Deep Brain Stimulation for Parkinson’s Disease—A Review

Christopher R Honey, MD, DPhil, FRCS¹ and Manish Ranjan, MBBS, MCh²

1. Associate Professor of Neurosurgery, Surgical Centre for Movement Disorders, University of British Columbia, Vancouver, Canada;
2. Associate Professor of Neurosurgery, National Institute of Mental Health and Neuro Sciences, Bangalore, India

Abstract

The majority of patients with Parkinson’s disease (PD) can be treated with medications. As the disease progresses, however, certain symptoms may evolve that are refractory to medical therapy but ideally suited to surgical intervention. Tremor, dyskinesia and motor fluctuation can be effectively treated with deep brain stimulation (DBS). This article highlights which PD patients can benefit from DBS and summarizes how the operations are performed and what are the expected outcomes (and potential complications). The relevant literature is reviewed for experienced clinicians and our personal bias is highlighted for those new to the field (and hoping to avoid our early mistakes).

Keywords

Parkinson’s disease, deep brain stimulation, tremor, dyskinesia, motor fluctuation, complication, outcome

Any surgical procedure requires two things to be successful: selecting the correct patient and performing the operation correctly.

The various operations of deep brain stimulation (DBS) for Parkinson’s disease (PD) are not particularly difficult. They comprise a series of steps that must be performed in an appropriate sequence and can be learned by most neurosurgeons within a year of fellowship training. The selection of the ideal patient, however, is much more difficult and is as much an art as a science.

This article will summarize how DBS can be used to help patients with PD. The relevant literature will be presented for a comprehensive overview but we will focus on our personal experience (and bias) to provide practical guidelines. Each of the three main brain targets for this technique will be discussed and suggestions on patient selection, surgical technique, post-operative care and expected outcomes will be provided.

The current popularity and wide acceptance of DBS for PD began in the early 1990s. Publications from the teams in Grenoble¹² and Lille¹³ re-ignited interest in this technique after earlier publications had introduced the concept of DBS for PD but had not gained wide acceptance.³ The concept that DBS could create a beneficial clinical effect without destroying tissue was very appealing. Prior to this technology, neurosurgeons could only destroy target areas in the brain. A variety of structures had been lesioned in an attempt to ameliorate PD, including the motor cortex,⁴ the spinal cord motor pathways⁵ and the basal ganglia.⁶ The early experience (prior to 1960) was fraught with morbidity and mortality.⁷ The more recent experience has been aided by accurate neuroimaging, intra-operative electrophysiologic confirmation of targeting and reproducible lesioning. During thalamotomy, macrostimulation of the ventral intermediate nucleus (Vim) with high-frequency stimulation (100 Hz) was known to block contralateral tremor whereas ‘low’-frequency stimulation (50 Hz) drove the tremor.¹ Permanent implantation of an electrode to chronically stimulate the Vim at high frequency was proposed to suppress tremor and tested as a method to avoid the complications associated with bilateral thalamotomy.¹,² Following a unilateral Vim thalamotomy, the contralateral side could be treated with DBS. Beneficial effects (i.e. blocking tremor) were obtained by increasing the voltage of stimulation and deleterious side effects (e.g. dysarthria) were avoided by reducing the voltage. The effect of DBS could be titrated.

The ability to titrate the effect of DBS has remained its greatest asset. Adjusting the effect of DBS post-operatively to gain more benefit in a progressive disease or back away from a side effect is appealing to both the surgeon and patient. The concept that ‘we have not burned any bridges’ is also very appealing to many potential patients. Prospective patients often arrive for their surgical consultation emboldened by the concept that the surgeon is ‘only’ inserting an electrode in their brain and not burning any tissue. The review of potential risks of DBS is often surprising for the patients and is an essential part of their pre-operative assessment.
With the success of Vim DBS in reducing tremor following contralateral thalamotomy, it was not long before DBS was used primarily to treat tremor without any prior thalamotomy. DBS appeared to work like a reversible lesion and was therefore tried in the pallidum instead of pallidotomy. At this time, surgeons began exploring the subthalamic nucleus (STN) as a target for PD and DBS was used in this target prior to any significant experience with lesions in this target.

