigation computer, and the fiducials are registered. The frameless assembly is then used to plan a trajectory to the target of interest. The reported advantages of the frameless systems are related to arguments of increased efficiency of surgical planning and imaging acquisition before the day of surgery and enhancement of the patient’s comfort with less immobilization of the head and neck (Fig. 10).

Currently, there is no major advantage to using one system versus another; the surgeon’s preference guides the selection process. Relatively few centers perform frameless DBS surgeries compared with the number that perform frame-based DBS. A randomized prospective study is necessary to determine the levels of patient comfort, precision, outcome, and efficiency inherent in one system versus another.

Imaging

Ventriculography

In the late 1960s, Guiot et al. (128, 129) defined the position of various deep nuclei based on the distance between the AC and PC and the height of the thalamus, as obtained from ventriculography (Fig. 11). This method was the cornerstone of functional neurosurgery for decades and is still used in several centers worldwide (30, 34, 177). However, the advent of modern imaging has, for the most part, replaced ventriculography with computed tomographic (CT) and MRI scans.

CT Scans

A thin-cut stereotactic CT scan (approximately 2-mm slices, with no gap and no gantry tilt) can be easily obtained to localize the AC and PC and subsequently be computationally fused with an MRI scan on a stereotactic planning station. CT scans are free from the image distortions inherent to MRI and allow the stereotactic space to be defined with a high degree of accuracy.
MRI Scans

MRI is the imaging modality of choice in stereotactic targeting and planning. Various sequences can be used. The most common are a T1-weighted, volumetric acquisition of the whole brain with gadolinium enhancement, a T2-weighted axial and coronal acquisition, and inversion recovery (IR) sequences. The T2-weighted and IR sequences delineate the STN and GPi well. The thalamic nuclei, however, are not visualized well on MRI scans of 3 T or less.

Anatomic Targeting

Anatomic targeting is the initial method for localizing the structures of interest. The goal is to achieve the most precise localization using multiple data sources. Different centers use various combinations of anatomic targeting strategies. In general, one can target via an indirect method using reformatted anatomic atlases and formulas of known distances, or via direct targeting approaches. The STN and GPi can be directly visualized on T2-weighted and IR MRI scans. Currently, imaging resolution is not sufficient to visualize the VIM. Emphasis here is placed on anatomic targeting of the STN, because it is the most common target used for PD, but brief descriptions of GPi and VIM targeting are also included.

Indirect Targeting Formulas and Brain Atlas Approaches

Indirect targeting techniques use the stereotactic coordinates of the AC and the PC as determined by imaging (Fig. 12). The locations of the STN, GPi, and VIM can be subsequently determined based on their average anatomic distances with respect to the AC, PC, and midcommissural point (MCP). Typical anatomic coordinates for the sensorimotor components of these nuclei can be calculated. This includes the STN (11–13 mm lateral to the midline, 4–5 mm ventral to the AC-PC plane, and 3–4 mm posterior to the MCP), the GPi (19–21 mm lateral to the midline, 2–3 mm anterior to the MCP, and 4–5 mm ventral to AC-PC plane), and the VIM upper extremity target (11–12 mm lateral to the wall of the third ventricle, at the level of the AC-
PC plane, and anteroposterior location between two- and three-twelfths of the AC-PC distance anterior to the PC). A standardized brain atlas can be used to locate the x, y, and z coordinates of the STN, GPi, and VIM in relation to the MCP (Figs. 3 and 4). The stereotactic atlas can be stretched and morphed using surgical navigation software to better fit each patient’s anatomy. However, despite these technological advances, it is important to realize the limitations of the stereotactic atlases. The data in most atlases are based on a small number of brains. The Schaltenbrand and Wahren atlas (313) uses one brain for the frontal series and one brain for the axial and sagittal series. The Talairach and Tournoux atlas is based on one brain (339). The morphology and position of the STN is different in each atlas (257, 301), and the actual size and the position of the STN are highly variable among patients (136, 301) and within the stereotactic atlases.

Direct Targeting

With the advances in neuroimaging technology, direct visualization of the various nuclei has become possible. Although computed tomography offers excellent stereotactic precision, it can be difficult to visualize various targets and periventricular landmarks (375) when using it. MRI offers the advantage of excellent anatomic resolution in multiple planes. This allows for localization of the AC and the PC on T1-weighted images (Figs. 3 and 4), the visualization of the pallidum on IR and T2-weighted sequences (Fig. 5), and identification of the STN on axial, sagittal, and coronal T2-weighted images (Fig. 13) (32). The advantage of directly visualizing deep targets is implicit; one works with the patient’s individual anatomic variation rather than relying on a fixed brain that was sectioned several decades ago. Some centers rely entirely on MRI scans to calculate anatomic targets (272, 330, 334). There are questions, however, regarding the accuracy of the exact location of these targets within the stereotactic space because of distortion on MRI scans (311). To reduce the possibility of MRI-related inaccuracies, several centers use a protocol of merging the anatomically superior MRI scans to stereotactically acquired CT scans (19, 220, 323, 375).

Several authors have described strategies to further refine image-based targeting. Arguing that the relationship of the AC-PC line and the STN may be variable and inconsistent, they propose the use of a landmark that is physically closer to the target of interest (16, 24, 78, 330). In 2000, Bejiani et al. (24) described using the anterior border of the red nucleus as a landmark for the AP coordinate of the STN. This approach has also been used by others (17, 78). Axial and coronal T2-weighted images are particularly important for adequate visualization of the STN, as a sharp contrast can often be observed between the nucleus and the surrounding white matter. The red nucleus and the STN can be clearly visualized. The STN lies anterior and lateral to the red nucleus and, in this regard, the anterior border of the red nucleus can be used as a landmark for the STN target (Figs. 3 and 13). Starr (330) later described the relationship between the center of the red nucleus and the middle of the electrode array as another internal landmark for targeting the STN. In the authors’ experience, the interpeduncular distance can also serve as a good surrogate for the laterality of the STN target (unpublished data).

The possibility of directly visualizing and targeting the STN and GPi has brought forth innovative imaging application possibilities for DBS surgery. The use of intraoperative MRI to perform DBS surgery is being investigated by Martin et al. (235). Their preliminary results show that successful DBS implantation can be performed in patients under general anesthesia with only anatomic targeting. This approach has multiple inherent advantages that will facilitate its acceptance and widespread use once additional studies demonstrate that the safety and efficacy are equivalent to the traditional techniques.

Trajectory Planning

Imaging is necessary for accurate targeting as well as for planning of the surgical trajectory to the target. The strategy is to avoid surface and subcortical vessels and to have an angle of approach that passes through a large segment of the structure of interest. The precise entry point may be refined on the planning console, such that the trajectory passes through the crown of a gyrus rather than into a sulcus, as well as away from the vessels associated with the wall of the ventricle, thereby helping to avoid hemorrhagic complications (Fig. 14).

