



Parkinson's
Disease
Foundation

Deep Brain Stimulation

for
Parkinson's
Disease





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DEEP BRAIN STIMULATION for Parkinson's

Surgery for Parkinson's disease (PD) has come a long way since it was first developed more than 50 years ago. The newest version of this surgery — deep brain stimulation, or DBS — was developed in the 1990s and is now a standard treatment. Although it is certainly the most important therapeutic advance since the development of levodopa, DBS is not for every patient. It is most effective — sometimes, dramatically so — for individuals who experience disabling tremors, wearing-off spells and medication-induced dyskinesia.

It is very important that a person with PD who is thinking of surgery be well informed about the procedures and realistic in his or her expectations. We hope that this booklet will answer some of the questions that patients and their families may have. This publication is an update of the earlier *Surgery for Parkinson's Disease*, written by Dr. Blair Ford and published by PDF in 2002.

A feature of this booklet is that you do not have to start at the beginning and read it all the way through. You can choose the subjects that interest you most and read them in the order that suits you best.

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INTRODUCTION

Surgery for Parkinson's disease (PD) was developed decades before the advent of any of the effective medications that we use today. For most of the past century, innovative surgeons worked to refine surgical treatments for PD. During the 1940s and 1950s, these procedures consisted of surgically-created lesions in deep parts of the brain to control symptoms of tremor and rigidity. In one frequently-performed procedure, the pallidotomy, a surgeon created a tiny lesion in an area of the brain known as the globus pallidus. When levodopa was introduced as a treatment for PD in the late 1960s, interest in surgical approaches waned dramatically. For the next 30 years, medications dominated the treatment of PD.

Unfortunately, clinical experience has since shown that medical therapy for PD has significant shortcomings. After several years of taking medications, including levodopa (the current "gold standard" of anti-parkinsonian agents), many patients with PD experience a shortening of benefit following each oral dose, a problem called "wearing-off." Many of them also develop drug-induced, involuntary writhing and twisting movements, known as dyskinesias. It was these limitations of medical therapy that re-awakened a strong interest in developing effective, surgically-based techniques for the treatment of PD.

The new techniques of deep brain stimulation are the products of several advances: improved understanding of brain electrical circuitry, developments in brain imaging techniques, improvements in neurosurgery and innovations in medical technology. DBS is the state-of-the-art surgical treatment for Parkinson's disease, and has replaced all earlier types of surgery, including pallidotomy. The goal of this booklet is to describe DBS and to address some of the issues that patients and their families should consider.

HISTORICAL Perspective

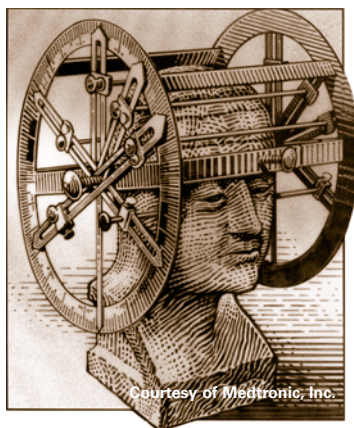
It may not be intuitive that shutting down brain cells using an electrode, or destroying brain cells using earlier surgical interventions, will help symptoms of PD. It is even more surprising that scientists discovered the basis for these approaches before they understood how the brain controls body movement. As with many important discoveries, surgery for PD began by trial and error, not according to a predetermined theory.

The basis for surgery in the treatment of PD began in the early 1900s, when researchers first began to perform neurosurgery guided by brain maps, known as stereotactic surgery, in animals. Neurosurgeons Horsley and Clark developed techniques that allowed them to place lesions — surgically created holes — deep in the brain with great accuracy by injecting tiny amounts of corrosive chemicals. Over the next 40 years, neurosurgeons applied lesion-making techniques to the human brain but no surgeon was able to relieve parkinsonism without injury to the motor system, resulting in weakness.

In the 1940s, Dr. Russell Meyers was the first to perform surgery in the basal ganglia, a deep brain region that is responsible for controlling movement.

He found that he could reduce the tremor and rigidity of PD in almost half his patients without causing weakness or other motor deficits. This crucial observation led to the development of all of modern neurosurgery for PD, including DBS.

In subsequent decades, surgeons perfected the techniques of placing lesions in the brain. Many different brain sites were targeted: the globus pallidus, the thalamus, the subthalamic nucleus and individual fiber tracts connecting different parts of the basal ganglia [see *Figure 1, page 7*]. Lesions were created using thermal electrodes that heated brain tissue at their tips, enabling the precise destruction of a small volume of brain tissue.



The accuracy of surgical targeting was improved by electrophysiological recording techniques, first developed in the 1960s. Using tiny electrodes inserted deep into the brain, Dr. Hirotaro Narabayashi was able to find cells in the thalamus that fired in synchrony with the tremor of Parkinson's disease. This site was later confirmed to be the key brain target for tremor control. The procedures for making lesions in the thalamus and in the globus pallidus, respectively, were given the names of thalamotomy and pallidotomy.

These early approaches were followed by the development of our current state-of-the-art procedure: deep brain stimulation (DBS), pioneered in France in the early 1990s by Dr. Alim-Louis Benabid. While preparing to create a lesion in the thalamus of a patient, Dr. Benabid noticed that he could stop the tremor simply by giving an electrical stimulation to the same area. He speculated that a wire providing continuous electrical stimulation would be an effective treatment for Parkinson's tremor.

This idea led to the development of the deep brain stimulator, a device that has proven superior to all earlier surgical approaches that were based on creating lesions. Within less than 10 years from its development, deep brain stimulation replaced the thalamotomy and pallidotomy operations, both of which were less effective and carried an increased operative risk.