How DBS exerts its effects remains controversial. Since high-frequency DBS in the thalamus or pallidum had similar clinical effects to lesions, it was assumed that DBS worked by inhibiting neuronal firing. This reasoning was used to support surgeons targeting the STN, which had been shown to be overactive in primate models of PD. More recently, however, it has become clear that the effect is probably more complex. DBS may work by desynchronizing pathologic rhythms in the basal ganglia.

DBS brings a new set of problems to the management of PD. There are complications associated with surgery (brain hemorrhage and infection), stimulation-related and neuropsychiatric issues, there is the need for intensive follow-up care to adjust the stimulation and the technology is expensive. Nonetheless, the ideal patient receiving the ideal operation can enjoy stunning benefits. It all begins with selecting the correct patient.

**Patient Selection**

*The surgeon must aim to improve the quality of life of their patient not just reduce a given symptom.*

The majority of patients with PD are adequately managed with medications. A small portion of patients, however, will have medically refractory symptoms that can be ameliorated with surgery. The selection of these patients is just as important as the performance of surgery in determining the final outcome. The general neurosurgeon does not require help assessing the need for surgery in a patient with a traumatic epidural hematoma or tumor causing brain herniation. What is the alternative? The functional neurosurgeon, however, must be satisfied that the medical alternatives have failed before considering surgery. This presents a problem for the neurosurgeon unfamiliar with PD medications.

The solution in many centers has been a close collaboration between the neurosurgeon, neurologist and other specialists. This is a recurring theme in DBS for PD—it requires a team to deliver ideal care.

Patients referred from family doctors for DBS (often at the request of the patient) are often just not optimized with their medications and are therefore not surgical candidates. For example, a patient referred for surgery because of disabling dyskinesias may benefit from a reduction in their medications or the addition of amantadine. It has been our practice to ensure all patients referred for surgery have had a consultation with a neurologist familiar with the treatment of PD. This reduces the proportion of surgical consultations that are not yet appropriate candidates for surgery. If the family practitioner must be careful not to refer patients for surgery too soon, the neurologist must be careful not to refer patients too late. End-stage PD is refractory to maximal available therapy. Loss of response to oral dopamine often parallels a lack of response to STN or globus pallidus internus (GPI) DBS (although Vim DBS may continue to be effective). It is clear that there is a window of opportunity for successful DBS for PD. Early in the disease, medications are effective and surgery is unnecessary. Later in the disease, surgery may help certain symptoms and improve quality of life (the subject of this article). Finally, for some patients in the end stage of the disease, neither medications nor surgery can help. Neurologists must not wait until the end stage of PD before considering a surgical referral because the surgery would be ineffective (and not offered). When to make a surgical referral will be influenced by the neurologist’s impression of the balance between the degree of patient suffering and their neurosurgical colleague’s complication rate. When does a symptom warrant surgical intervention? The answer ultimately lies with the patient. They can estimate what the quality of their life would be like after surgery (once the surgeon explains the expected benefits) and balance this against the chance of their life being worse due to complication. The neurologist can increase the likelihood of success, first by selecting patients whose quality of life will improve dramatically after surgery, and second by selecting a surgeon with a low complication rate.

When a patient arrives for surgical consideration of DBS for PD there are two questions that must be answered in sequence. First, are they a surgical candidate? This is answered by the neurosurgeon after determining if the symptoms interfering with the patient’s quality of life can only be improved with surgery. Only after that determination should the second question be posed. Do they want surgery? The second question can only be answered by the patient once they understand the expected benefits and potential risks of surgery. At the present time, there are three types of patients who can benefit dramatically from DBS for PD. Each of the three corresponds to a different DBS brain target: the thalamus, the pallidum and the STN.