Neurophysiological Assessment and Verification

All surgeries for movement disorders are initially based on anatomic targeting techniques. However, physiological verification of these targets is a necessary step before final implantation of the DBS electrode can occur. This is crucial because anatomic inaccuracies due to image distortion, brain shift, cerebrospinal fluid loss, and pneumocephalus can lead to final target deviation (124). A DBS lead that is misplaced by as little as 2 mm can result in inaccuracy when locating the final target.

In a more practical sense, neurophysiological techniques are necessary to refine lead positioning within a target and to optimize clinical outcome and minimize stimulation-related side effects. In the lesioning era preceding DBS, physiological verification was a major requirement before the creation of

![Figure 13. High resolution axial (A) and coronal (B) T2-weighted MRI scans showing the STN and structures in close proximity to it. STN, subthalamic nucleus; SNR, substantia nigra reticulate; RN, red nucleus.](image-url)
lesions. Presently used physiological techniques include microelectrode recording (MER), semi-MER, macrostimulation, and DBS lead stimulation. The degree of dependence on these techniques varies widely. The exact detail of mapping for each target is beyond the scope of this article; however, generalities are provided and details can be obtained in the references provided.

**MER**

The MER technique uses microelectrodes with high impedances (typically >0.4 mΩ) with a tip diameter in the range of 2 to 4 μm (124, 158, 207). These microelectrodes are capable of recording single units as well as delivering stimulation in the microamp range (typically <100 mA). A hydraulic or electrical microdrive is used to advance a microelectrode in submillimetric steps. United States Food and Drug Administration-approved microelectrodes are commercially available and are made of tungsten or platinum/iridium.

Some centers use a single MER penetration as confirmation of the anatomic targets, whereas others rely on one or more tracks that reveal a set of acceptable criteria, such as an approximately 5-mm long area of STN (231). There are also centers that use a multiple-track penetration approach for very detailed physiological mapping of the borders of the nuclei. The hope is to improve treatment efficacy and limit postoperative side effects that are related to undesired stimulation of bordering structures (123, 373). In a survey of 36 DBS centers in North America, Ondo and Bronte-Stewart (269) found that 97% of centers use MER for assistance in lead placement. The average number of tracks was 2.5 per electrode, with a range of 1 to 18 tracks. They also reported that most centers use macrostimulation to assess the final clinical response.

Although most centers advance one microelectrode at a time, several centers advance multiple microelectrodes simultaneously and assess a larger area of the target (24, 31). Delivering stimulation through the microelectrode, when feasible, is performed at some centers to assess side effects resulting from proximity of the track to other structures such as the internal capsule (124, 372).

MER allows for the delineation of the physiological signature of various nuclei and white matter tracts. Single neurons, multiunit activities, and local field potentials can be discerned with characteristic sound and visual expressions. The frequency and pattern of activity are observed, thus helping to confirm location based on characteristic physiological signatures. The boundaries between white matter and nuclei are important to distinguish, as are the length of the desired nucleus and an assessment of the surrounding structures. The MER physiology of the STN, GPI, and VIM is discussed briefly below.

**The STN**

The information obtained in the track, such as the presence or absence of thalamus or SNr, could also aid in determining the trajectory in relation to the nucleus, i.e., medial, lateral, anterior, or posterior. Figure 15 shows a sample MER trajectory aimed at the STN. The thalamus is typically the initial structure encountered by the MER. The specific thalamic nuclei recorded depend on the AP angle of approach, but typically include the nucleus reticularis (Rt), the Voa, and the Vop. There are two typical cell activities: bursting units (interburst frequency, 15 ± 19 Hz) and irregular tonic firing (~28 Hz) cells. The background activity is substantially less dense than the background activity of the STN. After exiting the thalamus, a decrease of background activity coupled with the resolution of, generally, fewer firing units indicate the zona incerta (ZI) and fields of Forel. Activity in these areas has a similar bimodal distribution of bursting and tonic firing units, usually with low firing rates. A substantial increase in background neuronal activity signals the entry into the STN. This increase in background activity, perhaps the most distinguishing characteristic of the STN compared with the other structures encountered in this procedure, can precede the resolution of single-unit activity indicative of the STN by 1 to 2 mm. Mean firing rates have been reported in the 34- to 47-Hz range, with standard deviations in the 25-Hz range. Bursting units are common. The pattern of activity is typically irregular. Cells that respond to passive movement of the limbs are encountered in the dorsolateral part of the STN. Within this motor area, lower extremity-related units tend to be...
strategy is then to identify the border between the sensory nucleus and the VIM where the cerebellar afferents are received. Once the border is identified and the somatotopic laterality is established, the DBS electrode can be placed approximately 3 to 4 mm anterior to the border of thalamic sensory relay nucleus to avoid current spread into the sensory nucleus and development of persistent paresthesias as a side effect of stimulation.

Despite the widespread use of MER, whether the utility of MER approaches is superior to other methods is an area of debate and controversy. There are centers that still use only macrostimulation, and they report comparable results (137). There is a need for a prospective randomized study comparing MER to non-MER approaches to reconcile this issue. In addition to MER, there are centers that use semi-microelectrodes to map the corresponding nuclei and white matter. Semi-microelectrodes have lower impedances and cannot discriminate single neurons, but do provide good physiological data regarding the structures being traversed (108, 393).

Macroelectrode Mapping and Stimulation

Macrostimulation involves stimulation in the range of milliamps to determine benefits and side effects. There are several different ways of delivering macrostimulation. Macrostimulation can be performed with a lesioning probe or, most commonly in the United States, the DBS electrode itself can be used as the macroelectrode (269). This is advantageous as the results obtained during surgery are likely to be reproduced with chronic stimulation from the DBS. Still, macroelectrode/DBS stimulation is one of the important steps for DBS surgery as it provides insight into therapeutic efficacy and stimulation-induced side effects.

DBS Electrode Implantation

In planning the implantation, it is important to understand that the active site of chronic stimulation may not be the bottom of the target at the bottom of the trajectory. In the STN implant, for example, the bottom contact of the quadripolar STN electrode is seldom used because the optimal site for stimulation is believed to be at the dorsolateral segment of the nucleus or immediately dorsal to it (146, 308).

The two commercially available electrodes have four contacts of 1.5 mm in height and 1.27 mm in diameter and differ only in the spacing between contacts: 1.5 mm in the 3387 model and 0.5 mm in the 3389 model (Medtronic, Minneapolis, MN) (Fig. 16). Fluoroscopy is used at many centers to monitor the DBS lead implantation and ascertain that it is assuming a straight trajectory that does not deviate from the intended target. Once implanted, the electrode may cause a microlesional effect that is manifested by transient improvements in tremors and, in the case of PD, rigidity and bradykinesia. Such an effect is seldom observed during GPI surgery for dystonia.