Deep brain stimulation on one side of the brain was first approved by the U.S. Food and Drug Administration (FDA) in 1997 for the treatment of tremor. It was approved for implantation on *both* sides of the brain in 2002 as a treatment for other parkinsonian symptoms — specifically, rigidity, slowness of movement and dystonia. In the years since then, thousands of patients worldwide have undergone this treatment. Deep brain stimulation continues to evolve and further improvements are likely as time goes on.

HOW Does Deep Brain Stimulation Work?

When an electrical signal is given to the deep brain structures, normal electrical activities of brain cells are shut down. Why does this help PD? The answer relates to the nature and design of the human motor system. Normal muscle tone, speed of movement and coordination all depend upon a complex flow of signals in electrical pathways of the brain. The parts of the motor system are arranged in connected loops that maintain continuous cycles of electrical activity. An electrical signal that begins in one part of the loop goes back to its starting point, establishing a feedback mechanism that prevents excessive activity from developing.

In patients with PD, the electrical feedback loops of the deep brain structures cycle abnormally. Normal movement is replaced by unwanted tremor, rigidity and slowness. By using a deep brain electrode that provides an electrical current, it is possible to jam abnormal signaling between brain structures. This does not remove PD from the brain but it shifts the electrical activity of the system towards the normal state and thereby reduces the main motor symptoms of PD.

Unlike the earlier pallidotomy, which created a permanent lesion in the brain, DBS produces electrical effects that are largely reversible and can be varied by programming. DBS can be applied to several sites including the thalamus, the globus pallidus and the subthalamic nucleus. DBS on one side of the brain generally reduces symptoms of PD only on the opposite side of the body. For patients with symptoms on both sides of their body, DBS must be done on both sides of the brain.

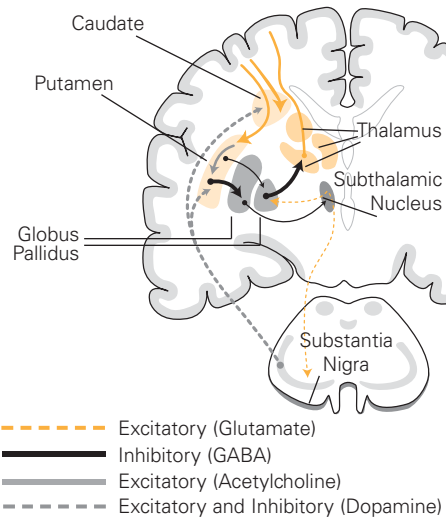


Figure 1. Map of basal ganglia showing targets for surgery: globus pallidus, thalamus and subthalamic nucleus

APPROACHES to Deep Brain Stimulation

Deep brain stimulation can be delivered to any desired brain structure. In PD, three targets have consistently shown the most important anti-parkinsonian effects: the ventral intermediate (VIM) thalamus, the subthalamic nucleus (STN) and the globus pallidus (GPi) [see *Figure 1, page 7*]. These brain structures were the targets of earlier procedures: the thalamus was the site of the thalamotomy and the globus pallidus, the site of the pallidotomy. But procedures that involved creating permanent lesions, despite their effectiveness, were replaced in the late 1990s by deep brain stimulation, which had the advantages of safety, reversibility and adjustability. A summary of neurosurgical procedures for PD is described in Table 1 on page 13.

In the following section, specific operations are described in detail.

THALAMIC STIMULATION

Thalamic stimulation is for tremor. The thalamus is a large, round, oblong mass of cells that acts as a relay station for many important functions including motor control. A region on the undersurface of the thalamus called the ventral intermediate (VIM) nucleus is the critical center for all types of tremors.

Electrical stimulation of the VIM thalamus can completely and reliably stop a tremor on the opposite side of the body. Thalamic stimulation on both sides of the brain will reduce tremors on both sides of the body, as well as midline tremors of the jaw, neck and trunk.

Thalamic stimulation will suppress tremor of any cause: Parkinson's tremor, essential tremor (ET), multiple sclerosis and dystonic tremors. In patients who have both essential tremor and Parkinson's disease tremor ("ET-PD"), thalamic stimulation may provide control of tremor



Figure 2. A deep brain stimulator, showing the battery and electrode tip

that is superior to deep brain stimulation in other targets. Sometimes patients with bilateral thalamic stimulation experience slurred speech or poor balance as an adverse effect, but these symptoms can be reversed through adjustments in stimulator settings.

SUBTHALAMIC NUCLEUS STIMULATION

The subthalamic nucleus (STN) is a small lens-shaped structure of about 6 mm in length located right beneath the much larger thalamus. The STN can be identified accurately using mapping techniques and a DBS electrode can be placed right through it — much like a toothpick skewers an olive. Stimulation of the STN influences its connections to the globus pallidus and can have broad anti-parkinsonian effects. It can improve not only tremor, but also slowness, rigidity, dyskinesias, speech, handwriting and dystonia. The anti-tremor effect of STN stimulation is comparable to that of thalamic stimulation.

STN stimulation has been performed in thousands of patients at many medical centers around the world and is now considered the most effective surgical intervention for PD. The largest single-center clinical experience is held by the surgical group in Grenoble, France, where the technique of DBS was pioneered. In carefully selected patients, STN stimulation can reduce parkinsonian symptoms in the unmedicated state by 30 to 60 percent, as measured by standard rating scales. With this degree of improvement, patients who suffer from disabling wearing-off periods may experience a significant reduction in the severity and duration of these episodes. In some patients, the wearing-off periods can be completely eliminated, enabling them to function independently throughout the day.

Many patients find that they require less anti-parkinsonian medication after STN stimulation. Some can stop their medication altogether. As a result of the decreased need for medication, and also because of a direct stimulation effect, there may be a dramatic reduction — or even elimination — of dyskinesias. As noted earlier, the beneficial effects of STN stimulation generally parallel those of levodopa, but do not surpass the best result of medication treatment. Its main advantage, therefore, is improvement in wearing-off spells and dyskinesias.

