Subthalamic Stimulation for Parkinson's Disease

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Abstract

Subthalamic nucleus stimulation by means of permanently implanted brain electrodes is a very effective therapy for all the cardinal features of Parkinson's disease. In appropriate patients, motor improvement is accompanied by a significantly improved quality of life and a reduced necessity for medication. This article briefly reviews the indications, technique and postoperative management of patients undergoing subthalamic nucleus stimulation.

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Parkinson's disease is a progressive neurodegenerative disease. The hallmark features of PD include tremor, rigidity, bradykinesia and eventually postural instability. Ultimately, gait disturbances, especially freezing and bulbar dysfunction, develop. Despite optimal medical therapy, the progression of PD will often result in steadily worsening function and increasing disability. The long-term side effects of dopaminergic drugs – namely choreatic dyskinesias and the unpredictable motor fluctuations – may themselves cause additional functional and social disability. Stereotactic neurosurgery targeting the subthalamic nucleus can offer these patients a very significant amelioration of the parkinsonian syndrome, and it also has prominent medication-sparing effects. Thus postoperatively, most of the drug-induced side effects will often resolve too.

History

The history of surgery for movement disorders has been reviewed in a previous article [1]. Most of the emphasis in early surgical series was placed on resolving tremor. However, other symptoms of PD were not effectively controlled by ablative surgery within the thalamus. Researchers were hampered by the lack of an animal model of PD.

In 1982, a number of young people were admitted to hospital in California suffering from an acute and irreversible parkinsonian syndrome including bradykinesia, akinesia and muscle rigidity. Some of them also exhibited some degree of resting tremor. It transpired that the synthetic heroin analog that they were self-administering was contaminated with a mitochondrial toxin, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine [2,3]. Post-mortem studies revealed severe selective nigral cell loss closely resembling that seen in idiopathic PD.

This incident marked the beginning of a new era in PD research. For the first time researchers had a promising new primate model for the disease [4–8]. Monkeys treated with MPTP exhibited most of the cardinal symptoms of PD, including akinesia, bradykinesia, hypometric movements, cogwheel rigidity, flexed posture and loss of facial expression [4,8–12]. The work with parkinsonian monkeys led to the proposal of a "box and arrow" model of basal ganglia connectivity and function [13,14].

In 1990, two groups working with this monkey model of PD published an important discovery [15,16]. The tiny subthalamic nucleus was found to be significantly overactive. When this small nucleus was ablated, all the symptoms of parkinsonism in the monkey dramatically subsided. The application to humans came 3 years later. Based on observations that high frequency electrical stimulation of the motor thalamus during surgery could ablate tremor, Benabid's group working in Grenoble, France, and others had already begun implanting electrodes within the motor thalamus of patients with tremor [17,18]. In 1993, they applied this technology to the STN of parkinsonian patients. As with thalamic stimulation, the electrical impulse had the same effect as an ablative lesion. STN stimulation demonstrated a dramatic resolution of *all* the cardinal parkinsonian symptoms including tremor [19].

The renaissance of pallidotomy in the 1990s occurred in an almost identical parallel timeline and the new pathophysiologic models undoubtedly provided impetus for this [20]. Laitenen et al. [21,22] had begun "revisiting" the pallidal target of Leksell in 1985 using modern-day technology; lesioning the internal pallidum (globus pallidus) could successfully eliminate drug-induced dyskinesias and reduce rigidity, bradykinesia and tremor. Although this work was published in 1992, the preliminary data had previously been presented at international meetings. Dogali and Beric in New York and DeLong and Bakay in Atlanta pioneered the procedure in the United States. They chose the pallidal target over the subthalamic nucleus for fear of hemiballismus as a complication. Microelectrode-guided pallidotomy became the procedure of choice for medically refractory PD and was approved by the U.S. Food and Drug Administration in 1995. However, as with thalamotomy, bilateral procedures were often associated with significant morbidity. For this reason and others, bilateral pallidotomy has essentially been abandoned.