With DBS intraoperative test stimulation, the patients are assessed for clinical benefits and side effects. The typical parameters mirror the settings used for chronic stimulation.
and include 1 to 5 V, 90 μs pulse width, and 130 Hz frequency. The larger the difference between clinical improvement thresholds and side-effects thresholds, the better the therapeutic window of stimulation for the patient. During macrostimulation, the patient is monitored for symptomatic improvement such as tremor, rigidity, and bradykinesia. Dyskinesias may appear during stimulation and are generally a positive predictor of the efficacy of chronic stimulation (157, 290). The importance of side-effect determination should be underscored, especially for patients in whom the therapeutic efficacy is unclear or situations in which the patient’s cooperation is hampered (30, 31, 330).

Once the DBS electrode is implanted at the final location, it must be secured to the burr hole at the cranium. Continuous fluoroscopy is helpful to monitor the potential for electrode displacement. Anchoring and securing the lead can be achieved by various techniques depending on the surgeon’s preference and expertise. These include securing the lead to the cranium with ligature embedded in dental cement or using mini-plates and screws, DBS manufacturer-provided plastic burr hole ring and cap, or the Medtronic Stim-Loc anchoring device (Medtronic). Once secured, the distal end of the DBS lead is attached to the extension wire or to a connector that will protect the contacts. The distal tip is tunneled subcutaneously to the parietal/occipital region. The excess lead can be coiled around the burr hole device or placed along the path of tunneling to serve as strain relief.

**Implantation of the Pulse Generator**

The second stage of the DBS procedure is implantation of the implantable pulse generator (IPG), also referred to as the “neurostimulator,” and placement of the extension lead that connects the DBS lead to the IPG. Currently, there are two types of available IPGs: single channel (Medtronic Soletra) for one DBS lead, and dual channel (Medtronic Kinetra) for two leads. This is the last step of surgery, and it is performed under general anesthesia. This step can be performed the same day or in a delayed or staged fashion.

The patient is placed in a supine position, with the head turned to the opposite side of the intended site of IPG implantation. In brief, an infraclavicular subcutaneous pocket is created for the IPG, and the proximal end of the DBS electrode is exposed in the parietal region. A subcutaneously implanted extension wire is tunneled from the parietal region to the infraclavicular pocket, thus connecting the DBS electrode to the IPG pocket in the chest. The most common location for the IPG placement is infraclavicular, and it is typically marked 1 to 2 cm below the clavicle and 4 cm away from the midline or 2 cm from the lateral manubrial border. However, certain patients may require placement in other locations due to body...
Outcomes of DBS for Movement Disorders

The literature relevant to movement disorder surgery is extensive: There are more than 1000 published articles pertaining to DBS for movement disorders. In addition to the retrospective and case report format of much of the literature, the reversibility feature (turning DBS on and off) on-demand allows for controlled, blinded assessments, making it one of the better-studied neurosurgical interventions. In addition, validated rating scales for movement disorders have been established and are used in most surgical trials. These standardized, disease-specific rating scales allow for outcomes to be expressed in a more objective fashion that is specific to the disease of interest.

STN and GPi DBS for PD

DBS has become the surgical procedure of choice for movement disorders, replacing stereotactic ablative procedures, for the most part, in countries where access to this technology is available. Outcomes from DBS are expressed more frequently as absolute or as percent score reductions in the Unified Parkinson’s Disease Rating Scale (UPDRS) Part III (motor) during the medication-off state. Thus, UPDRS Part III is a standard outcome scale indicating motor benefits from a therapy. Data on the impact of DBS upon activities of daily living (ADLs), percent reduction in dyskinesias, or incremental “on time” periods without dyskinesias are inconsistently reported. Reductions in dyskinesias can be considered as a direct effect of DBS or may be secondary to a reduction in medication requirements (183, 369).

Prospective studies have reported on the outcomes of GPi and STN DBS for the cardinal symptoms of PD. Both targets are shown to be beneficial (177, 183), although a trend exists among these studies to indicate that STN DBS is more effective. In addition, STN DBS tends to allow for a greater reduction in the postoperative medication burden with consequent reduction in dyskinesias (80, 86, 181, 183, 282, 303). Direct comparisons of GPi versus STN stimulation have been performed in small samples of patients. The outcome data from these studies were not conclusive enough to exclude the GPi as an accepted DBS target for PD (368) and generally corroborated the advantage of using the STN in improving UPDRS Part III scores and L-dopa intake (15, 59). In addition, a recent report of long-term bilateral pallidal stimulation in 11 PD patients confirmed the therapy’s sustained efficacy in alleviating dyskinesias. However, motor scores that had been alleviated in the first year deteriorated during the 5-year follow-up to an extent greater than would be expected from disease progression alone. The lost motor benefits were not regained with additional programming, but were successfully recaptured in four patients by repositioning the electrodes from the GPi to the STN (378). As discussed below (in Complications of DBS Surgery), it is possible that STN stimulation is more prone to cognitive and behavioral complications (see Cognitive and Neurobehavioral Outcome and Complications with DBS). However, outcomes from upcoming randomized, prospective large studies are expected to provide more insights into the relative efficacy and risks associated with STN versus GPi DBS for the treatment of PD.

The encouraging results of STN DBS originally reported by Benabid and the pioneering Grenoble group (26, 31, 180, 181, 214–216, 289) motivated a large number of studies in the past decade that have further validated the safety and efficacy of this procedure (80, 67, 79, 93, 94, 102, 107, 134, 145, 160, 165, 208, 212, 225, 258, 271, 276, 281, 304, 307, 315, 318, 344, 359, 360, 362, 394). A meta-analysis of the literature published in 2006 reviewed the literature from 1993 to 2004. The mean reduction in UPDRS Part III scores among the 34 articles included in the study was 52% (comparing the DBS-on, medication-off state to the medication-off, DBS-off state). There was a large variation in reported outcomes, ranging from 82 to 17%. The mean reduction in UPDRS Part II scores was 49.9%, ranging from 72 to 29.5%. As noted above, the preoperative response to L-dopa is considered a good outcome predictor of response to surgery and is, therefore, a heavily considered determination regarding a patient’s candidacy for surgery. The correlation between L-dopa response and positive outcomes after STN DBS was confirmed by this meta-analysis as well as other studies (384).

