

# Deep Brain Stimulation for Treatment of Parkinson's disease

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**ABSTRACT:** The field of Pharmaceutical Sciences has for long been dependent on looking for biological techniques for the treatment of diseases and to cure abnormalities in our anatomy. The modern day developments have supplemented the age old as well as the new medicinal techniques with the help of state of the art techniques which are now being used worldwide. There has been a surge, in particular, in the field of 'Electroceuticals'. As the name suggests, it is the amalgamation of pharmaceutical techniques with electronic applications. Electroceuticals, a term that has been recently coined by British pharmaceutical giants GSK encompasses a wide range of bioelectronic medicine that mainly employ electronic stimulations to affect and modify the functions that occur in our body. There has been an advancement using this method, particularly in the DBS technique used for the treatment of motor disorders like Parkinson's disease and Dystonia. The traditional DBS technique had its flaws and issues which were proving to be detrimental to the patient's health suffering from PD symptoms. Current research and device instruments have helped reducing these factors considerably. Here, we have tried to explain the phenomenon of Deep Brain Stimulations briefly and have explained the possible mechanisms of treatment. Also being discussed are the current research and advancements that have taken place in this field, thus showing how electroceuticals has helped better the technique for the treatment of movement disorders, in particular, Parkinson's disease.

**KEYWORDS:** Deep Brain Stimulation, Parkinson's disease, Neurostimulator, Electroceuticals.

## ABBREVIATIONS:

- CT – Computed Tomography
- DBS – Deep Brain Stimulations
- GPi – Global Pallidus
- MRI- Magnetic Resonance Imaging
- NINDS- National Institute of Neurological Disorders and Stroke
- PD – Parkinson's Disease
- STN- Subthalamic Nucleus
- Vc – Ventrocaudal Nucleus
- VIM – Ventral Intermedius Nucleus

## INTRODUCTION

Parkinson's disease (PD) is a chronic and progressive movement disorder, signifying that symptoms continue and deteriorate over time. The origin and cause is unknown, and although there is currently no cure, there are treatment routes such as medication and surgery to manage its symptoms.

Parkinson's involves the breakdown and death of vital nerve cells in the brain, called neurons. Some of these dying neurons produce dopamine, a chemical that directs messages to the part of the brain that controls movement and coordination. As PD progresses, the amount of dopamine produced in the brain decreases, leaving a person unable to control movement normally.

Both men and women are affected and the frequency of the disease is significantly higher in the over 50-age group. Clinically, the disease is characterized by a drop in impulsive movements, gait difficulty, postural instability, rigidity and tremor.<sup>[1]</sup>

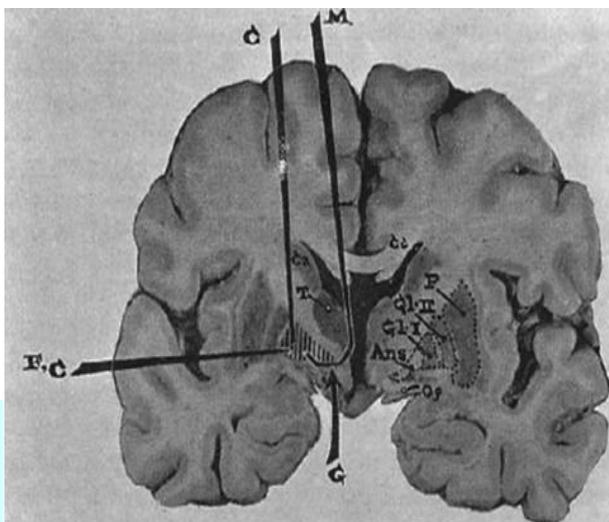
Administration of the drug levodopa has been the standard treatment for Parkinson's disease, a process called pharmacotherapy. Once it reaches the brain, levodopa is converted to dopamine. Treatment with levodopa does not, however, inhibit the progressive changes of the brain typical of Parkinson's disease. The drug may also produce side effects in some people, due to its change to dopamine before reaching the brain.

There has been an increase in the use of surgical treatments for PD. Surgical treatment for PD includes ablative surgery, DBS, and transplantation.

Deep Brain Stimulation, a process involving high frequency electrical stimulation by means of electrodes implanted into the brain has recently become an accepted technique for the treatment of several movement disorders and in particular for Parkinson's disease.

Chronic DBS stimulation provides a non-destructive and reversible method of disturbing the abnormal function of basal ganglia (the part of the central nervous system that coordinates movement) circuit. It can be adjusted as disease progresses or adverse event occurs.<sup>[1]</sup>

The Food and Drug Administration (FDA) approved DBS as a treatment for Parkinson's disease in 2002. While DBS has proven effective for some patients, potential for serious complications and side effects exists.

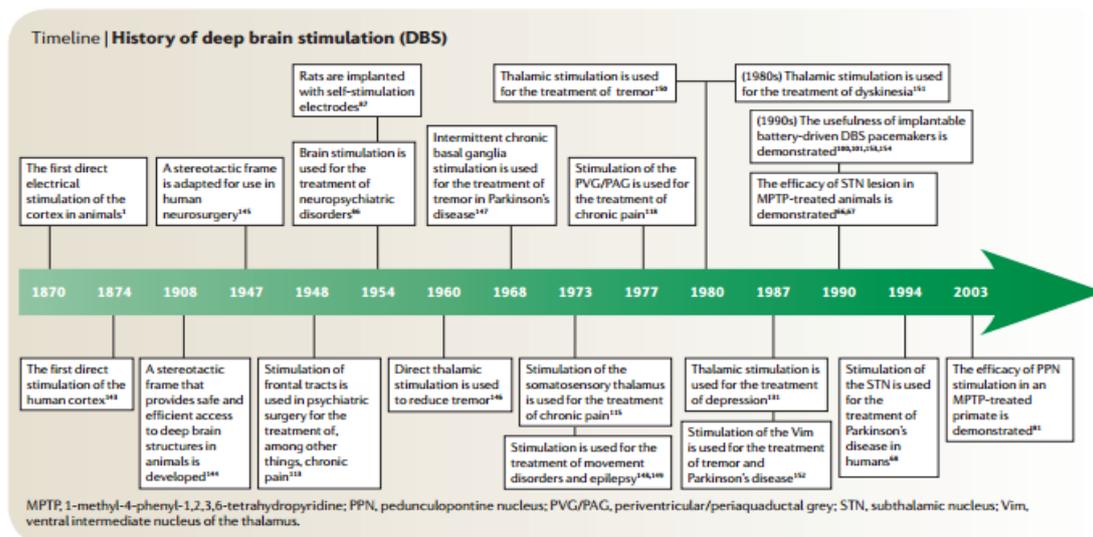


### THE HISTORY OF DBS<sup>[2]</sup>



The early pulse generator.<sup>[2]</sup>Meyer's approach to the basal ganglia<sup>[2]</sup>