PD = Parkinson's disease

MPTP = 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine
STN = subthalamic nucleus

Unilateral pallidotomy may still be an appropriate intervention for selected PD patients with an asymmetric or unilateral symptomatology, especially those with prominent dyskinesias, or occasionally for patients who live too far from an expert center or cannot afford deep brain stimulation surgery [23].

The last few years have witnessed a growing trend preferring stimulation over lesional surgery and favoring the STN over the pallidal target [24], although further studies are in progress. The Gpi is emerging as the preferred target for the treatment of dystonia, especially the genetic forms of primary generalized dystonia due to mutations in the genes *DYT1* and *DYT11*.

Thus, the development of STN stimulation represented a very significant step forward in the surgical therapy of PD patients. For the first time, *all* the cardinal symptoms of PD could be *bilaterally* and *reversibly* controlled. DBS targeting the STN was approved for PD by the American FDA in 2001 and is now performed in many centers worldwide.

Mechanism

Several theories have been proposed to account for the lesion-like effect of high frequency stimulation, however the precise mechanism explaining this phenomenon remains intensely debated [25,26]. While the implication has been that HFS inhibits the neuronal activity of the target, it is more likely that HFS acts via a resynchronization (*or desynchronization*) of abnormal output patterns present in disease or via a "jamming" of these abnormal patterns, with HFS acting as "blank noise" [27].

Indications and contraindications

Parkinsonism is a common syndrome observed in many neurodegenerative disorders other than Parkinson's disease, such as progressive supranuclear palsy, multiple system atrophy, and dementia with Lewy bodies. Parkinsonism secondary to vascular insults or drugs is also not uncommon. The diagnoses of the various disorders is based on the clinical presentation and course, the response to dopaminergic therapy, the presence of other symptoms (including ocular abnormalities, autonomic dysfunction, dementia, corticobulbar signs, cerebellar deficits), or other signs implying a more widespread pathology. Among all these disorders only patients with *idiopathic PD* are candidates for STN deep brain stimulation, although it has recently been reported that MPTP-induced PD also responds well [28].

The patient must have a good response to L-dopa even in advanced disease, since this defines the extent of the motor benefit obtained from stimulation. To justify the risk of surgery the disease process must be causing significant motor disability despite best medical management. Typically, patients will be suffering from severe, prolonged "off" periods, marked motor fluctuations, and often from drug-induced dyskinesias in the "on" state. Since tremor responds so well to deep brain stimulation, patients with severe tremor, even unresponsive to L-dopa, are also good candidates.

Drug-resistant symptoms such as freezing of gait in the "on" condition, poor balance and frequent spontaneous falls during "best-on" are relative contraindications to STN stimulation. Patients with bulbar dysfunction, especially poor swallowing, should probably not undergo surgery since dysphagia may occasionally worsen and expose the patient to an increased risk of aspiration. Severe hypophonia, even if it responds to dopaminergic medication, does not always respond to STN stimulation; and as most patients reduce their medication postoperatively it may actually worsen.

The issue of age is a relative one. Most programs accept patients until the age of 70 years. There is a general tendency today to operate on younger patients for several reasons. Overall results tend to be better with fewer cognitive complications. In addition, younger patients are less likely to have any significant brain atrophy.

Subthalamic nucleus stimulation by way of a permanently implanted electrode is a safe and effective therapy for advanced Parkinson's disease

Prominent dysautonomic symptoms, such as orthostatic hypotension, always raise concern about the possibility of multiple system atrophy and are therefore considered a relative contraindication to surgery. These symptoms will certainly not gain benefit from deep brain stimulation unless they are caused mainly by medications. Magnetic resonance imaging brain scan should exclude significant atrophy or other abnormalities such as prominent ischemic changes or hydrocephalus.

Prior to surgery any bleeding tendency must be corrected. Aspirin or coumadin must be stopped well before surgery to ensure a normal coagulation profile. Blood pressure must be well controlled.