A few prospective, controlled studies have provided fundamental contributions to the DBS literature and merit more detailed discussion. In 2001, the DBS for PD Study Group reported on the outcomes of 96 patients undergoing STN and 38 patients undergoing GPi DBS. The improvements in UPDRS Part III motor subscores at the time of the 3-month follow-up (assessed with double-blind evaluations after patients were randomly assigned to stimulation-on or -off states) were 49 and 37% for these groups, respectively. A continuation of this study was reported in 2005 with 3-year or longer follow-up period for 69 patients from the initial study. The 3-year or longer follow-up data demonstrated that the effects of DBS for PD are long-lasting. The long-term benefits of DBS were later substantiated by Krack et al. (177). Forty-nine consecutive patients treated with bilateral STN DBS were assessed at 1, 3, and 5 years after implantation. The mean reductions in UPDRS Part III scores at these time points were 66, 59, and 54%, respectively. ADLs were also improved. A significant decrease in efficacy was observed when the first and fifth years after surgery were compared. Nevertheless, most of these patients were dependent upon others before surgery and continued to enjoy independence throughout the entire follow-up period. Similar 5-year follow-up results were reported by Schüpbach et al. (315), with 54% reductions in UPDRS Part III scores and a 40% maintained reduction in UPDRS Part II scores. Additional long-term outcome studies with follow-up periods ranging from 2 to 4 years reported on mean UPDRS Part III reductions of 48% in 25 patients (170), 43% in 20 patients (367), 55% in 22 patients...

Rehabilitation, quality of life, and cosmesis are aspects that need to be addressed as well. The trends toward more personalized and less invasive treatments are continuously expanding. In this area, DBS has demonstrated its role as a safe and effective procedure over the past decade, and this evolution is expected to continue in the near future.
Similar results were observed when comparing the outcomes of 17 patients undergoing thalamic stimulation to the outcomes of 17 patients who had previously undergone thalamotomy. Although the effects from tremor suppression were very similar in both groups, complications, particularly intracerebral hemorrhages, were more common among patients with thalamotomies (35 versus 0%). Likewise, cognitive deterioration and hemiparesis occurred, respectively, in 29 and 12% of patients who had undergone thalamotomies but in none of those with thalamic stimulation. Although thalamic stimulation is chronically effective for most patients (37, 57, 213, 222, 228, 293, 316), reductions in efficacy during longer-term follow-up periods have been reported (32, 173).

The vast majority of thalamic DBS procedures have been targeted at the upper extremity function. However, lower extremity, head/neck, and axial tremor are also common problems that negatively impact quality of life for patients with essential tremor. Putzke et al. (293) reported on the outcomes of 22 patients with head, voice, or trunk tremor undergoing bilateral, staged, DBS thalamic implants. Bilateral stimulation was more effective than unilateral stimulation in alleviating axial tremors; however, as for bilateral thalamotomies, the rate of neurological complications was higher in patients who underwent bilateral stimulation. Dysarthria was observed in 27% of patients with bilateral stimulation, whereas none of those undergoing unilateral stimulation experienced the same problem. Likewise, disequilibrium was more common during bilateral stimulation. Although unilateral stimulation was comparatively less effective, it still demonstrated a significant reduction in axial tremors when compared with the preoperative baseline and stimulation-off periods. These findings are supported by the work of Koller et al. (172) in a prospective assessment of 38 patients with head tremor undergoing unilateral thalamic stimulation. In this study, 71% of patients presented with tremor alleviation at 3 months. The effects remained generally stable over the long-term (1 yr) follow-up period. Stimulation settings varied minimally during this period, further corroborating the stability of the effects. Although staged bilateral procedures are often preferred for axial symptoms, they may not be safer than simultaneous implantation procedures (337).

**GPI DBS for Dystonia**

Stereotactic ablative surgery of the GPi (pallidotomy) has been attempted in the past in patients with generalized dystonia. Encouraging results have been reported (91, 92, 150, 371) but, unlike reports of thalamotomies for treating tremor, the best results are not observed immediately, but rather, after several weeks or months (218, 224). Unilateral and, in particular, bilateral pallidotomies may carry a higher risk of neurological morbidity, including lethargy and hemiparesis (270, 345), even in the absence of hemorrhagic complications. Excellent results from bilateral stimulation of the GPi were initially reported for an 8-year-old child with severe dystonia (75). In this age group, bilateral pallidotomies were considered by the authors to be particularly risky (74), and DBS was attempted as a compassionate, last-resort alternative. The results encouraged formal assessment of this technique with prospective cohorts. In most

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**Thalamic (VIM) DBS for Tremor**

(see video at web site)

The standardized assessment of tremor can be achieved via the Tremor Rating Scale (TRS) (151, 329). Stereotactic thalamotomies targeted at the VIM nucleus are well-established procedures for the management of tremors from PD or essential tremor (8, 103, 115–117, 166, 167, 253–255, 343). In managing patients with PD, thalamotomies alleviate tremors without significantly affecting the other cardinal symptoms of PD. Unilateral thalamotomies are considered relatively safe, but bilateral procedures carry an elevated risk of neurological deficits such as dysarthria and cognitive deterioration (237). Chronic stimulation was considered a potential alternative to thalamotomy, at least partly because the known tremor-alleviating effects of acute stimulation were used for physiological confirmation during ablative stereotactic interventions (116, 255). In addition, thalamic chronic stimulation had already been demonstrated to be feasible and safe for patients undergoing ablative stereotactic interventions for chronic pain conditions (153, 154, 192, 211, 298–300, 354). Benabid et al. (35, 36) initially applied thalamic stimulation contralateral to thalamotomy in patients with PD. Their preliminary experiences revealed a greater efficacy of thalamotomy over stimulation. In 1991, the results of chronic VIM stimulation for tremor were reported in a series of 32 patients with essential tremor or PD who had undergone 43 thalamic stimulation implants (11 patients underwent bilateral stimulation). At a mean follow-up period of 13 months, 88% of the implanted DBS electrodes resulted in major or complete relief from tremors. DBS, initially considered an alternative to stereotactic thalamotomy, gradually became the surgical procedure of choice for the treatment of essential tremor, as it demonstrated similar efficacy rates and lower risks (174, 275, 316, 343). A direct comparison between thalamotomy and thalamic stimulation was reported by Schuurman et al. (316). Seventy patients with PD, essential tremor, or tremor from multiple sclerosis were randomized to stimulation or ablative surgery groups. Patients with unilateral symptoms underwent a single intervention contralateral to the symptoms. Patients with bilateral tremors underwent either bilateral thalamic stimulation or a unilateral thalamotomy with contralateral stimulation. Patients with PD and essential tremor who had undergone thalamic stimulation performed significantly better in ADLs than those undergoing ablation. Sixteen adverse effects occurred among the patients randomized to the thalamotomy group. In comparison, only six patients with thalamic stimulation experienced adverse effects, which were successfully resolved with stimulation cessation. Pahwa et al. (275) reported similar results when comparing the outcomes of 17 patients

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(271), 57% in 29 patients (148), and 45% in 20 patients (365). The latter study also reported on complete withdrawal of medication (replaced by stimulation) in 10 out of 20 patients. Such a dramatic and early reduction of medication intake may have accounted for some of the complications observed by the authors, such as dysarthria and cognitive problems (200).
of the literature, treatment outcomes for generalized dystonia are measured using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), whereas treatment outcomes for torticollis are assessed using the Toronto West Spasmodic Torticollis Rating Scale. The former has a total of 120 points (higher is worse) and takes into account the severity at each segment as well as the provoking factors. The latter scale, which is specific for torticollis, takes into account severity, disability, and pain.