Morten L. Kringelbach, Ned Jenkinson, Sarah L.F. Owen & Tipu Z. Aziz

## 1. DBS Device (The Brain Pacemaker)<sup>[3]</sup>

Similar to a cardiac pacemaker, a medical device is used to transport electrical stimulation to precisely targeted zones in the brain to treat symptoms.

It is an implantable device, made up of three main components:

1. Quadripolar brain electrodes,
2. Pulse generator (Neurostimulator) and,
3. Extension wires.

### Quadripolar brain electrodes

The quadripolar leads are implanted into the part of the brain involved with the disease process, using stereotactic neurosurgical technique. Current enhancement of the knowledge of basal ganglia circuitry and pathophysiology of the diseases has concentrated the focus of movement disorder surgery to three, very important gray matter structures:

1. The thalamus,
2. The globus pallidum and,
3. The sub thalamic nucleus.

The lead implantation is usually carried out in awake stage under local anaesthesia to optimize the recording of physiological information during the mapping procedures, as well as to elicit the patient's report of stimulus induced side effects.

### Pulse Generator

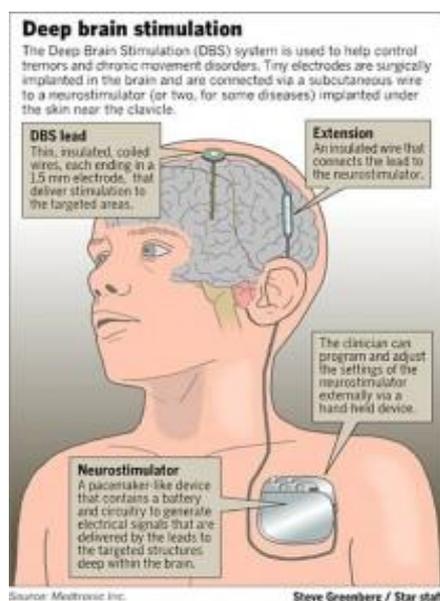
Pulse generator/neurostimulator is a small box shaped instrument that generates the electrical signals. These are then sent to the electrodes. It is usually implanted under the skin over subclavicular region. They are used to convey electrical stimulation to targeted sites in the brain that control movement, blocking the irregular nerve signals that cause tremor and PD symptoms.

The first of its kind was developed by Medtronic.

### Extension Wires

Extension wires are tunneled under the skin and are connected to the lead and pulse generator. These are insulated wires passing under the skin of the head, neck, and the shoulders, connecting the lead to the neurostimulator device.

Source: [Neurosurgical Associates of San Antonio: Deep Brain Stimulation](#)



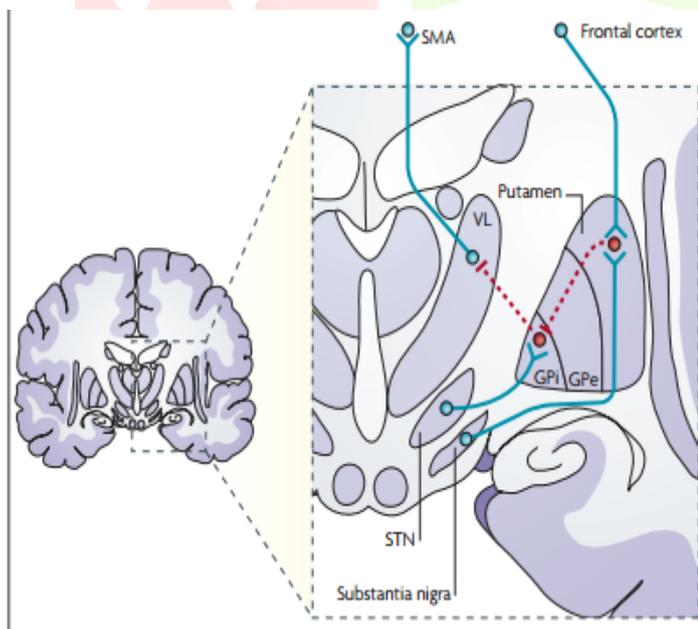
After a period of a few days or weeks of device implantation, the stimulation parameters are programmed. Before the procedure is started, a neurosurgeon uses magnetic resonance imaging (MRI) or computed tomography (CT) scanning to detect and trace the exact target within the brain where electrical nerve signals produce the PD symptoms.

Once the system is put in place, electrical impulses are transferred from the neurostimulator present up along the extension wire and the lead and finally into the brain. These impulses restrict and block the electrical signals that cause PD symptoms.

For DBS, there is no clearly described mechanism of action, though there are numerous likely possibilities. High frequency of stimulation may generate a global hyperpolarisation of the cell membrane causing a loss of excitability. The stimulus could jam signal flow out of the abnormal functional areas. Although the mechanism of DBS is yet to be effectively worked on, doctors have enough experiences in using DBS to feel confident of its safety and effectiveness.