Active psychological or psychiatric illness is a contraindication to surgery. Any existing cognitive deficits may worsen after surgery and these patients may therefore also be excluded. Finally, patients must be able to cooperate with a long procedure under local anesthetic and this is another important assessment to make prior to surgery.

It cannot be stressed enough that the decision to proceed to surgery is multidisciplinary. At the very minimum, the team should include a neurologist, neuropsychologist and a neurosurgeon, all of whom have experience in the selection and evaluation of patients for this procedure.

Gpi = globus pallidus
DBS = deep brain stimulation
FDA = Food and Drug Administration
HFS = high frequency stimulation

Evaluation

Patients who fulfill the criteria as surgical candidates undergo further evaluation. This evaluation may be performed during a short hospitalization. On the day of admission, a neuropsychological evaluation is performed in the "on" condition. Overnight the patient's medication is withdrawn and the following morning, in the "off" condition, a full motor examination is performed using the UPDRS (Unified Parkinson's Disease Rating Scale) and the Hoehn and Yahr scale. Response to a challenge of levodopa is evaluated and the patient is examined in the "on" state using the same scales as well as the Abnormal Involuntary Movement scale (AIMS). Video recording of the patient is performed in both the "off" and "on" conditions. Patients are assessed by a physiotherapist, specifically to try and identify functional issues such as contractures that may make postoperative rehabilitation problematic. The patient also undergoes a preoperative MRI as part of the plan for image-based targeting.

During the weeks prior to surgery it is usually recommended to gradually decrease dopaminergic therapy in order to reduce the risk of confusion from dramatic withdrawal of medications during surgery.

Technique

All anti-parkinsonian medications are stopped on the evening before surgery so that the patient is "off" during the period of surgery. The purpose of this is twofold: firstly to prevent dyskinesias that would make the surgery impossible, and secondly so that the beneficial effects of stimulation during the surgery will be easily detectable. Microrecording within the pallidum may also be more informative with the patient off medication.

The basics of the technique are as previously described [1]. Since the STN target is so small, the procedure is essentially one of multiple validations of the image-based targeting. Validation is achieved by intraoperative microelectrode recording, "macrostimulation," intraoperative fluoroscopy, and postoperative computed tomography or MR imaging.

On the morning of surgery, the stereotactic frame is affixed to the patient's head under local anesthetic and a CT scan is then performed. Sophisticated computer software is used to fuse the preoperative MRI and CT images and to plan the surgery [Figure 1]. The coordinates and trajectory to the STN target are calculated.

The patient is then transferred to the operating room. Surgery is performed under local anesthetic, with the patient awake. The patient is made comfortable on the operating table so that he or she will remain cooperative and motivated throughout the procedure, which lasts several hours. After sterilizing the skin, an incision is made under local anesthetic just above the hairline a few centimeters from the midline. A small hole is drilled in the skull bone. A "micro" electrode (20 µm tip) is introduced into the brain through a 1.3 mm cannula and very slowly advanced toward the target. By extracellular recording of the electrical activity of cells along the trajectory, physiologic confirmation of the image-based information is obtained [Figure 2]. "Macrostimulation" via a 1 mm exposed section of the same electrode, using parameters similar to those generally used for chronic stimulation, is performed to assess the effects of stimulation of the target on rigidity and tremor, as well as any unwanted side effects.