**Tremor-dominant Parkinson’s Disease**

*(Thalamic Deep Brain Stimulation)*

Every patient with PD has a constellation of symptoms that affect them in a unique way. Although each patient is different, certain patterns emerge across the disease. Two distinct patterns can be recognised by their different clinical features and neuropathologic findings. "Tremor-dominant" patients have a slower progression of symptoms and can be disabled by tremor and yet still remain mobile with medications. "Akinetic-rigid" patients have a faster progression, more cognitive impairments and develop motor complications with or without tremor. For patients with tremor-dominant PD, thalamic DBS can be considered if their tremor is disabling. These patients can present for surgical consideration a decade after their diagnosis and still on relatively low doses of medications. Their clinical course does not appear to be rapidly changing. The slope of their clinical deterioration is shallow and therefore their future quality of life can be reasonably predicted by extrapolating their progression of symptoms forwards. Tremor in these patients can be severe and is often the overwhelming factor in their reduced quality of life.

Tremor occurs at rest but can become exhausting. The tremor will dampen on the initiation of movement but, as the arm is held still for any activity (e.g. holding a cup to the lips), the arm will shake again. This tremor can be present in the upper and lower limb as well as the jaw and body. What degree of tremor is intolerable will depend entirely on the patient. The
it is our opinion that the effect of STN DBS mimics that of dopaminergic medication except that it can be applied smoothly throughout the day instead of in dosing intervals. The ideal patient will therefore have enjoyed a good response to dopaminergic medications pre-operatively. That response may be partially obscured by dyskinesia or motor fluctuations but there must be one moment in a typical day when the patient has a good response to the medications. If that is the case, then STN DBS will be able to ‘capture’ that moment and extend it longer throughout the day. Patients will not have a better motor function than before surgery; they will just spend more time at that best level of functioning. Patients who have motor problems when they are at their best (i.e. when they are ‘on’) are therefore not good candidates for STN DBS. Patients with freezing or imbalance when on will continue to have those problems after STN DBS. Conversely, if their ‘off’ freezing, tremor, rigidity or balance problems improve with medications then those symptoms will improve following STN DBS. The adjustment of the DBS parameters following STN DBS is the most complicated of the three brain targets and can induce unwanted side effects.

The Surgical Technique of Deep Brain Stimulation

Surgeons make errors at the beginning of their career when they are on the learning curve and later in their career when they are not paying attention.

There is a learning curve for performing DBS for PD. We would recommend that surgeons spend their first 30 cases in an environment where an expert can mentor them and pre-empt any learning errors. Lapses in concentration can be avoided by obsessively following a reliable sequence of events. Unfortunately, the checklists designed to prevent our orthopedic colleagues from removing the wrong limb are not detailed enough for functional neurosurgery. We have found that the constant intra-operative teaching of a fellow (and providing an environment where anyone can raise a concern) reinforces following the correct operative steps.

All DBS techniques for PD begin with imaging the brain target and calculating its location with an external reference grid that can be used to guide the electrode into the target. This can be performed in many ways. Each method has strengths and weaknesses but none can claim an overall accuracy of less than 1 mm. The current gold standard (based on historical precedent, number of annual cases and peer-reviewed evaluations) is frame-based magnetic resonance imaging (MRI) stereotaxis. We acknowledge that there are many centers producing excellent work with frameless technology and remember that all of our early work was carried out with ventriculography and computed tomography (CT) guidance. How you perform your stereotaxis is not as important as doing it well. Our procedure is to place the frame pre-operatively under local anesthetic and then perform an MRI. The ideal sequence for visualizing the brain target will vary between machines but guidelines have been published. Some centers perform the MRI as an out-patient to allow pre-operative planning in the office and some centers use both the CT and MRI imaging. Some centers have used general anesthetic and reported good results. Ultimately, how you image the target is not as important as your ability to reliably get to within 1–2 mm of the ideal location. The final electrode position will be refined with intra-operative electrophysiology.