The NINDS is an organisation that supports research on DBS to determine its safety, dependability, and efficiency as a treatment for PD. Currently, NINDS-supported scientists are working on determining the site(s) in the brain where DBS surgery would be the most effective in reducing PD symptoms. These researchers are also trying to compare DBS to other PD therapies to find out which is more effective and preferable.<sup>[13][14]</sup>

- **The Quadripolar Brain Electrodes**



*DBS for the treatment of movement disorders such as Parkinson's disease, dystonia and tremor has mainly targeted structures in the basal ganglia.*

*The main area of focus for the electrodes are the Thalamus, STN and GP. Division of Engineering, Mayo Clinic, Rochester, MN 55905, USA. ckimble@mayo.edu*

- Traditional bio-electrodes are made and plated with noble metals such as platinum or gold so that they are minimally toxic.
- There is also a need for a rough surface to reduce interface impedance and improve the electrical potential stability.
- Thin film technology is of prime importance for the production of these electrodes. Thin film processes makes possible the production of sensors and devices on flexible substrates for use in implants.

- Certain nerve cells have a tendency to become overactive in Parkinson's patients to the point of triggering uncontrollable muscle excitation in tremor patients, and electrical stimulation has been found to interfere with this unusual activity. This is done with the assistance of these electrodes and the pulse generator.

### Basic Engineering Requirements

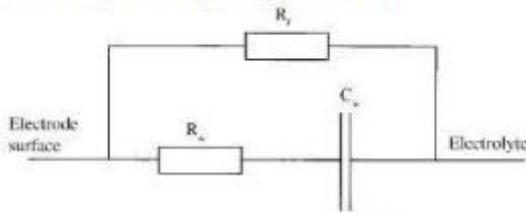


Figure 1: Model of implanted electrode. Resistance  $R_w$  and Capacitance  $C_w$  are due to material properties and geometry and Resistance  $R_f$  is faradic resistance of electrolyte. (Wallman 1999)

The electrode-electrolyte interface is represented as a serial capacitance and resistance, along with a Faradic resistance. This can be seen in Figure 1. For a good signal coupling, it is important to have a large capacitance for recording electrodes and a small resistance for stimulation electrodes. This constitutes the basic engineering requirements.<sup>[4]</sup>

An important feature of stimulation microelectrodes is its safe charge injection limit. The microelectrodes cannot exceed a certain limit of current density, otherwise gas evolution of oxygen or hydrogen may occur. Polycrystalline electrodes are limited to 5mC/cm<sup>2</sup> whilst the conventional Tin electrodes have a safe limit of 20mC/cm<sup>2</sup>. The Au electrodes have a limit of 3mC/cm. However, polycrystalline electrodes can only cause an evolution when a negative potential is applied, thus demonstrating that these are well suited for the stimulation of electrogenic cells.

The use of thin film electrodes allows for the advantages of synchronized stimulation of a large number of electrodes and thus a large number of cells. However, it is vital to achieve a low specific phase boundary impedance in order to gain effective charge transfer from the microelectrode to cells.

No redox processes, i.e. faradic currents should be involved in the charge transfer since tissue may be sensitive to the products formed in the reaction. Consequently, there should be an entirely capacitive coupling throughout the double layer capacitance of the electrode.

### • The Pulse Generator (Neurotransmitter)<sup>[5][6][7]</sup>

In this section, we would be discussing about the various kinds of neurotransmitters being used for DBS surgery.

#### 1.2.1 KINETRA

The Kinetra® Dual-Channel Neurostimulator, is built on the basis of Solettra/Activa. These are therapy neurostimulators that are used for the treatment of people with debilitating (old and weak) movement disorders, such as advanced Parkinson's disease and Dystonia.

It uses a single or a pair of surgically implanted medical instruments called neurostimulators, which are similar to the technology used for cardiac pacemakers, to convey electrical stimulation to precisely targeted sites on each side of the brain with the help of DBS extension or DBS leads. The Kinetra houses two extensions/leads, thus providing bilateral neurostimulation from a single neurostimulator. It offers additional advantages for the patient than what a single channel stimulators can provide.

The neurostimulator further consists of electronic circuitry and a voltage supply in the form of a battery, which are sealed in a titanium case. The operation of the neurostimulator is aided by a clinician programmer, a therapy controller, and a control magnet.

#### Key features:

- Battery and microelectric circuitry generate controlled electrical pulses.
- Easy to operate
- Handheld device
- Patient can adjust parameters like pulse width, voltage and frequency.
- **Device description:**
  1. The Kinetra allows bilateral DBS with the aid of two leads which are programmed individually with the help of a single pulse generator. The special programming featuring in the Kinetra system are of two different techniques to set the defined parameter (custom limits or auto-tracking):
  2. The day cyler (a technique being used to coordinate the patient's therapy schedule to the 24 hour clock).

3. Cycling (in this particular mode, cycle time ON is that duration of time where stimulation is delivered and cycle time OFF is the time between stimulation periods).
4. Soft Start/Stop (this causes the amplitude to increase from zero to the selected output amplitude and to decrease from the selected output amplitude to zero).

Different tests to check the neurostimulator battery:

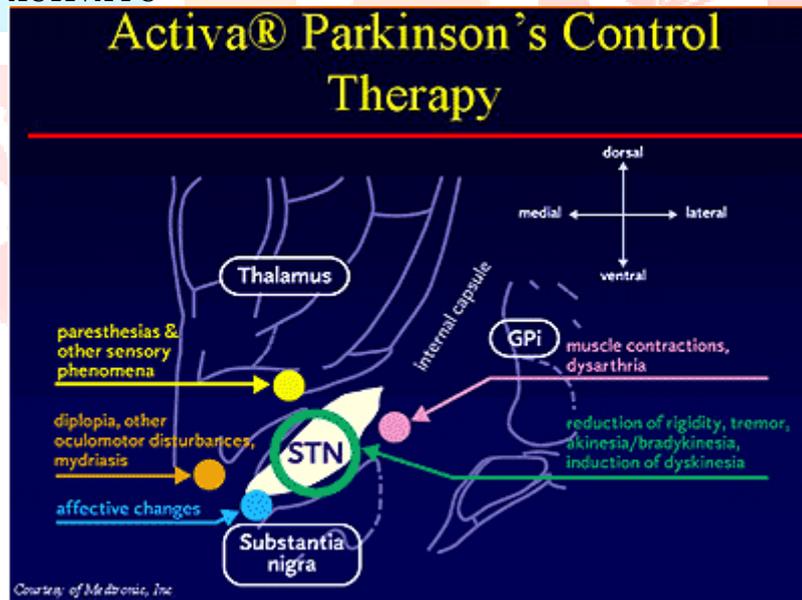
1. Status (OK, low, or end of life)
2. Capacity (in volts), use (full or percentage used)
3. Battery current (in microamps).