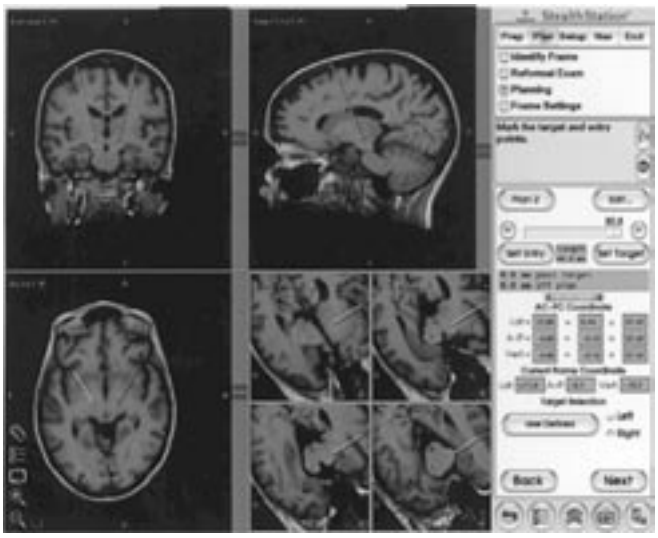

Figure 1. A final stage in surgical planning. The STN target has been chosen as a function of distance from third ventricular anatomy. The trajectory has been designed to avoid penetration of a brain sulcus or the ventricle.

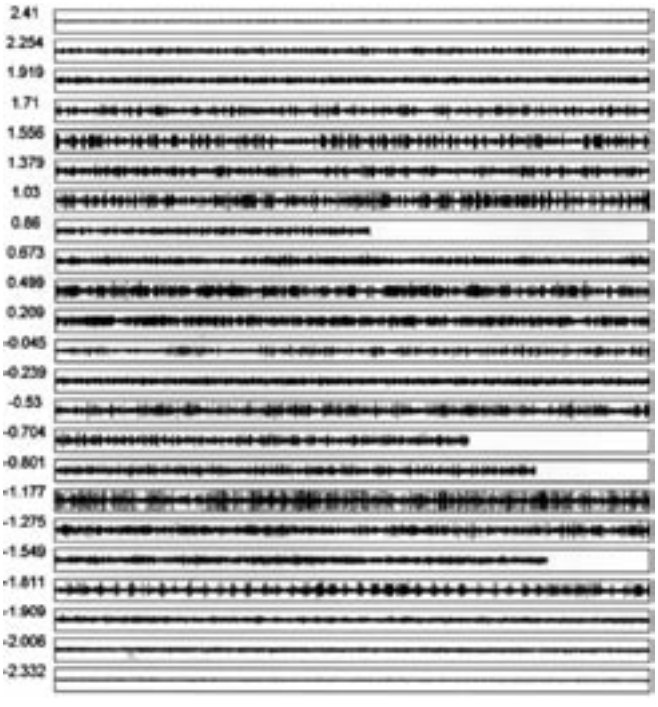

Figure 2. A typical extracellular microrecording trace. Entry into the STN at 2.3 mm above target is shown by increased background noise and spontaneous firing patterns typical of STN units. Exit from the STN is seen at 2 mm below target.

UPDRS = Unified Parkinson's Disease Rating Scale

When the final target has been confirmed as a composite of image-based and physiologic targeting, the permanent quadripolar "macro" electrode (diameter 1.27 mm) is introduced and secured to the skull bone. Position is verified with lateral fluoroscopy. In most cases the surgery is performed bilaterally and the identical procedure is repeated on the other side of the brain. This first stage of surgery may take between 3 and 8 hours.

It should be pointed out that the use of microrecording as a localization tool remains controversial [29]. The debate is beyond the scope of this review; however, it is perfectly feasible and safe to perform deep brain stimulation surgery with or without microrecording [30,31].

The second stage of surgery to implant the pulse generator is performed under general anesthetic. We currently use the Medtronic Kinetra generator (USA), which can receive extensions from both electrodes. The entire system is implanted under the skin, with the generator usually positioned in the upper chest wall. This stage of surgery usually takes approximately 1 to 1½ hours. Patients are usually discharged from hospital 48 hours after surgery.

Postoperative care

Optimal care of the patient after surgery is more of a learned art than a teachable science. Often, just the introduction of the electrodes into the STN may result in a "microlesional effect." "Off" symptoms usually improve, but dyskinesias may be worsened. These effects are temporary and may take 1–2 weeks to stabilize. It is for this reason that we do not attempt to initiate stimulation during this initial period.