Motor fluctuations (Subthalamic Deep Brain Stimulation)

The beneficial effect of a given dosage of PD medication tends to last for a shorter period as the disease progresses. This is initially overcome by shortening the dosage interval. Eventually some patients are taking their PD medications every three hours and still not getting consistent benefit. They usually report that it takes a variable amount of time for the medications to start working (30–60 minutes after swallowing), then they get benefit for an hour which then starts to wear off before the next dosage. Patients will therefore fluctuate in their symptoms from bradykinetic-rigid to moving well to peak-dose dyskinesia, then back to moving well and finally bradykinetic-rigid. This cycle is repeated with each dose. This pattern is called motor fluctuations and can be ideally treated with STN DBS.
The anatomic target can be determined by its expected position relative to standard internal landmarks or by directly visualizing it. The standard internal landmark is the mid-point (MCP) of a line between the anterior (AC) and posterior (PC) commissures. The locations of the AC and PC can be difficult to determine in some patients if they are elongated vertically in the sagittal plane, but it is important to select the posterior aspect of the AC and the anterior aspect of the PC, since these co-ordinates were developed when ventriculography was used (when you saw the indentation of the AC into the third ventricle, not the actual AC). Image quality will be degraded by motion artefacts and we avoid dyskinesia in GPi and STN DBS patients by withholding their PD medications the night before surgery and blocking tremor with judicious use of intravenous midazolam during the MRI.

Images are then uploaded to a neuronavigational computer for trajectory planning. The neuronavigational computer has two benefits. Firstly, it can re-align the brain so that the AC and PC lie on the same axial plane (regardless of how the frame was applied). Moving away from the MCP towards the target can then be performed accurately because the frame has not introduced a pitch, roll or yaw error.72,88,89 Prior to neuronavigational computers, it was crucial to apply the frame parallel to the AC–PC to avoid these errors. We believe it continues to be good practice to place the frame orthogonal to the AC–PC line, using the glabella–inion or infra-orbital–meatal lines as a guide. Secondly, it allows a trial of virtual electrode passes through the brain to determine if any would pass through a blood vessel, sulcus or ventricle.90 We perform a thin-cut T1-weighted sequence with gadolinium and use a ‘probe’s eye view’ to ensure no vessel would be hit during our electrode pass. This step is time-consuming but is probably the single most important improvement in technique over the last decade that has reduced complications.

During the surgery, there are a set of common surgical techniques regardless of the target and some specific nuances for each. It is our practice to place patients supine on the operating table, flexed at the hips and knees and head elevated with the skull at the entry site almost horizontal. This places the skull above the heart and risks venous air indentation of the AC into the third ventricle, not the actual AC). Image quality will be degraded by motion artefacts and we avoid dyskinesia in GPi and STN DBS patients by withholding their PD medications the night before surgery and blocking tremor with judicious use of intravenous midazolam during the MRI.

The deepest point for the Vim nucleus (and thus its target for the tip of the DBS electrode) is as follows:

- X (lateral) = 11 mm from edge of third ventricle;
- Y (anteroposterior) = halfway between MCP and PC; and
- Z (vertical) = at the level of AC–PC.

We prefer to approach at an angle of 65° up from the AC–PC line in the sagittal plane and close to vertical in the coronal plane. Although a vertical approach in the coronal plane is ideal for thalamotomy, it does present risks for thalamic DBS (e.g. injuring periventricular veins, electrode deflection off the side wall of the ventricle and CSF leakage). The benefit of a vertical approach is that it keeps the electrode as far away as possible from the internal capsule (and its resultant stimulation-induced side effects) and it keeps the electrode in the hand region of the nucleus without deviating into a different part of the homunculus as you move deeper. The final decision is made individually, but primarily in response to the location of periventricular veins.