In 2004, Coubes et al. (74) reported on the long-term results of 31 patients with primary generalized dystonia, 14 of whom were positive for the DYT-1 gene mutation. There was an overall mean improvement of 50% in the BFMDRS at 3 months, with additional gains observed at the 2-year follow-up evaluation, reaching a mean improvement of 65%. DYT-1-positive patients had improved more (74%) than patients with DYT-1-negative disease (58%). Subsequent series also found better outcomes among primary dystonia patients (92), with most dramatic improvements observed in patients with disease of early onset (184). Gradual improvement (or maintenance) of results after 3 years has been demonstrated (364), further validating DBS for treatment of generalized dystonia. Significant and sustained long-term improvements have been reported in patients with spasmodic torticollis (49).

Pallidal stimulation for dystonia has been formally assessed in prospective, controlled, multicenter studies. Results from a series of 22 patients with primary generalized dystonia (seven of whom were DYT-1 positive) were described by Vidalihet and the French Stimulation du Pallidum Interne dans la Dystonie Study Group (363). At the 3-month follow-up, investigators who were blind to the status of stimulation assessed dystonia severity through video recordings. At 12 months, the dystonia-movement scores had decreased to a mean of 21, compared with a baseline preoperative mean score of 46.3. Similar blinding methodologies were used by Kupisch and the DBS for Dystonia Study Group (194) to assess patients with primary generalized or segmental dystonia. Greater reductions in the dystonia-movement scores were evident in the stimulation group (15.8 points, 39.3%) than in the sham stimulation group (1.4 points, 4.9%). Surprisingly, there were no significant differences in the degree of amelioration of patients who were positive for the DYT-1 mutation versus those who were negative for the mutation. Significant differences were also not apparent when the outcomes of patients with generalized dystonia were compared with those with segmental dystonia.

In summary, GPi or STN DBS has been demonstrated to be effective in alleviating the symptoms of medically refractory PD in multiple reports in the literature. These results were confirmed by prospective series with double-blinded assessments and were largely sustained at 5-year follow-up evaluations. A trend exists in favor of STN versus GPi DBS that must be verified once the outcome of additional studies comparing GPi and STN is available.

Chronic stimulation of the VIM thalamus has become the procedure of choice for the treatment of tremors because of its associated high efficacy rates and low risks. VIM DBS is also highly effective for PD tremor, but it is rarely performed today for PD because both STN and GPi DBS significantly improve tremor as well as other manifestations of PD. Patients with axial tremors tend to benefit from bilateral stimulation, which carries a higher risk of adverse neurological effects.

Bilateral pallidal (GPi) DBS is safe and effective for alleviating primary generalized and segmental dystonia, but the results may not be evident until after several weeks or months of stimulation. Patients who are positive for the DYT-1 mutation and those with disease of early onset may experience greater benefits.

In reviewing the outcomes of movement-disorder surgery, it is important to emphasize that there should be more randomized, prospective, and controlled studies in the future. In addition, systematic and standardized assessment, reporting, and publication of outcome and complications are necessary. This includes the use of published and accepted standardized rating scales for tremor, PD, and dystonia, with evaluations performed by a blinded observer who is unaware of the stimulation status (on versus off). The implementation and publication of standard and rigorous study designs and outcome reporting will facilitate the acceptance and development of DBS surgery as a standard therapeutic modality for movement disorders.

Cognitive and Neurobehavioral Outcome and Complications with DBS

The vast majority of data documenting neurobehavioral outcomes after DBS involve patients who underwent surgery in the STN. The most common neuropsychiatric side effect in the immediate postoperative period after STN DBS is transient confusion, with an incidence that ranges between 1 and 36% (5, 18, 61, 72, 95, 107, 131, 138, 177, 244, 250, 281, 285, 286, 303, 352, 380, 389, 390). Evidence of greater neuropsychological deficits before surgery is significantly associated with increased confusion after surgery (284). In general, the data suggest that the most frequently observed long-term neuropsychological change after STN DBS is a decline in word fluency. A recent meta-analysis of the available data confirmed this finding (281). The meta-analysis revealed much smaller, yet significant, declines on measures assessing executive function, verbal learning, and memory. These findings are consistent with those reviewed elsewhere in the literature (380, 390). However, it is critical to recall that the majority of available neuropsychological outcome studies have not included control groups, did not statistically control for potential practice effects, and generally consisted of small groups, resulting in reduced power; this makes it very difficult to ascertain significant cognitive effects unless the related effect sizes were very large. Virtually no studies have clearly identified potential risk factors for increased cognitive decline after STN DBS. Aybek et al. (18) recently reported that the incidence of conversion to dementia in PD patients who underwent STN DBS over a 3-year follow-up period was similar to the incidence reported for medically treated patients. Furthermore, risk factors for the development of dementia in surgical patients were similar to those identified in non-surgical PD patients and included increased age, presence of hallucinations, and reduced scores.
on measures of executive cognitive function. The preliminary data suggest that DBS in the STN may result in greater cognitive and neurobehavioural changes than GPI DBS in patients with PD (15, 303, 378). This observation might reflect the relatively smaller size of the STN with the increased proximity of associative (cognitive), limbic, and motor circuits, and the subsequent increased likelihood of misplaced electrodes and/or current spread to non-motor circuits. More detailed, prospective studies are necessary to ascertain the relative neurobehavioural risks associated with STN versus GPI DBS for the treatment of PD. Despite the methodological concerns and relatively limited data, it appears that STN DBS is a relatively safe procedure from a neuropsychological perspective in well-selected patients.

Neuropsychiatric symptoms have also been reported after STN DBS, and several studies have reported hypomania, depression, apathy, and suicidality (380). Postoperative hypomania was reported in 4 to 15% of STN patients in four studies (79, 147, 177, 306), and postoperative depression has been reported to occur in up to 1.5 to 25% of patients (147, 156, 177, 236, 245, 272, 302, 306, 348, 358, 379). The extent to which medication changes after surgery contributed to the reported changes in mood state is not well known. Overall group depression scores have been reported to improve at 3 and 12 months after surgery in multiple studies (79, 89, 285, 379); however, most studies relied on reporting group mean depression scores, which may be misleading. A more accurate indication of the number of patients who met criteria for depression before and after surgery is a more clinically relevant variable. Some uncontrolled series have documented suicide attempts and/or suicides after placement of DBS electrodes in the STN (45, 177), but, once again, there are no data to indicate a clear relationship to stimulation. Within the first 3 postoperative months, apathy, which can respond to administration of dopaminergic medication, can occur, although the incidence is unknown. In contrast, more permanent apathy was identified in 12% of patients, in whom 80% had associated decreases on executive cognitive measures (177). It is important to recognize that all of the neuropsychiatric symptoms previously described are evident in medically managed nonsurgical patients with PD. Consequently, it is very difficult to ascertain, on the basis of the current literature, the extent to which STN DBS is truly associated with increased neuropsychiatric symptoms versus the role of underlying ongoing disease progression.