Typically, patients return a week to 10 days following implantation, for programmed stimulation. This can be done either in an outpatient or inpatient setting, preferably in the "off" condition. The first step in postoperative programming is to assess the efficacy and side effects of stimulation via each of the four individual electrode contacts on each macroelectrode separately to determine the optimal electrode(s) for chronic stimulation. The best target symptom to assess is rigidity since it responds to changes in stimulation within seconds and because it is a reliable and stable sign, independent of patient cooperation or mood. The choice of active stimulation electrodes and electrophysiologic parameters (amplitude, pulse width and frequency) are determined when the optimal combination of best effect, minimal side effects, and least battery expenditure is achieved. Subsequent visits are exploited for "fine tuning" of stimulation parameters and adjusting medication dosages.

Although many patients achieve a significant reduction in medication, we do not routinely aim for this immediately. Dramatic reduction of medications may result in neurobehavioral changes; therefore, this decrement should be pursued gradually and cautiously. Usually, patients initially drop their night-time dosages (because they tend to sleep better) and only later alter their daytime medication. It may take a few months and several programming sessions until the patient's neurologic status stabilizes and enables steady stimulation combined with pharmacologic treatment.

Results

STN stimulation improves overall motor function by at least 60%, usually enables a significant reduction of dopaminergic treatment, and often dramatically improves the quality of life in PD. The effects are long-lasting, with reports of sustained benefit for up to 5 years [32,33]

The most dramatic effect is the reduction or abolition of tremor, but there is also a significant reduction in most "off" symptoms, including gait, balance, rigidity and manual functioning. Many patients may regain complete functional independence for the whole day as on-off motor fluctuations resolve or are very significantly attenuated. Drug-induced dyskinesias are indirectly reduced or abolished as a result of a reduced drug regimen.

There is much evidence favoring the cognitive and neurobehavioral safety of STN deep brain stimulation. Most studies demonstrated that diminished verbal fluency was the most common worsened neuropsychologic functioning, whereas changes in global cognitive abilities, memory, attention, and frontal/executive functions were inconsistent or transient. STN stimulation is associated with improvements in self-reported symptoms of depression but may increase apathy. Other behavioral changes such as severe depression, hypomania or psychosis have been described but these are comparatively rare and mostly transient [34,35].

Deep brain stimulation is largely replacing ablative surgery as the preferred method for surgical management of movement disorders

Chronic STN-DBS improves sleep quality as well, probably through increased nocturnal mobility and reduction of sleep fragmentation. There is an improved subjective sense of well-being, an increase in motivation, and a decrease in fatigue, anxiety and tension [36]. Other, non-motor manifestations of PD do not respond to STN-DBS. These include dysphagia, olfactory dysfunction, musculoskeletal problems such as fixed deformities, and autonomic and sensory dysfunction. However, pain secondary to dystonias will often subside.

Complications

Side effects related to the surgical procedure are usually minor. Occasionally there is a transient postoperative confusional state, especially in older patients. Intracerebral hematoma is an inherent risk of any neurosurgical procedure and may occur in up to 3% of DBS patients, at least half of whom are asymptom-

atic. Permanent neurologic deficits are rare. Hardware complications are relatively common, occurring in some series in up to a quarter of the patients, consisting of electrode malposition, device failure or breakage, erosion of the components of the device through the skin, infection, and premature loss of battery life [37]. Improved technology and meticulous attention to detail during the procedure significantly reduce these risks.

Stimulation-induced side effects – including parasthesias, speech disturbances, confusion related to stimulation, diplopia or difficulty with eye movements as well as motor contractions – may occur but usually respond to changes in stimulation parameters.

General complications may include a worsened previous neuropsychological impairment in the level of dementia, weight gain, eyelid opening apraxia, and aggravated speech impairment.

The occasional reports of detrimental psychiatric sequelae, specifically depression and suicidal thoughts [38,39], have been of particular concern but these are rare and their incidence can be decreased if dopaminergic therapy is reduced cautiously or renewed if depression appears.

Of the 29 patients who have been operated at Hadassah Medical Center since January 2003 for the implantation of electrodes for movement disorders, 22 were for PD. Of these patients, seven have concluded 1 year follow-up, of whom two have reached 18 months. The remaining 15 patients were operated during the last 12 months. Two patients had a previous unilateral pallidotomy at another center.