A therapy controller called the Access Therapy Controller or a magnet is used to control the Kinetra. The Access Therapy Controller is a hand held battery powered device. It is used for turning the neurostimulator device on and off. It is also used for checking the neurostimulator battery status. Additional functions of the therapy controller involve, adjusting stimulation amplitude, pulse width, and rate within a physician prescribed range of settings. The amplitude (0 to 10.5 V) and pulse width (60 to 450  $\mu$ s) can be automated separately for each channel. The stimulation frequency (2 to 250 Hz) is similar for both the channels. Three lengths of extension cable are available. They depend on whether the stimulator is in a subclavicular (51 or 66 cm) or abdominal location (95 cm). Quadripolar leads and unipolar leads are two types of leads that can be used. The Kinetra weighs 80.5 g and measures 60  $\times$  77  $\times$  13 mm. It consists of a titanium case enclosing a silver vanadium oxide battery and the electronic circuit of the stimulator.

### DEMERITS

Some Kinetra implantable neurostimulators experience a failure of wire connections between the electronic hybrid circuit and battery. This may lead to a sudden termination of therapy. Sudden cessation of therapy can result in the immediate return or deteriorating of symptoms of PD due to the progression of the disease state.

#### 1.2.1 ACTIVA PC



biomed.brown.edu(Activa PC Parkinsons)

- Activa PC is the first, non-rechargeable Deep Brain Stimulation (DBS) neurostimulator.
- The Activa PC neurostimulator consists of an electronic circuit-board. It is powered by a non-rechargeable, long-life battery. The Activa PC neurostimulator can provide extended, maintenance-free symptom control, and does not require constant attention.
- The Activa PC neurostimulator is discreet and unobtrusive, and it resembles the size and shape of a cardiac pacemaker. It has a volume of just 39 cubic centimetres. It is only 15 millimetres thick, and it weighs a mere 67 grams. This is a full 24% smaller than Medtronic's first-generation Kinetra® device, ensuring a significantly greater comfort to patients.

**Key Features:**

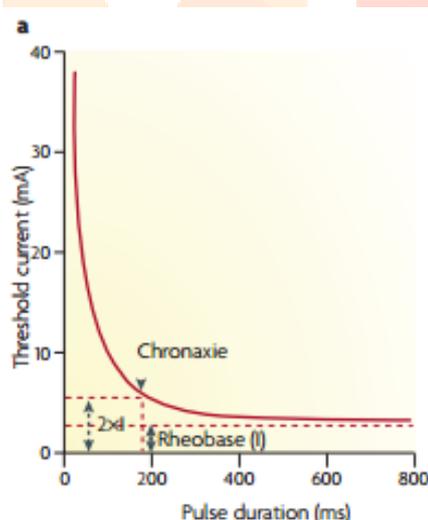
- No battery maintenance required
- MRI Safety
- Targeted electrical pulses

<b>Activa PC</b>	<b>Kinetra</b>
<b>1. Non-rechargeable</b>	<b>Rechargeable</b>
<b>2. Long battery life</b>	<b>Short Battery Life</b>
<b>3. Size-65*49*15</b>	<b>Size-61*76*13</b>
<b>4. Targeted Electrical pulse</b>	<b>Controlled Electrical Pulse</b>
<b>5. Maintenance Free Device</b>	<b>High Maintenance Device</b>
<b>6. Patients cannot modify the neurotransmitter parameters</b>	<b>Patients can change the parameters</b>

**Neurophysiological Principles of DBS**

Traditionally, the point of departure for understanding the mechanisms of DBS has been to associate the effects of stimulating a particular brain area with the therapeutic results of neurosurgical lesions.

DBS of both the normal and the diseased brain primarily depends on a number of parameters, including the physiological properties of the brain tissue, which may change with disease state, the stimulation parameters (including amplitude and temporal features), and the geometric configuration of the electrode and the neighbouring tissue.

**Physiological Properties**

Electrophysiological Factors of DBS

- The physiological, particularly, the electrical properties of normal and diseased brain tissue depend on the presence of different types of neurons and supporting glial cells. These use diverse types of ion channels having variable voltage-sensitive properties.
- The result of DBS on the various neural components depends on the non-linear relationship between the stimulus duration (pulse width) and the amplitude (voltage or current) that is required to stimulate the neural component.
- The minimal current required to stimulate a neural component with a long stimulus duration is called the rheobase (the amplitude threshold).
- The chronaxie time is the minimum duration of time that is vital to excite a neural component using half the intensity that elicits a threshold stimuli. The chronaxie of myelinated axons is around 30–200  $\mu$ s, whereas the chronaxies of cell bodies and dendrites are considerably larger, at around 1–10 ms.

### Stimulation Parameters

- These comprise of factors like tremor, rigidity, bradykinesia, paresthesia and chronic pain in patients during DBS surgery.
- The actual DBS parameters, consisting of the stimulus amplitude, duration and frequency band, change with the treatment and with the targeted brain region.
- Currently, with most commercially available stimulators, these parameters can be externally changed and fine-tuned.

### Geometric configuration

- The geometric configuration of the neural elements along with the electrode, influences the effects of the stimulation on local and distal neural elements.
- Additionally, the effects on distal neural elements depend on the distance between the neural elements and the electrode, both the rheobase and the chronaxie rise in proportion to the distance. This signifies that the responsiveness of more distal elements decreases as the distance from the electrode increases.
- Thus, the stimulation volume is not a fixed cylinder around the stimulation electrode. Instead it varies with the position of the electrode and the properties of the surrounding neural tissue.