The neurobehavioural outcome literature after DBS in the GPI and VIM is much more limited than that pertaining to STN DBS. Many studies examining cognitive and neuropsychiatric outcomes after GPI DBS documented no significant declines. Isolated studies identified mild declines on measures of word fluency and visuocconstructional skills (380). There are very few studies examining neurobehavioural outcomes after VIM stimulation, and interpretation of the available data is confounded by small samples of patients with mixed diagnoses. In general, most of the data revealed no significant cognitive or neuropsychiatric declines. Improvements in verbal memory were documented in two studies, whereas declines in word fluency were documented after left-sided VIM stimulation in one study (380).

In summary, the neurobehavioral outcome literature suggests that the cognitive effects associated with DBS in the STN, GPI, and VIM are relatively minor in well-selected patients. The neuropsychiatric outcome data are more limited, and surgeons should be alert to the possibility of neuropsychiatric symptoms after surgery, particularly STN DBS, but it is still unknown whether these symptoms reflect neurosurgical/neurostimulation effects or ongoing disease progression.

Complications of DBS Surgery

Understanding the complications of any surgical procedure helps in anticipating, preventing, recognizing, and promptly intervening on such occasions. The complications of DBS surgery can be mainly classified into four categories. These include intracranial hemorrhages, infections, hardware-related issues, and stimulation-related complications. The incidence of reported complications is variable among centers and has been changing over the past few years as a result of the increased experience of the surgical team, advancement in techniques, and improvement in devices. Another factor contributing to the observed variability in complication reporting is the lack of a systemic and consistent process for complication definition, recording, and assessment. For example, not all centers reporting outcomes obtain postoperative imaging to evaluate for a hemorrhage that is nonsymptomatic. Instead, imaging is only performed if there is clinical change in the patients. Similarly, the reporting of infections is inconsistent because the definition of “infection” varies (i.e., an infection that requires hardware explantation versus a superficial wound infection).

Intracranial Hemorrhage

Intracranial hemorrhage is one of the most important complications of movement-disorder surgery. Intraoperative hemorrhages are reported to occur in 0.2 to 12.5% of all STN DBS cases (43, 46, 47, 50, 84, 121, 139, 161, 171, 173, 175, 177, 211, 212, 229, 347, 356, 361). The correlation of hemorrhage with the type of procedure is an area of controversy. According to Blomstedt and Hariz (50), there is no significant difference between the hemorrhage risk in lesioning (1.6%) versus DBS surgeries. Terao et al. (347), however, reported a lesion surgery bleeding rate of 15.8% (thalamotomy, 21.7%; pallidotomy, 11.8%) versus a hemorrhage rate in DBS operations of 3.4% (347). Hemorrhages can be extradural, subdural, and intraparenchymal. Intraparenchymal hemorrhages are the most common and typically occur in the tract of the electrode or in the periventricular region in close proximity to vessels associated with the ventricles (Fig. 17). The size of the hemorrhages is generally small. There is little agreement on the predictors of intraoperative hemorrhages in patients who undergo DBS. The common factors identified include:

1) High blood pressure: the practices of carefully controlling blood pressure and painstakingly planning the trajectory, avoiding vasculature seen on the contrast-enhanced preop-
Intraoperative images, help reduce the incidence of hemorrhages. There is a statistically significant association of hemorrhagic complications with hypertension (118). Bleeding occurs in 10.71% of hypertensive patients and 0.91% of those who were normotensive ($P = 0.0111$). The same study also documents that the combination of MER and hypertension increases the risk of hemorrhage to 16.67% (118).

2) MER: an increased incidence of bleeding in hypertensive patients who underwent MER ($P = 0.034$) was observed by Gorgulho et al. (118). There are reports that strongly imply MER as a risk factor for hemorrhage (137), and there are studies that state otherwise (46, 47, 372). It is difficult to draw any conclusion from the available literature pertaining to increased risk of hemorrhage with MER.

3) Target: some studies have documented that the GPi is more prone to hemorrhagic complication compared with the STN or the thalamus. Binder et al. (47) have shown a 7% risk of GPi hemorrhage compared with 2.2% risk of STN hemorrhage. In 2001, the DBS study group reported similar results (GPi, 9.8%; STN, 2.9%) (80). It has been suggested that anatomic peculiarity of the vasculature in the GPi region may be responsible for the increased incidence of hemorrhage (47). The GPi is supplied by the lenticulostrate arteries that come from the anterior circulation. These arteries are more prone to the effects of hypertension and may also be developmentally different (47).

4) Trajectory planning: the use of image fusion of CT and MRI scans helps in performing accurate targeting. The images that help most in avoiding hemorrhagic complications are the postcontrast T1-weighted MRI scans. These images reveal small paraventricular, sulcal, intraventricular, and ependymal vessels (Fig. 14) and assist with the planning of a vessel-free trajectory.

**Infections**

Reported infection rates for DBS surgery vary widely, from less than 1% to as high as 15% (11, 43, 46, 47, 51, 50, 76, 80, 84, 87, 112, 124, 168, 171, 175, 194, 212, 229, 259, 265, 346, 349, 356, 361, 374, 376). This is probably because different clinical definitions are used for identifying infection. The criteria for diagnosing infections are not well defined in the reported literature. DBS-related infections have a variable presentation in terms of time and location. Typically, the infection presents within 3 months after surgery, and the most common site was at the IPG (Fig. 18) (51, 80, 168, 194, 229, 349, 356, 374, 376). Infections of the IPG tend to present soon after surgery, as do infections at the burr hole. Infections at the connector may be related to erosions. This scenario was more common in the past, when the extension connectors were larger. The introduction of the lower-profile extension connector has significantly reduced the incidence of erosions.

Clinically, the infections presented as cellulitis, erythema, drainage, dehiscence, or stitch abscess. The common bacterial pathogens isolated are Staphylococcus aureus, S. epidermidis, Serratia sp., Klebsiella sp., and sometimes, Escherichia coli and mixed flora. Most of the published data fail to address any specific predictors for the infections. The risk of brain abscess from DBS infection is extremely low, with only one case reported (240).

The important management decision is whether to remove or keep the hardware. Very superficial infections can be treated with oral or intravenous antibiotics. Deep-tracking infections require surgical intervention. However, if there is no purulent or necrotic material in direct contact with the hardware, debridement, irrigation, and a hardware-sparing approach can work. If the pus is in direct contact with the hardware or if the hardware is exposed, it should be promptly removed. In most cases with localized infection, partial hardware-removal strategies can be successfully used, such as removal of the infected IPG and retaining of the DBS lead that is not infected. After several weeks of antibiotic therapy, the removed hardware can be safely replaced.