Intra-operative electrophysiologic confirmation of the target is performed with a macroelectrode (Radionics 1.5 mm exposed tip, 1.8 mm diameter). The stimulation parameters will vary between equipment but 50 Hz, 1 ms pulses at 1.0 V (typically 500 Ω) will just begin to cause paresthesia in the thumb (VC) when the electrode tip is appropriate in Vim. This will confirm both anteroposterior location (<1.0 V is too close to VC) and laterality (paresthesia in face is too medial). High-frequency stimulation (180 Hz at 0.1 ms) should block tremor at 1.0 V without side effects. The macroelectrode can then be replaced by a permanent DBS electrode under fluoroscopic guidance and locked in place. The scalp wound is closed, the frame removed and the implantable neural stimulator (INS) placed under general anesthetic during the same operation. We do not test the electrode on the ward before implanting the INS.
Movement Disorders  Parkinson’s Disease

because we have never had a good intra-operative response that was not duplicated post-operatively and a prolonged trial on the ward invites infection.

The second stage of the procedure (implantation of the INS) can be performed in many ways but we prefer keeping the connector (joint between the electrode and extension wire) high up near the burr hole and tunnelling from the scalp to the infraclavicular location with an exit wound behind the ear. The connector is covered with a waterproof boot (clear for right and opaque for left) and sutured to exclude fluid. Patients receive antibiotics before surgery and for 24 hours after.

**Pallidal Deep Brain Stimulation**

The pallidal target is the GPi. The GPi lies immediately above the optic tract and lateral to the internal capsule. Direct visualization can guide targeting, although many groups still use co-ordinates relative to the MCP. As in the thalamus, we have not found that micro-electrode recording has added to the operation and a meta-analysis suggested it increased the risk of complications.

The deepest point for the GPi nucleus (and thus its target for the tip of the DBS electrode) relative to the MCP is as follows:

- **X** (lateral) = 21 mm lateral from the midline;
- **Y** (anteroposterior) = 2 mm anterior; and
- **Z** (vertical) = 4–6 mm below.

We adjust the initial anatomic target to be as inferior as possible but still 2 mm superior to the dorsolateral edge of the optic tract. We prefer to approach at an angle of 65° up from the AC–PC line in the sagittal plane and often are 10–20° lateral in the coronal plane in order to come through the middle frontal gyrus and avoid sulci.

Intra-operative electrophysiologic confirmation of the GPi target is performed with a macroelectrode (Radionics 1.5 mm exposed tip, 1.8 mm diameter). The stimulation parameters will vary between equipment but 50 Hz, 1 ms pulses at 3.0–5.0 V (typically 900 Ω) will cause contralateral hand or face contractions (or paresthesia) due to internal capsule stimulation. There is no symptom to titrate the DBS against because we have never had a good intra-operative response that was not duplicated post-operatively and a prolonged trial on the ward invites infection.

The complications of DBS for PD are both general (related to placing an electrode in the brain) and target-specific (related to stimulation-induced side effects). Pushing the electrode through the brain can tear a blood vessel and cause bleeding. We have had no deaths but two symptomatic hemorrhages in 400 cases (0.5 %). Even a small bleed can result in unsatisfied patients. For example, tremor reduction of 80 % in someone expecting perfection will leave the patient unhappy and the surgeon wondering why.

**Outcome – Benefits and Complications**

Symptom control may satisfy the surgeon but improvement in quality of life is what satisfies the patient.

If the patient’s expectations are met, then they will be satisfied with the outcome of the operation. Setting appropriate expectations and then meeting them is a complex process. Firstly, the symptom causing reduced quality of life must be addressed. Secondly, the patient must be educated as to what are the realistic results of surgery. Finally, the surgery must be performed correctly. Lapses in any of these steps will result in unsatisfied patients. For example, tremor reduction of 80 % in someone expecting perfection will leave the patient unhappy and the surgeon wondering why.