### Mechanisms of DBS<sup>[8]</sup>

According to current research, it has been proposed that the overall effect of DBS is to inhibit the neural activity in the region stimulated. However, whether this is actually the case is currently not known. Various mechanisms have been proposed in an attempt to explain how DBS could mimic the effects of a lesion. We describe the various mechanisms that have been proposed to account for the inhibition or disruption of the pathologic outflow by high-frequency DBS, ranging from depolarisation block to stimulation-evoked release of  $\gamma$ -aminobutyric acid and explain the preliminary findings that show that stimulation within these structures can result in inhibition.

<u>POSSIBLE MECHANISMS OF ACTION</u>	<u>DESCRIPTION</u>
Inhibition (Depression)	Depolarises axons terminating in the target structure resulting in the release of inhibitory neurotransmitters.
Depolarisation Blockade	Increases the threshold needed to produce an action potential, so firing of inhibitory neurotransmitters is not effective.
Adjustment of Neural Activity	Adjusts firing pattern so that it is more accurate and constant.

Figure Source: www.medscape.org (Medtronic backed programme)<sup>[14]</sup>

### Basic Principle

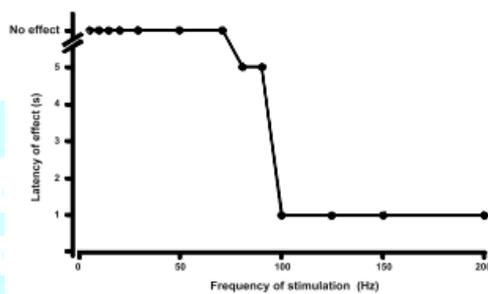
- On the basis of basic physiological principles, it has been observed that the effects of DBS are due to excitation of the neural elements (axons, cell bodies) surrounding the tip of the electrode. Thus it increases firing of the axons projecting away from the region stimulated.
- In its first major use, DBS was used to activate a descending pain inhibitory pathway originating in the periventricular grey.
- DBS in the tactile thalamic relay nucleus, the ventrocaudal nucleus (Vc), also used for improving pain, is well known to produce parasthesia, seemingly due to activating thalamocortical neurons and subsequent excitation of neurons in primary somatosensory cortex.
- In the past 10 years, high-frequency (HF) electrical stimulation of motor thalamus, globus pallidus internus (GPI), and the subthalamic nucleus (STN) has become increasingly common as an alternative to lesions.

**Phenomenon of Stimulation**

- Stimulation within the thalamic ventral intermedius nucleus (Vim), STN, and GPi could potentially activate a variety of diverse neural elements with differing effects
- Since the current intensity decreases with distance from the electrode tip, the kinds of neural elements excited will differ depending on their distance from the electrode.
- Since the nuclei are not homogeneous, the effects of stimulation are likely to vary, depending on the location of the electrode within the nucleus.

**Effects of Stimulation Frequency**

- Increasing the stimulation frequency should result in an increased effect on the target structure of the neurons that are being stimulated.
- For example, increasing the frequency of stimulation in the awake human thalamic Vc or optic tract results in increased intensity of the perceived sensation and decreases the threshold current necessary to evoke a sensation.



**FIG. 1.** Graph showing dependence of block of dyskinesias on frequency of stimulation in the globus pallidus pars interna. Stimulation with 5 mA, 100- $\mu$ sec pulses was delivered between two adjacent contacts of the deep brain stimulation lead. For stimulation frequencies below 80 Hz, there was no effect on the dyskinesias. Complete block occurred for frequencies over 80 Hz. The latency of onset decreased from 5 seconds to 1 second as the frequency increased from 80 to 100 Hz. Modified with permission from Wu et al.<sup>10</sup>

This is a graph between the Latency of effect vs. the frequency of stimulation being used. As observed, the beneficial effects of DBS in the Vim, GPi, and STN appear to be markedly frequency dependent and occur primarily if not exclusively only at high frequencies (over 100 Hz). Over this barrier, the latency of onset dropped from 5 to 1 second, thus causing microstimulation.<sup>[8]</sup>

Microstimulation at high frequencies in sensory structures generally results in positive sensations such as parasthesia, sounds, or flashes of light, suggesting excitation of the neurons in the regions stimulated.

However, because the therapeutic effects of DBS are similar to those produced by making a lesion (Thalamotomy), it seems reasonable to propose that HF stimulation in these

three regions actually leads to a depression of neural activity in the region stimulated rather than to excitation, and that is what is generally assumed occurs.

An important biomedical application of MEMS is thalamic stimulation. This deep brain stimulation is intended to help Parkinson’s disease patients by regulating brain signals normally transmitted from the thalamus, resulting in elimination of physical tremors. These stimulations improve several number of aspects of motor function, particularly movement time and force production. In addition to this, quadripolar electrodes that allow examination of the therapeutic effects induced by stimulation are in the research and development as well

Studies were made recently on the examination of the effects of stimulation on the firing of single neurons recorded in GPi, SNr, STN, and motor thalamus in awake patients. The two major types of observations made were: the effects of single shock stimuli on spontaneous firing rate, and the effects of high-frequency trains on spontaneous firing rate after the termination of the stimulus. Some of these findings have been published.

Low frequency vs. high frequency

Low frequency stimulation	High frequency stimulation
Low-intensity stimuli reliably produced short duration inhibition	Low-intensity stimuli frequently resulted in inhibition after the termination of the train
The inhibitions are usually of the order of few milliseconds	The inhibitions are usually of the order of few hundred microseconds
The excitatory afferents in thalamus are more excitable and/or numerous than the inhibitory afferents in contrast to the situation in GPi, in which the opposite situation apparently prevails.	In thalamus, high-frequency stimulation (100–333 Hz; current 5–40 mA) from either a nearby stimulating electrode or directly from the recording electrode was found to produce a prolonged inhibition lasting up to 10 seconds in many cells.