**Hardware-related Complications**

Hardware-related complications are the most common, with a varying incidence that ranges from 2.7 to 50% (27, 71, 138, 140, 175, 229, 232, 279). These include DBS electrode fracture, extension wire failure, lead migration, skin erosion, IPG malfunction, and pain over the pulse generator (11, 43, 46, 47, 50, 76, 84, 87, 112, 118, 124, 168, 171, 175, 212, 265, 347, 356, 361). They can be subdivided into complications associated with the lead, those associated with the extension wires, and the IPG (51, 71, 132, 175, 229, 265, 278, 321, 376).

Because the brain lead is the most delicate part of the hardware, it can malfunction or get damaged due to a variety of
Lateral cranial x-ray showing two DBS leads, one of which is broken with a curved end (arrow). This patient presented with loss of efficacy and local pain due to the hook-like part of the electrode pressing on the scalp.

Stimulation-related Complications

These are complications associated with programming of the DBS system after surgery. For the most part, these complications are reversible and require vigilance of the programmer. However, if a DBS lead is placed suboptimally, even the most expert programming cannot help, and the patient may require revision surgery.

The most common stimulation-induced complications are dyskinesias, worsening of axial symptoms, speech dysfunction, capsular stimulation, and ocular symptoms. Stimulation-induced dyskinesias can be a good sign of accurate placement and are generally self-limiting (179, 217). They are observed after STN DBS and may require adjustment in stimulation parameters or change of dosage of dopaminergic medications (87, 217). Worsening of axial symptoms such as freezing and balance and gait disturbance have been reported in some studies (59, 87, 104, 127, 170, 271, 394). It has been suggested that changing the active contact and adjusting the stimulation parameters are generally helpful (87, 127). Dysarthria or hypophonia as a side effect of STN stimulation is observed in 4 to 17% of patients (59, 87, 104, 127, 170, 271, 394). The etiology is considered to be the spread of current to the capsule. Moving the active contact away from the capsule or reducing the amplitude may help reduce this side effect (87). Capsular stimulation can also cause muscle contraction that can be focal or general-ized on the side contralateral to the stimulation. The treatment for this is steering the current away from the capsule by adjusting the stimulation-field parameters (87). Stimulation can also induce side effects in ocular movements causing either monocular deviation (spread to oculomotor nucleus), conjugate gaze deviation (spread to capsule) or eyelid apraxia (87, 179).

Overall, the stimulation-induced complications must be monitored with the neurologist and the programming team.

In summary, as the number of DBS surgeries increases, there will be more complications. The hypervigilance of the team is necessary to avoid, recognize, and manage complications associated with DBS implants.

Neurorestorative Surgical Approaches for PD

DBS is currently the best surgical approach for movement disorders with respect to safety, efficacy, and proven track record. However, DBS is an implantable device, with its associated complications, and it treats the symptoms of the patient and not the underlying disease. In this context, restorative strategies aimed at treating the underlying disease pathophysiology are important.

A variety of surgical neurorestorative approaches have been developed in an attempt to prevent the loss of nigral neurons and stimulate the regeneration of nigrostriatal projections. These include the delivery of protein trophic factors, the delivery of therapeutic genes, and the transplantation of a variety of potentially restorative cell types.

Delivery of Therapeutic Growth Factors

Translational research on growth factors for PD has focused on the glial-derived neurotrophic factor (GDNF), family ligands, and neurturin. Much of the literature supports the ability of these proteins to protect dopaminergic neurons from a variety of toxic insults in cell culture and rodent and primate models (3). These observations led to two separate open-label studies of GDNF infusions into the human parkinsonian putamen (114, 324). Both open-label studies demonstrated significant improvements in UPDRS scores in the recipients. The second study demonstrated a gradual return to baseline in the first year after cessation of GDNF delivery. Enthusiasm generated by these open-label trials led to an international, multicenter, randomized placebo-controlled trial sponsored by Amgen (Thousand Oaks, CA) and Medtronic. In this study, patients were randomized to receive either GDNF or vehicle through bilateral putaminal catheters. The approach was abandoned by the sponsors after the safety and efficacy data were reviewed, including the development of anti-GDNF antibodies in some of the patients, and the observation that some monkeys had developed cerebellar lesions attributed to putamenal GDNF therapy. Results of the study at the time of termination revealed no significant difference between the placebo and treatment groups, although positron-emission tomographic imaging revealed increased dopamine production in the treatment group in the region immediately adjacent to the cannula tip (199). Proponents of intraparenchymal GDNF infusion therapy cite potential problems with catheter design and drug dis-
A second trial has been pursued by Oxford Biomedica (Oxford, England) for stereotactic injection of a lentiviral vector carrying three separate transgenes: tyrosine hydroxylase, AADC, and guanosine triphosphate cyclohydrolase I. Together, these gene products are capable of driving autonomous production of L-dopa with subsequent dopamine production. Thus, unlike the Genzyme strategy, the Biomedica vector, named Prosavin, will drive dopamine production independent of L-dopa administration (388). The company plans a Prosavin trial in either England or France.

A third gene-therapy approach has been advanced by Neurologix (Fort Lee, NJ). This approach induces subthalamic and pallidal inhibition through the expression of glutamate decarboxylase in the STN. Glutamate decarboxylase is the enzyme that changes glutamate to GABA. Thus, inhibition is affected by the production of GABA in the STN, and a reduction in efferent glutamate. Twelve patients received unilateral STN injection at three escalating doses (n = 4 patients per group) to minimize risk. Investigators reported sustained improvements in UPDRS motor scores at 12 months (24% off state and 27% on state), with no serious adverse events related to gene therapy. Positron-emission tomographic studies confirmed reduction in thalamic metabolism (163). As the Neurologix project was the first PD gene therapy trial to pass through regulation, particular care was required in addressing safety over efficacy (as reflected in the decision to inject unilaterally). The authors note that effects were proportionally larger on the side contralateral to infusion, which lends weight to the hypothesis that gene-based STN inhibition can provide a benefit beyond placebo.

**Cell Transplantation Delivery**

The approach of cell transplantation has the longest history, and perhaps, the most complex landscape. A wide variety of cells have been studied as potential means to provide neuroprotection and potentially replace lost dopamine neurons. Initial efforts used autografts of adrenal medullary cells as a potential source of dopamine but failed to show consistent improvements (97). Subsequent efforts involved the transplantation of fetal mesencephalic tissue containing nigral dopamine cells transplanted into the putamen. Results in this study proved inconsistent as well, with some patients showing improvements. However, a subset of patients developed an exacerbation of dyskinesias thought to be a result of heterogeneous and uncontrolled production of dopamine throughout the putamen (106, 305). Contemporary efforts at neural transplantation have involved putamenal implantation of retinal pigment epithelial cells grown in a bead matrix called Spheramine (Titan, San Francisco, CA). Retinal pigment epithelial cells can produce L-dopa, but also appear to have trophic/protective effects on adjoining neurons (305, 335). An ongoing Phase II, controlled, multicenter trial is under way to assess the safety and efficacy of Spheramine implants.