Most patients with advanced PD require STN stimulation on both sides of the brain to control symptoms on both sides of the body. STN stimulation on one side generally helps parkinsonian symptoms only on the opposite body side. For patients who have tremor or other symptoms on only one side, one-sided STN stimulation may be considered. Gait and speech problems generally require STN stimulation on both sides of the brain. STN stimulation can also improve parkinsonian symptoms in patients who have undergone previous pallidotomy or thalamotomy surgeries.

More research on outcomes will be needed before we know which patients will benefit the most from STN stimulation. Some patients who undergo DBS have developed problems with memory and thinking, but those with a good cognitive baseline before surgery are less likely to experience these symptoms.

Parkinson's disease is a progressive disorder. No medical or surgical therapy to date has been able to prevent the development of late symptoms that do not improve with medication, such as memory problems or lack of balance.

GLOBUS PALLIDUS STIMULATION

The globus pallidus, named for its pale appearance, is a dense wedge of nerve tissue that occupies the center of the basal ganglia region. The deepest portion of the globus pallidus, named the posteroventral medial globus pallidus interna (GPi), is the site of the pallidotomy operation, and represents the main outflow connection from the globus pallidus to the thalamus. The globus pallidus is a larger and more complex structure than the STN, with a complicated internal circuitry. Like STN stimulation, globus pallidus

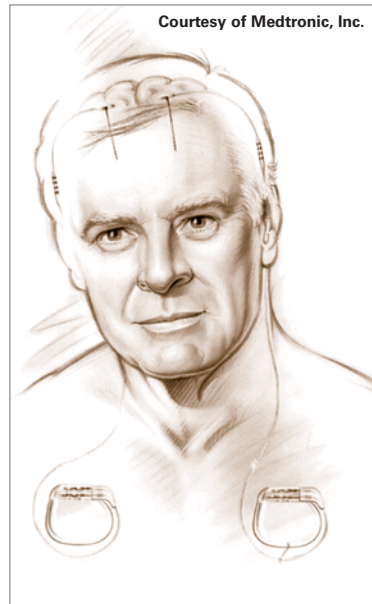


Figure 3. Deep brain stimulators are implanted on both sides of the brain, with connecting wires and batteries.

stimulation has broad beneficial anti-parkinsonian effects. Because the globus pallidus is so large, the entire deep brain electrode resides within it as contrasted with the STN, a much smaller structure in which the electrode protrudes out both sides.

Globus pallidus stimulation has effectiveness similar to that of STN stimulation but the operation is performed less frequently due to the surgeon's preference or training. In randomized comparisons between the two techniques, the result of bilateral globus pallidus stimulation is the same as that for STN stimulation, a 30 to 60 percent improvement in parkinsonian symptoms in the unmedicated state. Globus pallidus stimulation can also have an important benefit on parkinsonian dyskinesias and dystonia.

An important advantage of surgery at the STN site is that patients who go through surgery are usually able to reduce their medications by a greater amount than those who go through stimulation of the globus pallidus. Based on this observation, it has been argued that the reduction in dyskinesias following globus pallidus stimulation is a direct effect of the procedure whereas with STN stimulation, the dyskinesias are improved mainly as a result of the decreased medication requirement.

TABLE 1. SUMMARY OF NEUROSURGICAL TREATMENTS FOR PD

Type of Surgery	Deep Brain Structure	Effects and Outcome
Lesion-Based Surgery	Thalamotomy	<p>Lesion is created in VIM thalamus</p> <p>Effective treatment for tremor on the opposite body side</p> <p>No effect on slowness or rigidity</p> <p>Effectiveness may decrease over time</p> <p>Bilateral thalamotomy not advisable because of potential adverse effects on speech</p>
	Pallidotomy	<p>Lesion is created in globus pallidus</p> <p>The state-of-the-art surgical treatment for PD up until 1990</p> <p>Reduction in tremor, slowness, rigidity and dyskinesia on the opposite body side</p> <p>Beneficial anti-parkinsonian effects decrease over time</p> <p>Bilateral pallidotomy is associated with cognitive and behavioral impairments</p>
Deep Brain Stimulation	Thalamus	<p>Deep brain electrode in VIM thalamus</p> <p>Effective treatment for tremor on the opposite body side</p> <p>Benefit appears to be longer lasting than thalamotomy</p> <p>Bilateral thalamic stimulation can be accomplished without significant adverse effects</p>
	Subthalamic Nucleus (STN)	<p>Deep brain electrode in subthalamic nucleus (STN)</p> <p>Effective treatment for tremor, slowness, rigidity, dystonia and dyskinesia on the opposite body side</p> <p>Bilateral procedures well tolerated</p> <p>Usually allows patients to decrease medications by a greater amount than those who undergo GPI stimulation</p>
	Globus Pallidus (GPi)	<p>Deep brain electrode in globus pallidus</p> <p>Effective treatment for tremor, slowness, rigidity, dystonia and dyskinesia on the opposite body side</p> <p>Bilateral procedures well tolerated</p>

THE KEY Issues

WHO SHOULD CONSIDER SURGERY, AND WHO SHOULD NOT?

Surgery is not for everyone.

The best candidate for deep brain stimulation is someone who has had Parkinson's disease for 10 to 20 years, and experiencing wearing-off motor fluctuations, episodes of extreme slowness and stiffness caused by a failure of medications, and dyskinesias, twisting movements that are caused by excessive medication. A smaller group of patients who undergo surgery do not have severe fluctuations but do suffer with tremors that cannot be stopped using medication.

Perhaps the most important determinant of a successful outcome is the patient selection. Patients who are younger and whose primary symptom is tremor have better results than do older patients who have balance impairment.