## Patient Selection and Evaluation<sup>[9]</sup>

- The striking responses reported with deep brain stimulation (DBS) of the subthalamic nucleus (STN) and internal segment of the globus pallidus (GPi) have encouraged widespread interest in the use of this treatment modality for Parkinson's disease. Large numbers of patients are regularly referred to surgical centres for consideration of DBS.
- It is mandatory that criteria are established that can effectively predict the outcome of patients considered for DBS in advance of applying this therapy.
- Important issues necessitating the establishment of such criteria include the potential for surgical morbidity and mortality, which do not exist with medical treatment; the short- and long-term costs of DBS; the considerable time and effort required by the patient, caregivers, and medical staff in the postoperative period for programming and drug adjustments; the need for active ongoing follow-up and vigilance in assessing for device-related complications; and finally the very limited resources currently available to provide this treatment, including the limited number of experienced neurosurgeons and movement disorders neurology teams dedicated to the ongoing management of this complex treatment.

### • The Selection Criteria

Given these concerns, it is necessary to establish a rigorous selection process that will successfully characterize candidates who:

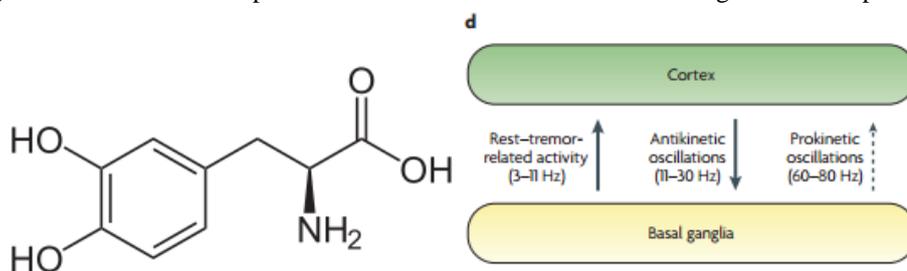
- (1) Will obtain the greatest benefit from the treatment
- (2) Will maintain this benefit sufficiently long to justify the time and the expense invested and
- (3) Are physically, cognitively, and emotionally able to tolerate all aspects of surgery and postoperative care.

### Degree of benefit

- Since the introduction of STN and GPi DBS, the benefit obtained from surgery has often been compared and contrasted with that obtained with levodopa.
- Levodopa, known mainly as L-DOPA is the drug often prescribed for PD. The body metabolises it to produce dopamine.
- Most PD treatments primarily aim to restore the proper balance of neurotransmitter acetylcholine and dopamine by increasing dopamine levels. Levodopa is drug that tends to lose its effect very quickly. Hence doctors prefer to give it at a very later stage of the disease. This has proven to be highly controversial in the medical world.
- There are certain inhibitors like Tasmar that block the enzyme that break down L-DOPA, but these cause liver damage.
- To prevent worsening of the disease condition, surgical DBS is preferred over levodopa medication. DBS regularly has been shown to improve the motor complications of levodopa, including reducing the amount of off-period time and improving all forms of dyskinesias.
- A recent study demonstrated that the severity of preoperative levodopa-related complications did not influence the postoperative outcome with respect to Unified Parkinson's Disease Rating Scale (UPDRS) scores.
- On the other hand, given the benefit to motor complications, patients experiencing substantial disability from these complications stand to benefit considerably from this intervention.
- This prospect emphasizes the need to evaluate the extent and severity of motor complications in the course of pre- and postoperative assessments.

## Duration of Benefit

- Most investigators believe that an important inclusion criteria for DBS is the diagnosis of idiopathic PD.



- e.g., L-DOPA is used for the treatment of multiple

*L-DOPA, a psychoactive drug that is being used as a medication for PD. Also shown is a schematic diagram of the neural oscillations that occur in Parkinson's disease. In the absence of dopamine in the striatum, i.e., if DBS is used instead, pathological oscillations arise in basal ganglia-cortical systems.*

le system atrophy (MSA), a degenerative neurological disorder. Using this drug may cause motor complications.

Theoretically, in the short-term, such patients might benefit considerably from DBS. However, the underlying disease generally progresses at a much more rapid pace than typical Parkinson's disease, and the response to levodopa wanes.

- Although there is little experience in the use of DBS in levodopa-responsive MSA patients, one would predict that any initial benefit to the surgical treatment might quickly be lost.
- Although DBS could have a short-term beneficial impact on disability, it is difficult to justify knowingly accepting such patients as candidates given all of the concerns and limitations.
- The same applies to PD patients suffering from serious intercurrent illnesses that are expected to substantially shorten longevity.

### Ability to tolerate surgery

The proper implantation of DBS devices into either the STN or GPi involves a relatively prolonged and demanding surgical procedure, which requires patient involvement and cooperation.

Patients must be physically capable of tolerating the rigors of surgery. This endurance is often impossible for extremely debilitated patients or patients with intercurrent medical illnesses such as significant cardiopulmonary disease.

This demand also applies to the postoperative care which commonly requires frequent periods of anti-Parkinson medication withdrawal.

Any significant, active mood or psychiatric disturbance should serve as a contraindication to surgery. A successful aggressive management of these issues may allow reconsideration of surgery in the future. All available functional stereotactic neurosurgical techniques for Parkinson's disease have the capability of causing de novo neuropsychological dysfunction.

It is critical that patient and family have a realistic expectation of the surgery and an understanding of what this process entails. Surgery should never be offered to a patient until this realistic understanding is fully established.

As DBS becomes more widely available and technology improves upon operative morbidity and optimizes outcome, it is inevitable that investigators and patients will push to expand acceptance criteria.

### Patient Evaluation

- How levodopa responsiveness is best defined? How dyskinesias (movement disorder) should be quantified, and under what circumstances should dyskinesias be assessed?
- These and similar questions on how to assess and evaluate parkinsonian patients undergoing experimental neurosurgical treatments have been addressed in the development of the Core Assessment Program for Neurosurgical Interventions and Transplantation in Parkinson's Disease (CAPSIT-PD).