Advances in stem cell technology have made it possible to manufacture dopaminergic neurons. A wide variety of protocols have been developed for the production of dopamine cells from embryonic stem cells, fetal-derived uncommitted and
committed progenitors, and even adult progenitors harvested from the subventricular zone. Parallel strategies have been developed to purify the dopaminergic cells from nondopaminergic cells in these preparations with the hope of creating a sustainable, practical source for pure, differentiated, human dopaminergic cells. Finally, a fusion of gene-delivery technology with transplantation (ex vivo gene transfer) provides a potential means to control these cells, hence reducing the potential for the runaway dyskinesias to occur that were observed in the fetal transplant.

Surgery for Movement Disorders: Future Directions

The field of functional neurosurgery has witnessed a renaissance over the past 20 years. This development has been fueled by progress in the neurobiology of movement disorders, surgical technical advancements, therapeutic device developments, and innovative approaches. The growth in our understanding of the neural circuitry of the disease has determined and refined our surgical targets. This increased understanding of the neurobiology of movement disorders will guide the discovery of additional targets for surgical exploration and translational clinical research.

The evolution of stereotactic surgical tools and techniques is facilitating safe and minimally invasive approaches that enable neurosurgeons to target various brain structures with reliable accuracy. This, coupled with rapid advances in imaging technology and capabilities, will play an important role in improving our capability to visualize brain structures and function with unparalleled resolution.

At present, DBS is the standard therapy of choice for movement-disorder patients who are medication intractable and who meet the surgical selection criteria. DBS has a proven safety and efficacy profile and long-term outcomes have been demonstrated by prospective, randomized studies. Technological advances in DBS systems have already resulted in improvements and will continue to do so. The next-generation DBS systems will be smaller and rechargeable, with current steering features and built-in sensing capabilities. A number of clinical trials are under way to explore the utility of gene therapy and cell transplantation and stem cell approaches with promising preliminary outcomes. In the near future, these technologies will provide additional options for neurosurgical management of movement disorders.

Functional neurosurgery is one of the most exciting and rapidly growing areas in neurosurgery. Despite significant advances, this arena of neurosurgery is still in its infancy. The movement-disorder surgery evolution can be argued to be a model approach for development of neurosurgical therapies. The lessons learned from movement-disorder surgical experience are already being applied to surgical treatment of psychiatric and other chronic neurological disorders.

REFERENCES


Cough IS: Ligation of the anterior choroidal artery for involuntary movement.


Cooper IS: Ligation of the anterior choroidal artery for involuntary movement.


COMMENTS

This ambitious article shows what a privilege it is to participate in the extraordinary world of movement disorder surgery. This narrow subspecialty is paradigmatic of the “golden age” of neurosurgery, combining so many of the elements that fascinate and inspire us: Its rise has been fueled by seminal discoveries in basal ganglia physiology, the technical approaches are rapidly evolving, and it represents a coming era where elective neurosurgery can greatly enhance quality of life for a prolonged period in serious neurological diseases.

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Deep brain stimulation for movement disorders joined the mainstream of neurological practice only in the last 10 years, yet as noted by Rezai et al. (who have played no small role in increasing access to this procedure for patients with movement disorders as well as other more novel indications), more than 1000 articles have been published on this topic. A detailed, comprehensive review of this complex field would require a whole supplement (1), but the authors provide a review that nevertheless addresses all of the major issues and is in a very readable form.

Certain aspects of surgical technique tend to inspire extensive debate among functional neurosurgeons, such as the use of framed vs. frameless devices, or the use of microelectrode recording techniques. Rezai et al. provide balanced views of these areas, correctly pointing out that these and other issues can only be resolved with prospective, randomized, blinded trials. However, it is not feasible to subject every nuance of functional neurosurgical procedures to such a metric. Ten years later, we still do not know from prospective randomized trials (Class 1 evidence) whether the subthalamic nucleus (STN) truly is a “superior” target to the globus pallidus internus, and what the relative risks and benefits are (although two such trials will be arriving soon, one from Emory and the Cleveland Clinic, and the other from the multicenter National Institutes of Health/Veteran’s Administration trial). Ten years later, we must still suffer the endless debate about the utility of microelectrode recording, now obfuscating the pioneering work on new potential targets for Parkinson’s disease (2, 3). As new indications, e.g., depression (7), and new targets, e.g., pedunculopontine nucleus (PPN), arrive on the landscape, new and old issues will arise, providing more fodder for prospective, randomized, clinical trials: Which is better, STN, STN + PPN, or STN then PPN (4, 5)? Which is better, gene therapy or cell therapy or deep brain stimulation? If gene therapy is better, then which gene therapy? Anterior internal capsule or Area 25 for depression? Medtronic (Minneapolis, MN) or Advanced Neuromodulation Systems (Plano, TX)? Which method is better: yours, or mine, or both, or neither? And has anyone yet subjected prospective, randomized, double-blind, sham/placebo-controlled trials to a prospective, randomized, clinical trial? Two such trials seemingly eliminated fetal cell transplantation for Parkinson’s disease, but were the trials fair? Perhaps we will even see this subject revisited in the years to come (6). If Rezai et al. reflect the state of the art for movement disorders alone 10 years later and approximately a century after surgery for movement disorders began, I suspect functional neurosurgeons will be well occupied for the next century too.

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In this article, Rezai et al. provide an excellent overview of the current status of movement disorder neurosurgery. The information is provided in a well-organized manner and the literature review is extensive. The conclusions presented are based on the available literature, gray areas in our knowledge are appropriately highlighted, and professional biases are minimized. This is a comprehensive first read for anyone interested in participating in this exciting field of neurosurgery.

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Rezai et al. provide an outstanding review of the history, present status, and possible future of movement disorder surgery that has progressed from gross ablations to precise lesioning to neuroaugmentation and neuromodulation. Initially based on empiricism and a crude understanding of the neural circuitry of the motor system, functional neurosurgery has been ever more refined by better understanding of extrapyramidal neurophysiology and cellular neurochemistry. As a result of modern advances in basic science, future procedures may go beyond simple manipulation of large cellular populations for the control of symptoms (as we do now with deep brain stimulation neuroaugmentation) to neurochemically target-specific cellular groups within these populations. In addition, genetically programmed stem cells may be used to repopulate central nervous system regions whose cells have been decimated by the underlying disease process. However, the ultimate therapy may focus on identifying and reversing the neurotoxic triggers that result in selective loss of neuromelanin-containing dopaminergic neurons in the substantia nigra.

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