TABLE 2. PATIENT SELECTION DETERMINES OUTCOME

Good Candidate for DBS	Poor Candidate for DBS
Typical PD with tremor	Atypical parkinsonism
Good response to levodopa	Poor response to levodopa
Dyskinesias	Memory problems, apathy or confusion
Wearing-off spells	Severe depression or anxiety
Good general health	Severe medical problems
Excellent family support	No social support

The best candidates for deep brain stimulation have:

- typical "classical" PD, defined by the presence of tremor at rest, rigidity and slowness
- symptoms that still respond to anti-parkinsonian medications even if the response is brief
- disabling parkinsonian symptoms in the "off" state
- uncontrollable medication-induced movements called dyskinesias

- severe tremors
- a good understanding of the potential benefits and risks of the operative procedures and evaluation procedures and the ability to give informed consent
- good general health
- a good emotional support network of family and friends.

Patients with these problems are not good candidates for surgery, and will likely not benefit from the procedure:

- atypical or rare forms of parkinsonism, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasoganglionic degeneration (CBGD) or a known acquired cause of parkinsonism such as stroke or brain trauma
- failure to experience any benefit from anti-parkinsonian medications
- severe memory loss, confusion, hallucinations or apathy (these problems may actually get worse as a result of brain surgery)
- experience of freezing, balance problems and frequent falling
- a severe chronic psychiatric disorder such as psychosis, depression, bipolar disorder, alcoholism or a personality disorder
- inability to understand the potential benefits and risks of the operative procedures or to give informed consent
- significant medical problems that would unacceptably increase the surgical risk, such as cancer or serious heart disease

Note that age is not an essential criterion for surgery. An otherwise healthy older patient with PD can safely undergo and benefit from this type of surgery. While advanced age does not preclude surgery, the best results are obtained in younger patients.

HOW TO PREDICT IF YOU WILL BENEFIT FROM DBS

It is important to recognize that some symptoms of PD respond better to surgery than others. The effect of surgery on slowness and stiffness can generally be predicted from the response to medication.

Some patients have an excellent response to levodopa and other medications, with almost complete suppression of symptoms, but suffer from spells of wearing-off during which they become stiff, immobile

and frozen. These individuals will do well with surgery because at least some of the time, their parkinsonism is levodopa-responsive.

Other patients have an incomplete response to levodopa. Even when experiencing their maximal medication effect, they have some gait or balance or speech impairment. These patients, who do not do as well on regular anti-parkinsonian medications, will not do as well with surgery. They will probably only experience relief of those symptoms that are eased by their medication. Patients who cannot walk independently at their best on levodopa will still not be able to walk after surgery.

TABLE 3. PREDICTING BENEFIT FROM DEEP BRAIN STIMULATION

DBS helps with:	DBS does not help with:
Tremor	Freezing
Rigidity	Backwards falling
Hand function	Tachyphemia: rapid, soft, stuttering speech
Dyskinesias	Flexed neck or posture
Wearing-off spells	Dementia or apathy
	Anxiety or depression

When should surgery be considered? Some have argued that surgery should be performed on patients with mild PD in order to delay the progression of disease or forestall complications of medication usage. This notion is not justified because there is no evidence that earlier surgery would accomplish these goals. Current surgical techniques, along with medications, provide benefit only by suppressing the symptoms of PD. There is no evidence that DBS is neuroprotective. The risks and inconveniences of surgery underscore its role as a treatment of last resort, after medication options have been thoroughly tried.

At some centers, patients who are considered candidates for deep brain stimulation undergo a simple test that can help predict the result of surgery. The test consists of observing a patient after a moderately large dose of dopamine medication. The usual procedure involves a dose of levodopa, and the test is called a “levodopa challenge.” At

other centers, the test involves an injection of the dopamine drug apomorphine. In either case, the improvement that follows a dose of levodopa or apomorphine tends to correlate well with the effects of deep brain stimulation.

Each patient is unique, and the goals of surgery are different for each individual. With some, the most pressing requirement is tremor control. With others, it is the need to reduce dyskinesias. It is very important that every patient contemplating surgery have a clear idea about what can and what cannot be accomplished by using this powerful intervention.

LONG TERM RESULTS

What happens in the years after DBS surgery? According to scientists at the medical centers with the longest follow-up data, patients with advanced PD continue to experience marked benefits for many years after the operation. Tremor, especially, remains well-controlled but rigidity and dyskinesias are also improved and do not return to the levels that they were before the surgery. A patient's ability to perform activities of daily living may gradually decline after the first year following surgery but remains 50 percent improved even after five years or more, according to long-term studies. Many patients can reduce their medications after surgery and this reduction can persist.

In the early months after surgery, patients typically return to the medical center for frequent stimulator adjustments. After the initial adjustment period, the stimulator settings tend to remain stable, and only limited additional programming is required to keep symptoms under control. Depending on the settings, the system battery, which is implanted in the chest like a pacemaker, will deplete and require replacement in three to five years.

Unfortunately, PD is a progressive condition. DBS does not prevent later complications of the disease, such as poor posture, speech impairment, gait freezing, balance problems, backwards falling or dementia. If these problems develop in a patient treated with DBS, the overall gains in quality of life after surgery may be lost even if tremor and dyskinesias remain well-controlled.

EFFECTS OF DEEP BRAIN STIMULATION ON THINKING AND MOOD

Most individuals tolerate brain surgery and deep brain stimulation without noticeable effects in their memory or thinking ability; in some studies, mood and behavior have improved.

Unfortunately, there is a small group of patients who experience cognitive decline after surgery. These individuals are typically more elderly and have pre-existing dementia that may include word-finding difficulty, inability to carry out a sequence of tasks, problems with judging space and apathy. The presence of dementia at baseline is not an absolute disqualification to DBS if the patient has tremor and other symptoms that would otherwise benefit. However if the results of pre-operative neuropsychological tests are poor, the appropriateness of DBS may be questioned.