### CAPSIT-PD<sup>[10]</sup>

- In 1992, the Core Assessment Program for Intracerebral Transplantations (CAPIT) was published. It provided the minimal necessities for a common patient evaluation protocol. Despite the intent, the program was found to be too laborious to carry out in large scale trials. It also seemed to lack the evaluation of cognitive functions and quality of life.
- Moreover, the CAPIT was designed for neural transplantation only and there hasn't been any revision since. Pallidotomy and deep brain stimulation have presently emerged as additional treatment modalities but there exists no common tool for evaluation of the technique.
- In 1996, within the framework of NECTAR (Network for European CNS Transplantation and Restoration), a dedicated program entitled "Neurosurgical Interventions in Parkinson's Disease" (NIPD) was funded by the European Union Biomed 2 program. Its intention was to develop a new Core Assessment Program for Surgical Interventional Therapies in PD (CAPSIT-PD) and to establish a European registry for patients with PD subjected to functional neurosurgery.
- The program comprises of four sections:
  - (1) selection criteria,
  - (2) definitions of concepts and terms,
  - (3) recommendations on frequencies and time periods to assess, and
  - (4) detailed discussions of which tests to use for quantification of symptoms and how to perform them.

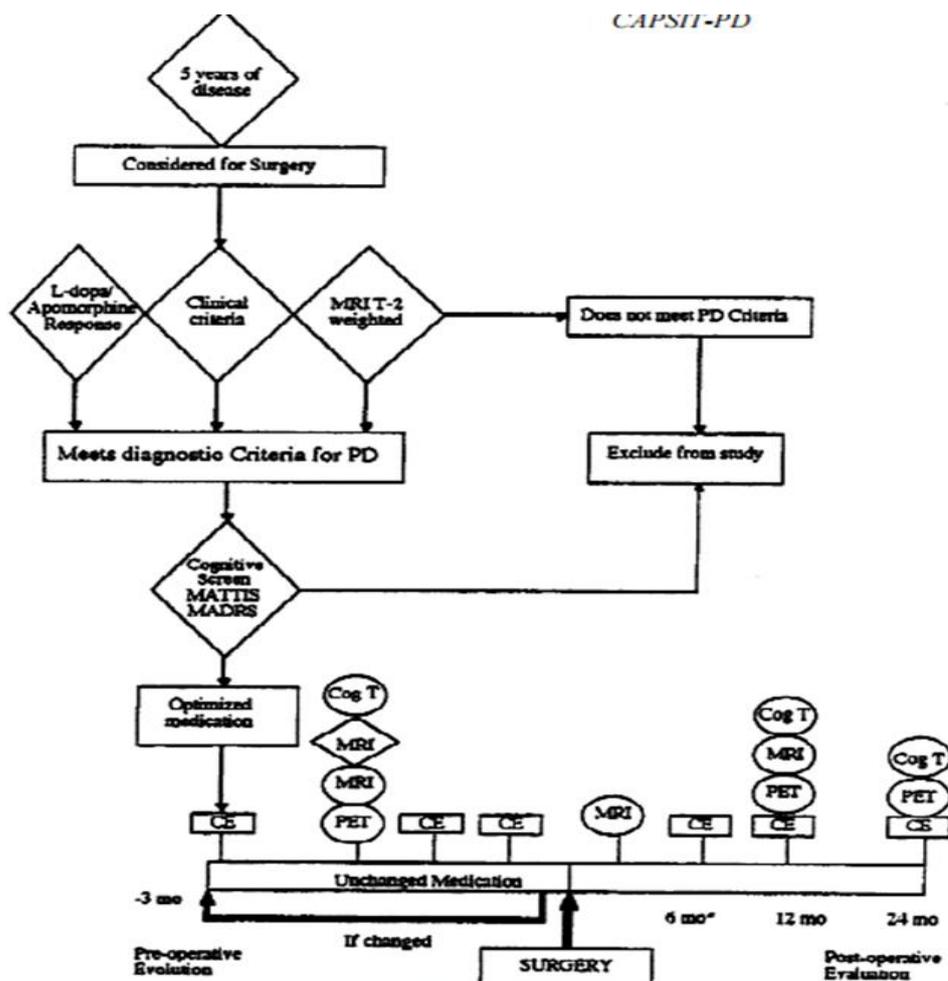


FIG. 1. Schematic outline and proposed flow chart of the Core Assessment Program for Surgical Interventional Therapies. The time points for the different items in the program are indicated by symbols (see text for details).

### • Selection Criteria

The CAPSIT-PD recommendation is that a patient should have a disease duration of at least 5 years before being considered for inclusion in a neurosurgical experimental protocol, to allow for atypical forms of Parkinsonism to become evident as elaborated in the Selection Criteria section. Also, by 5 years, the majority of patients will have been exposed to levodopa, facilitating testing and assessment, although treatment with dopamine agonists is also possible.

### • Definitions of concepts and terms

(Practically) Defined-off refers to the condition after a patient has received no antiparkinsonian medication for 12 hours. If a patient fails to tolerate this length of washout, the longest period tolerated should be defined and this shorter period should then be used for all subsequent evaluations.

(Practically) Defined-on refers to the condition during a pharmacological test when the patient and investigator agree that the functional benefits of the drug treatment are greatest, which may not reflect the patient's best possible treatment related anti-parkinsonian effect.

### • Recommendations on Frequencies and Time Periods to Assess

It is suggested that assessments are carried out during a 3-month preoperative period, during which the drug treatment is stable and after that at a minimum on 6, 12, and 24 months.

The CAPSIT-PD protocol suggests at least three preoperative measurements and that a mean is taken for the three preoperative measurements to represent the baseline.

This recommendation was based on data from such preoperative periods that demonstrated significant differences between the first and third evaluations.

### • Tests for Quantification of Symptoms

The core evaluation is a set of tests repeated pre- (three times) and post- (6, 12, 24 months) operatively and aims at defining the patients as comprehensively as possible, yet without excessive investment of time and effort. For details on the

performance of the tests, the reader is referred to the CAPSIT-PD publication. The patient fills out a patient diary for 7 days preceding the test day, with ratings of off, partial on, on, and on with dyskinesias, every 30 minutes during waking hours, and notes any falls, freezing, or dystonic episodes during these 30-minute intervals. Questionnaires on the quality of life (QoL) should be used, in particular the SF36 as well as a disease-specific scale. Preoperatively, the scales should be used before starting the preoperative evaluation to best reflect the patient's QoL before surgery. After the surgery, the scales should be completed simultaneously with the other assessments. The patient is then evaluated by a rater that preferably should be the same at all pre- and postoperative assessments. The patient can either be seen on an out-patient basis or as an in-patient.