All these patients exhibited a dramatically improved UPDRS score in the "off" state of more than 60% compared to the preoperative score [Figure 3]. There was an average reduction in "off" time by 90%. On average, patients reported a 60% reduction in medication. Four patients have stopped taking PD medication altogether. All patients but one have reported no postoperative drug-induced dyskinesias.

Our own complications have been one malplaced electrode, which was correctly relocated, and one superficial stitch abscess that was successfully treated with oral antibiotics. Two patients

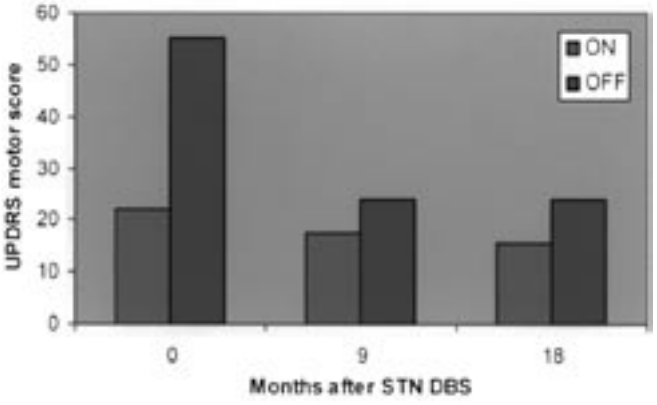

Figure 3. Graphic presentation of the averaged UPDRS for seven patients with at least 1 year of follow-up. A higher score represents worse disability. The dramatic postoperative reduction in "off" score is maintained over time.

experienced postoperative confusion that completely resolved. One patient had an asymptomatic chronic subdural collection that resolved spontaneously. In one patient the STN was small and hypocellular, and intraoperative stimulation was associated with side effects at a low threshold; this patient subsequently underwent reimplantation in the Gpi. One patient died during follow-up of an entirely unrelated cause (large bowel perforation, septic shock and multi-organ failure).

It is important to remember that inasmuch as each patient is an individual, so is their response to this therapy. Deep brain stimulation is palliative and does not cure PD, which continues to progress despite this surgery. A common misapprehension is that this surgery will return the patient to his/her condition prior to the onset of PD, but patients usually have to settle for a slightly lesser reality.

Depending on the parameters of stimulation, the generator battery may last on average for 4 to 5 years. The generator may be replaced under local anesthetic as a day-surgery procedure.

Discussion

STN deep brain stimulation is an effective, safe and cost-effective procedure for the management of advanced Parkinson's disease. Many issues warrant further discussion, some of which are addressed below.

Firstly, given that PD is not a life-threatening disease, are the risks associated with surgery warranted? We believe that this is a matter of subjective outlook. For many, loss of independence, loss of employment, involuntary movements and tremor, which can be socially embarrassing and disabling, are totally unacceptable. For them, the option of improved function easily outweighs any concerns of risk. What should be stressed, however, is that this procedure has a very low inherent risk and certainly a lower risk than bilateral ablative procedures. Secondly, when should a patient be referred for surgery? Clearly, the referring neurologist must be sure that every reasonable drug regimen has been pursued. Patients appropriately consulting our center with regard to surgery have suffered with PD for as little as 6 or 7 years or occasionally as long as 24 years! However, there is a developing tendency to refer patients earlier for surgery and certainly prior to cognitive decline, such that they preserve their psychosocial environment and are not forced to give up their jobs. Finally, although this surgery is not an easy financial undertaking, studies have shown that the operation is cost-effective in the long-term [40]. STN is now performed routinely in Israel and was recently included in the "basket" of health procedures for which insurers are obliged to reimburse.

Deep brain stimulation is a powerful tool that has already found its application in tremor (thalamic Vim), PD and dystonia (Gpi). There are encouraging reports that indicate it may be useful in intractable epilepsy, intractable depression, obsessive-compulsive disorder, and possibly Tourette syndrome.

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