A very small group of patients have become seriously depressed after surgery and several suicides have been reported. Such individuals invariably had pre-existing depression, a frequent problem in PD that requires careful attention and expert treatment. In most centers, the presence of depression is a disqualifying factor for surgery.

SURGERY — The Process

The prospect of having an operation of any kind is anxiety-provoking. To think of having brain surgery for Parkinson's disease is enough to tax the emotional resources of even the strongest patient and the most supportive of families.

PREPARING FOR SURGERY

Before surgery, the patient and family should educate themselves about the procedure. Deep brain stimulation is an elective procedure and, ultimately, the decision to proceed must be that of the patient. He or she should read the available literature and become acquainted with the practical aspects of deep brain stimulation. It can be helpful and reassuring to meet someone who has already gone through the experience. And of course, the patient and family must meet the surgeon.

After detailed discussions with the treating neurologist and the surgeon, the patient must undergo pre-operative screening tests. The tests include a brain imaging study, a general medical examination, blood tests, an electrocardiogram, a chest x-ray, neuropsychological testing and any other data collection required by the institution's protocol. If everything turns out right, the next step is scheduling the surgery.

THE BRAIN OPERATION IN STAGES

DBS involves the placement of an electronic device in stages. Each piece of the apparatus must be fitted into the patient and the procedures can be done in any order. A stimulator consists of three parts: (1) DBS electrode, or lead, (2) connecting wire and (3) battery [see *Figure 4*].

1. The DBS electrode is an insulated wire with four contacts at its end. The electrode is inserted deep into the brain so that its tip directly

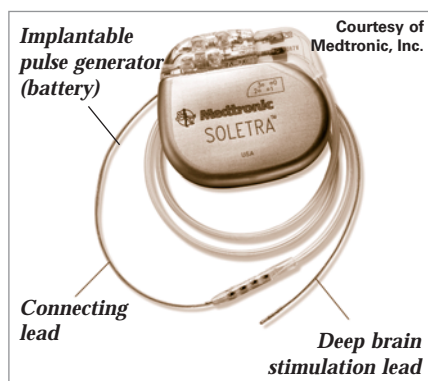


Figure 4. Deep brain stimulator apparatus

stimulates the target site. Its other end, near the surface of the brain, is anchored to the inside of the skull.

2. The connecting wire runs under the skin from the DBS lead at the scalp site, behind the ear and down the neck into the chest where it connects to the battery pack, or implantable pulse generator (IPG).

3. The battery, or implantable pulse generator (IPG), resides like a pacemaker beneath the skin of the chest wall under the collar bone. The IPG is a metal disc about two inches in diameter and one-half inch thick. It contains a small battery and a computer chip. The IPG sends electrical impulses through the connecting wire to the DBS electrode implanted in the brain.

By far the most complicated and time-consuming part of the operation is placement of the DBS lead, which requires careful brain mapping. Patients with symptoms on both sides require bilateral operations. Sometimes the two DBS leads are implanted in the same operation; at other times, they are staged over two operations that are weeks or months apart. Similarly, some surgeons place the entire apparatus — DBS lead, connector and IPG — in a single, marathon procedure while others first perform only the DBS lead insertion and delay the rest of the work to a second, out-patient procedure the following week. Some patients prefer the idea of staged procedures so they can recover between steps, while others “just want to get it over.”

THE DAY OF SURGERY

The day of brain surgery may seem endless. Procedures vary from hospital to hospital but the operations generally take three to six hours and are usually performed while patients are awake, without medication and experiencing PD symptoms at their worst. Thankfully, most patients lose track of the passing hours as they lie immobile on the operating table while the surgeons perform their delicate work.

The first step of the operation is placement of the stereotactic head frame, a large, open casing made of metal bars that is screwed into the patient's skull at several points. This procedure is done under local anesthesia and is not painful, though some patients complain of headache afterwards. Sometimes, the head frame is placed on the patient's head

the day before the operation, but it is usually done on the morning of surgery. Some surgeons insert the skull screws days in advance to facilitate attachment of the head frame on the day of the surgery.

The goal of the operation is to place, with millimeter accuracy, an electrode deep within the brain. The successful outcome and the risks of the procedure depend critically upon accurate targeting. After the head frame is attached, the patient undergoes a brain imaging scan while wearing the apparatus. The calibrations on the head frame are merged with the brain image to form a computerized map of the brain. This map becomes the blueprint for planning and measuring the trajectories of the electrodes into the deep brain regions of the basal ganglia. The entire head frame structure is then bolted to the operating table to maintain the head in a fixed position throughout the operation.

TABLE 4. STEP-BY-STEP PLAN OF OPERATION FOR DBS

1. Head frame is attached to skull
2. Magnetic resonance imaging is done for brain mapping
3. Burr hole is drilled in scalp under local anesthesia
4. Electrophysiological brain mapping using microelectrode is done
5. Deep brain stimulator electrode is inserted in brain
6. Implantable pulse generator (IPG) is placed in chest wall
7. Connecting wire is attached to IPG in the chest, and tunneled under skin of neck to deep brain electrode at the scalp site

The surgeon next creates an operative field by drilling a burr hole (a small opening in the skull made with a surgical drill) into the top of the skull — the passageway for the insertion of the stimulating electrode into the brain. The burr hole is made under local anesthesia, and since the brain is completely anesthetic (has no sensation), the rest of the operation is painless. Because of the need to communicate with the operative team, patients undergo surgery while awake. During the procedure, the neurosurgeon asks the patient a number of questions about how he or she feels and what symptoms he or she may be experiencing. Light anesthesia is sometimes used if the patient is uncomfortable.

As an additional means to ensure the accuracy of the surgical probe, some hospital centers perform electrical brain mapping during surgery. This technique uses tiny electrodes that can record electrical activity from individual brain cells within deep brain regions. The microelectrodes are much smaller and more delicate than the electrodes that provide the deep brain stimulation. They are used to identify cells within the thalamus, globus pallidus, subthalamic nucleus and adjacent brain structures, and help steer the main probe towards the desired surgical target.