The complications of DBS for PD are both general (related to placing an electrode in the brain) and target-specific (related to stimulation-induced side effects). Pushing the electrode through the brain can tear a blood vessel and cause bleeding. We have had no deaths but two symptomatic hemorrhages in 400 cases (0.5 %). Even a small bleed can result in catastrophic disability because the patients are already maximally compromised and have no ability to compensate. The literature reports death (1–2 %), hematomas (0.7–3.1 %), at varying rates. Placing a foreign object under the skin of an immunocompromised elderly individual invites infection and skin erosion. Infections and/or skin erosion are relatively common (1–15 %), but fractures in the leads and extensions can occur, especially if misplaced.
The literature has focused on reporting symptom reduction rather than patient satisfaction. Symptom reduction can be quantified and therefore comparisons can be made between techniques and centers and used for recommendations.

**Thalamic Deep Brain Stimulation**

In 1993, Benabid et al. reported 88% of PD patients obtained 'good' or 'excellent' reduction of tremor. Multicenter trials from North America (58% of patients had total tremor resolution) and Europe (85% of patients had contralateral tremor reduced by at least 2 points on the unified Parkinson's disease rating scale UPDRS tremor score of 0–4) confirmed the results. The appearance to be long-lasting. An initial review of the literature makes it clear that direct comparisons are difficult but a common theme emerges. DBS can reduce tremor in PD and the effects continue for at least five years. The magnitude of tremor reduction varies from patient to patient but averages an 80% reduction. This is typically enough to allow a PD patient to feed, clothe and clean themselves. Stimulation of Vim can be associated with dysarthria and paresthesia, which are rarely disabling and usually reversible with the adjustment of stimulation parameters.

**Palilal Deep Brain Stimulation**

In 1994, Siegfried et al. suggested DBS in the pallidum as a new therapeutic approach to alleviating all parkinsonian symptoms. They reported excellent improvement of motor symptoms and near-total elimination of levodopa-induced dyskinesia with pallidal stimulation in three patients with advanced PD. Various groups subsequently suggested similar experience with GPi DBS and reported improvement in the UPDRS off motor score by 31–58% and improvement of dyskinesia by 64–76%.

**Subthalamic Nucleus Deep Brain Stimulation**

STN DBS for PD was first reported by the Grenoble group in France. A later randomized trial showed that STN DBS was more effective than the best medical therapy in advanced PD with significant improvement in the UPDRS-III and Parkinson's disease questionnaire (PDQ-39) (Quality of life).

Benefits are consistent between the groups and can persist for four to ten years. STN DBS improves all cardinal dopaminergic symptoms. It requires a significant reduction in dopaminergic medication and therefore reduces medicine-related adverse effects. In a meta-analysis of outcomes following STN DBS, it was found that the average decrease in absolute UPDRS II (activities of daily living) was 13.35. The average reduction in L-dopa equivalents following surgery was 55.9% and the average reduction in dyskinesia following surgery was 69.1%. It was also noted that the average decrease in the duration of daily off periods was 68.2% and the average improvement in quality of life was improved to 34.5%. However, post-operative management of STN DBS is the most complex of the three targets; stimulation-induced side effects include neuropsychologic and behavioral complications, notably suicide and hypomania.

**Conclusions**

DBS has quickly become the favored treatment for specific symptoms of PD in nations that can afford the technology. The benefits of DBS (post-operative titration of effect) outweigh its disadvantages (infection and expense) in correctly selected patients. Lesions (palidotomy and thalamotomy) continue to have a role in the management of PD, but future research into the surgical treatment of PD will probably center around DBS. New targets, such as the pedunculopontine nucleus, have generated interest and publications but not yet gained widespread acceptance. Neurosurgeons will no doubt be emboldened by the concept that DBS modifies rather than destroys brain activity as they try to ameliorate the symptoms of PD, regardless of the location of new targets or the complexity of the operation designed to get there. Selecting the correct patient for the procedure will remain of paramount importance. The close collaboration between neurologist and neurosurgeon for the optimum management of their PD patients continues to be an excellent model for the provision of care in the neurosciences.
Movement Disorders: Parkinson’s Disease


Deep Brain Stimulation for Parkinson’s Disease—A Review