For patients who have symptoms on both sides of their body, electrode insertions need to be performed on both sides of the brain. After the first DBS electrode has been placed, the procedure is repeated on the opposite side. Another burr hole is made, the brain mapping is done all over again and the second-side insertion of the deep brain electrode is accomplished — all within the same operation.

AFTER THE OPERATION

The hospitalization required for a deep brain stimulator implantation is usually two or three days. Patients usually tolerate the procedure very well. Sometimes symptoms are dramatically improved after the DBS electrode is in position, even though the battery has not been attached and the system has not yet been activated. This effect is usually attributed to brain swelling at the tip of the electrode. After the operation, many patients find themselves exhausted, and perhaps slightly confused. Some complain of mild headache. These symptoms usually resolve within 24 hours. Most patients recover quickly and can be safely discharged from the hospital just one or two days after the surgery. Most patients should remain on their pre-operative medication at discharge, although some centers begin a medication reduction protocol at this point. Typically, patients return home with scalp staples or stitches in place, to be removed one week later in the surgeon's office once the scalp heals.

PLACING THE BATTERY

The DBS electrode requires a power source. Once the deep brain electrode has been inserted, the remaining surgical task is implanting the extension wire and the battery, or implantable pulse generator (IPG). This may be done at the same time as the brain implant or may be

deferred to a later date — usually, one week after the brain operation. The operation is relatively simple; the surgeon makes an incision under the collarbone, creates a small pocket in the muscle and inserts the IPG. The IPG is attached to the connecting wire, which is tunneled up the neck, behind the ear and to the scalp site where the external end of the DBS electrode was implanted previously. The connecting lead is attached to the DBS lead. At this point, the entire apparatus is in place under the skin. The chest wall pocket is closed using stitches or staples. The battery produces a visible bump on the chest, especially in patients who are lean.

Patients with electrodes on both sides of the brain have a choice: each electrode can be connected to its own battery, one on each side of the chest or both electrodes can be connected to a single, larger generator implanted on one side. Both options are acceptable, but there are practical and cosmetic differences. Having two batteries means two protrusions, one on each side of the chest. Having one battery means a protrusion on only one side — but the battery is larger and more noticeable. In the rare case of a battery failure or infection, individuals with a single battery will lose power in both stimulators.

The battery implants are performed under general anesthesia. The procedure can be performed during hospitalization or as an outpatient procedure. When patients wake up after the procedure, they may experience chest or neck discomfort and require mild painkillers. Once the batteries and wires are connected, the deep brain stimulation system can be activated. Sometimes, the initial programming is done immediately after the batteries are implanted, but often, this step is deferred. After the batteries are implanted, patients are discharged from the hospital, returning to the office the following week to have the stitches or staples removed. After the incision heals, most patients report that they do not feel the battery or the wires.

After the operation, patients usually resume their pre-operative medications, although, in some centers, doctors begin to reduce the PD medications at this point. All post-operative medication adjustments must be carefully supervised by the treating neurologist.

PROGRAMMING the Stimulator

For patients who undergo deep brain stimulation, the surgical operation is just the beginning.

Years ago, the notion of a patient coming to the office to have deep brain electrodes programmed by a physician or nurse would have seemed like science fiction. Now this scenario happens on a daily basis at busy centers where many such procedures are performed.

After the operation, patients are discharged to home. They must now begin a period of stimulator adjustments, performed over the course of several outpatient visits. The stimulator adjustments and settings are different for every patient. Some undergo surgery believing they will be immediately much better after the stimulator devices are activated. In practice, this improvement may take several weeks, even months, while the stimulator settings are being improved and the medications adjusted to an appropriate level.

Physicians and nurses who program the stimulator work with several variables at once: the way the electrode contacts are turned on, the frequency, the pulse width and the voltage. In the first months following implantation, patients may require frequent adjustments. After this period, the electrical settings usually stabilize.



Figure 5. A deep brain stimulator is programmed to control tremor.

Patients may check their deep brain stimulators using a hand-held device that resembles a television remote control. Provided by the stimulator manufacturer, the hand-held device is called Access Review. By holding the lightweight plastic remote over their implanted battery for a second and pressing a button, patients can determine whether their stimulators are in the “on” or “off” position. If the stimulator has inadvertently been turned off, pressing another button on the remote will turn

it back on. The Access Review device does not permit patients to adjust their stimulator parameters themselves or perform any troubleshooting, although future versions will allow this. Any problems with the stimulator require a visit to the medical center to have the device checked.

The life expectancy of the stimulator battery varies with output settings but is estimated at three to five years. As the energy in the battery becomes depleted, the efficacy of the stimulation starts to decline and PD symptoms increase. Patients can check the battery status using the hand-held device or the neurologist can do this in the office. When the battery is depleted, the implantable pulse generator (IPG) will require replacement under local anesthesia in an ambulatory surgical procedure that takes about one hour. The old IPG is removed from the chest wall site by re-opening the incision. The device is disconnected from the connecting lead, the new IPG is inserted and hooked up and the incision is again closed with stitches or staples. The procedure is done under general anesthesia. In the near future, it is expected that externally rechargeable batteries will eliminate the need for battery replacement.

RISKS of Deep Brain Stimulation

RISKS OF SURGERY

Potential complications of surgery for Parkinson's disease range from mild headache or drowsiness to more serious or irreversible effects, such as infection, stroke or hemorrhage. Some patients, especially those who are already suffering from mild cognitive problems, may experience post-operative sleepiness, disorientation, slowness of mental processing, hallucinations, poor motivation or depression. These events typically resolve within 24 or 48 hours but may last longer. After bilateral STN stimulation, some patients have experienced difficulty opening their eyes. To remedy this, some may need injections of botulinum toxin, a muscle relaxant.

At the medical centers that have the most experience with DBS, the risk of stroke or bleeding is less than five percent. The earlier lesion-based techniques, pallidotomy and thalamotomy, had a slightly higher incidence of permanent complications than deep brain stimulation because direct destruction of brain tissue was part of the operation.

Because deep brain stimulation requires implanted hardware, there is a risk of infection, sometimes requiring antibiotics or even replacement of an infected device. Despite every precaution, a skin infection can sometimes occur at the battery site in the chest wall, in the neck or at the scalp. Like all types of surgery, operator experience is the most important determinant of risk. The lowest complication rates are at major centers that perform this type of highly specialized surgery on a weekly basis.

ADVERSE EFFECTS OF STIMULATION

The process of programming the device is tedious and sometimes uncomfortable for the patient. Patients are often asked to withhold their medication for several hours while the stimulator personnel determine the optimal device settings. It may take hours of testing different electrode combinations before the best setting is determined. Sometimes, during a programming session, patients may experience temporary tingling or shocking sensations, and uncomfortable muscle spasms or contractions.

Additional stimulator-induced problems may include balance impairment, dizziness, speech difficulties or a general vague sensation of "not feeling right." There are rare reports of stimulation-induced feelings of depression or despair. Deep brain stimulation can also induce dyskinesias that resemble the dyskinesias caused by levodopa.

TABLE 5. REVERSIBLE ADVERSE EFFECTS OF STIMULATION

- Jolting or shocking sensations
- Numbness or tingling, often in the face or hand
- Dizziness or balance impairment
- Twisting movements that resemble dyskinesias
- Muscle spasms, usually in the face or hand
- Slurred speech
- Double vision
- Depression

All stimulator-induced effects are temporary and reverse promptly with a change in the stimulator output. After a programming session, it is a good idea for patients to wait at the center for an hour or so before returning home just to make sure that the new stimulator settings are well-tolerated and free of adverse effects.

Patients with implanted deep brain stimulators are generally free to participate in any physical activity they choose. However, it is important to use common sense and not to engage in activities that could subject the device or wires to a direct physical blow or acceleration. Examples of specific activities that could potentially harm the stimulator include contact sports or chiropractic neck manipulation. Sometimes, with repeated trauma, the connecting lead or the battery erodes through the skin, requiring replacement.

Deep brain stimulators may switch off by accident if patients walk through a magnetic field, such as a security device or theft detector. This is simply an inconvenience and carries no permanent risk to the

patient or stimulator device. When the stimulator switches off, however, PD symptoms can immediately return. If this happens, the patient may re-activate the stimulator using the handheld device. The manufacturer provides a list of appliances that may cause interference with deep brain stimulation.

There is an important warning for patients with implanted brain electrodes not to undergo ultrasound diathermy, a treatment that involves applying a heating coil to the skin. It is also recommended that patients with deep brain stimulators check with their neurologist before undergoing magnetic resonance imaging (MRI) scans, a technique that uses a powerful magnetic field. In theory, the DBS electrode is unaffected by magnetic fields, but some of the larger MRI scanners are very powerful.

In case of questions about the stimulator, patients should always contact their treating neurologist, who may recommend a return visit to the medical center for a device check.

FUTURE PERSPECTIVES on Surgery for PD

Deep brain stimulation is the most advanced surgical approach currently available for Parkinson's disease. For some patients, the procedure is miraculously effective. People who once experienced disabling tremors, severe dyskinesias or paralyzing wearing-off episodes may find themselves free of their former disabilities. For many others, however, deep brain stimulation does not solve their problems.

Deep brain stimulation is in its infancy and will almost certainly improve over time. Anticipated improvements include batteries that are smaller, last longer and are rechargeable. The original battery packs were capable of providing an electrical current only to a single electrode but now patients may choose a single side battery that is capable of powering both stimulators. Someday, the entire apparatus, including the generator, will be implanted in the skull, eliminating wires and batteries in the neck and chest. Other anticipated changes include an alarm feature that lets the patients know when the device is malfunctioning; advanced troubleshooting features; and the ability to program the deep brain stimulator over the telephone or Internet so that patients do not have to return to the office for these adjustments.

It seems likely that the numbers of effective brain targets will rise. As deep brain stimulation becomes more sophisticated, the stimulating electrode will have motion sensors that allow it to detect when a patient wants to make a specific movement. The stimulation electrode in current use has four electrical contacts arranged in a line. Electrodes of the future will have more contacts, and improved ability to direct electrical current into brain tissue. Someday, the stimulators will have branch leads implanted in other parts of the basal ganglia to produce network effects that more closely resemble the physiology of the person's motor system.

Other futuristic possibilities beyond DBS may include the surgical implantation of cells with regenerative capacity; gene therapies; and other treatments that can prevent or reverse the cell loss in PD.

TEN Commonly-Asked Questions

1 Who is the ideal candidate for surgery?

The ideal candidate for surgery is a patient with PD who responds well to levodopa and other anti-parkinsonian medications but who experiences dyskinesias or wearing-off spells. Such patients usually have had PD for 10 years or more and have reached a stage where even a complicated medication schedule, sometimes requiring pills every two hours or less, is not sufficient to control the wearing-off episodes.

People who never experience clear benefit from levodopa are unlikely to improve with deep brain stimulation, and therefore should not consider this approach. People who have an atypical form of parkinsonism, such as progressive supranuclear palsy (PSP), will also not benefit from surgery. To be a candidate for the operation, people must be in good general physical and psychiatric health, have no cognitive impairment and have a good support system of family or friends to help them through the ordeals of surgery and subsequent post-operative management.

2 Does surgery help all symptoms of Parkinson's disease?

Surgery for PD helps many, but not all, symptoms of PD. As a general rule, the symptoms that respond best to medication respond best to surgery. Tremor and rigidity can greatly improve with surgery, but slowness improves as well. Dystonic posturing of the limbs, often present in the early morning or during “off” spells, also responds well to surgery. Drug-induced dyskinesias may completely resolve after surgery. On the other hand, patients who experience stooped posture, poor balance, cognitive impairment or rapid stuttering speech, sometimes called tachyphemia, may not experience benefit in these symptoms after a surgical procedure.

3 Which is the best choice of deep brain stimulation for me?

The choice of which surgical technique is best for a given patient — and indeed, the decision to have surgery at all — depends on many factors. No two patients are alike. For most people with PD, the chance of significant benefit must clearly outweigh the operative risks. The choice

of surgical approach is best determined through careful discussions involving the patient, the family, the neurologist and the neurosurgeon.

The choice of surgery may depend on the patient's specific symptoms. Is the main issue a disabling tremor? Or is drug-induced dyskinesia the biggest problem? Other pertinent questions include: Has the patient had previous brain surgery? Does he or she live in an area that offers ready access to the medical center for DBS programming or troubleshooting? The techniques with the most benefit appear to be deep brain stimulation in the subthalamic nucleus or globus pallidus but there are patients for whom a different approach may be preferable.

4 Where is the best place to have surgery?

Although enthusiasm for surgery is widespread, the techniques are very specialized and the surgical skills and support systems that are necessary are not available everywhere. For this reason, patients and their families would be wise to seek out a center that has long-standing experience with DBS as well as resources specifically dedicated to the surgical treatment of PD. As with any complicated technical procedure, there is a learning curve, and surgeons with the most experience have the lowest complication rates.

The ideal center should have a clinical team devoted to the surgical treatment of PD, with a neurosurgeon specially trained in stereotactic surgery and an electrophysiologist to perform intra-operative brain mapping. There should be experienced neurologists and nursing personnel skilled in pre-operative screening and post-operative care, including programming the deep brain stimulator. It is essential that center personnel be available for immediate advice and evaluation should the need arise.

Considering the rapid pace of technological advance in this field, it may be worth considering whether the surgical center has a serious commitment to PD research, or whether the surgery is being offered simply to provide a clinical service. One telling question may be: does the surgical team regularly publish and report its results and complications to the medical community?

5 Does my insurance cover the cost of the surgery?

To date, most private insurers, as well as Medicare and Medicaid, have approved the surgery for PD and have covered all expenses completely. This is fortunate as the cost of the procedures is extremely high, running to as much as \$100,000 for the surgery, anesthesia, stimulator devices and hospital care. The FDA gave a general approval for deep brain stimulation in 2002, so this advanced treatment is now considered standard therapy, and not experimental.

6 Will surgery enable me to stop my anti-parkinsonian medications?

For many patients, DBS surgery will reduce the dependency on medication. Individuals who undergo bilateral subthalamic nucleus stimulation, for example, may reduce their medication by 50 percent or more in the months following surgery. For patients who experience adverse effects of their medications, such as hallucinations or dyskinesias, limiting medication intake is an important secondary benefit of the operation. Patients whose main problem is severe tremor may find their tremor so well controlled by surgery that medication becomes unnecessary.

7 What is the effect of surgery on the long-term course of PD?

The effect of surgery on the prognosis of PD is unknown. Most investigators believe that a surgical intervention will have little or no effect on slowing the progression of the disease even though relief of symptoms may be dramatic and long-lasting. Studies have shown benefits lasting at least five years. Tremor and dyskinesia are two symptoms of PD that may be permanently stopped by surgery. But other disabling symptoms of PD — gait impairment, falling, poor posture, soft speech — may worsen with time, despite surgery. As for the possibility of dementia, the long-term effect of surgery is unknown.

8 Will a decision to undergo surgery now disqualify me from better treatments that might be available in the future?

It is impossible to predict what new or improved therapy might be coming in the near future or who will be eligible for it. Deep brain stimulation, unlike earlier techniques, does not destroy significant amounts of brain tissue and is therefore, in theory, a reversible treatment. As such, having

DBS done now should not exclude an individual from a future, more promising therapy.

9 Is surgery for Parkinson's disease a cure?

No — at least, not yet. A cure for PD would be a treatment that can stop the disease from progressing and even reverse it. Neither deep brain stimulation, nor the older lesion-based techniques, nor medications, can provide this at present. At best, surgery may be able to control some or all of the disabling problems of PD, such as drug-induced dyskinesias, tremor, wearing-off fluctuations, slowness of movement, rigidity and tremor — but the disease remains progressive.

10 What are the chances of finding a cure for PD?

Many scientists believe that the cure for PD will come from a deeper understanding of what causes the disease. What is the reason that dopamine neurons in the basal ganglia begin to degenerate and die? If the cause of the neurodegeneration can be identified, perhaps a specific treatment could be applied to slow, stop or reverse its process.

Strategies of treatment in the future may include the delivery of substances or genetic material directly to degenerating brain cells. Future treatment may involve replacing dying cells using an alternative source of brain tissue, such as stem-cell lines or embryonic tissue. However, these techniques are in the earliest stages of development.

For sufferers of Parkinson's disease and their families, the progress is always too slow. But there are reasons to be optimistic. DBS revolutionized the treatment of PD and has improved the quality of life for thousands of patients. It is anticipated that many scientific advances will be translated into benefits for people with Parkinson's, and so the hope for a cure is linked with true promise and great optimism.



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The Parkinson's Disease Foundation (PDF) is a leading national presence in Parkinson's disease research, patient education, and advocacy for increased federal funding. PDF is working for the nearly one million people in the U.S. living with Parkinson's by funding promising scientific research and supporting people with Parkinson's, their families and caregivers through educational programs and support services.

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