- **Complications of DBS Surgery** <sup>[11]</sup>

Deep brain stimulation (DBS) for movement disorders (MD) such as PD and Dystonia is a surgical procedure that is symptomatic, i.e., it is non-curative. It is an elective procedure. It is performed "blindly" on structures present deep in the brain of a patient who is awake. It is considered to be non-ablative and minimally invasive. The main objective of this process is to decrease disability and improve life quality of the patient. Moreover, DBS is a life-long therapy which requires life-long maintenance and follow-up. At each step of a DBS procedure, complications might occur and will have to be managed or, preferably, avoided.

The complications that can arise are:

- **Before Surgery**
- **Patient Selection**
  - The most important preoperative aspect to avoid later complications is to find and choose the appropriate patient to be operated on.
  - The selection is primarily, but not exclusively, the responsibility of the referring neurologist. The patient's symptoms should be appropriate for benefit by the proposed procedure. In addition to this. The patient's general condition, mainly the cognitive status, should be compatible with the rigors of proposed surgical procedure.

#### Preoperative Imaging

- Present stereotactic imaging by means of computed tomography (CT) and/or magnetic resonance imaging (MRI) causes no complications in itself, except for its consequences in accuracy of hitting the targeted site during surgery.
- Misalignments of frame from the targeted site may have an adverse impact on the precision of reaching the desired functional target during surgery.
- Whatever the imaging method used, a stereotactic radiological study constitutes a vital part of the functional stereotactic surgery. It is the most important part of the surgery and it is the responsibility of the neurosurgeon to take care of that.
- No neurophysiological method used during surgery would make sense if the exploring electrode, whether one or more are not properly centred on the desired anatomic target. In fact, the lesser the accuracy of the imaging method, the more exploratory tracks will be needed. This exploration helps in prolonging surgical time, which will contribute to increased stress for the patient and increased risk for infection.
- Furthermore, multiple electrode penetrations might increase the risks of provoking a debilitating haemorrhage.

#### 5.1 During surgery and the postoperative period

##### Physiological Exploration

Intraoperative physiological corroboration of the radiologically defined anatomic target constitutes the most important step to thwart neurological complications in working stereotaxis. An important prerequisite is that the surgical team involved should be confident with the technique used. Both macroelectrode and microelectrode-based physiology require training. If one masters just one of these two techniques, it does not necessarily mean that the person will automatically master the other technique, unless trained properly.

The objective of the physiological exploration is to assess the target structure and the effects of intraoperative stimulation on the symptoms to be relieved by this surgical method. There is also a need to assess the effect of stimulation on a multitude of other normal functions, which should remain normal during and after surgery. The following needs to be assessed during intraoperative stimulation and preferably during intraoperative stimulation. The parameters that are involved are orientation, alertness, short-term memory, speech articulation and voice, swallowing, occurrence of dizziness or nausea, facial expression, limb strength, limb movements, limb coordination, limb dexterity, sensation at fingertips, cheek, tongue, and lips, eye movements, vision and visual fields. A periodic conversation with the patient should remain ongoing, and the patient should be asked to report if he/she feels anything abnormal, anywhere in the body, during stimulation.

##### 5.1.1 Implantation of Hardware

Permanently implanting a DBS lead exactly in the target spot defined by imaging and physiology is a labour intensive process. It is essential to confirm the positioning of the permanent electrode. This is done by stimulating the target with this very electrode after it has been secured to the burr hole.

- Dislocation of the electrode from the targeted site may occur if the electrode is poorly attached to the burr hole. Electrodes could also break if the connection between electrode and cable is positioned in the upper area of the neck, below the mastoid. Skin erosion may also occur above the connector site. Formation of seroma in the subcutaneous pocket receiving the pulse generator may occur if that pocket is too large in size.

### After Surgery (Immediate and Remote)

#### Hardware-Related Complications<sup>[12]</sup>

- Infection, skin erosion, electrode fracture, electrode dislocation, and hardware failure can all can transpire at any given period after surgery. This occurrence will almost invariably result in explantation of the system or parts of it and re-implantation of a new one.
- Furthermore, additional surgeries may need to be performed on an emergency or semi-emergency basis since a patient who had satisfactory results from the DBS procedure may not be able to tolerate the sudden re-emergence of symptoms when the DBS suddenly fails, mainly in cases where there is a reoccurrence of these symptoms. This is discussed further in the next main topic.

#### Environment-Related Complications

- Complications are bound to occur due to a negative influence on the implanted hardware from environmental factors.
- There have been reports that show there has been a sudden deterioration of patients with STN DBS, who needed emergency admission after their stimulators (Itrel II) had been accidentally turned off by dentist tools or other external magnetic devices.
- Many (not all) of the complications caused by external interference with the stimulators can be evaded if the new, magnetically shielded, neurostimulator (Kinetra) is used instead of the Itrel device.
- Patients with DBS who undergo treatment for other conditions may also be at risk of developing severe complications.

#### Stimulation and Target-Related Side Effects and Complication

- Complications or side effects associated to the stimulated target and its vicinity are possibly the most frequently encountered problems in patients. Many of the side effects may be adjustable or even reversible. However, this is at the cost of decreased efficacy of stimulation on the symptoms, when the previously effective electrical parameters are changed or the stimulation becomes inactive.

#### Hardware-Related Problems of DBS<sup>[12]</sup>

Deep brain stimulation for the improvement of movement disorders and pain is now a well-established therapy. A strange fact here is that very little has been published on the topic of hardware failure in the treatment of such conditions irrespective of clinical results are. Such device-related problems can cause significant patient morbidity and increased cost of therapy in the form of prolonged antibiotics, in-patient hospitalization, device replacement and repeat surgery.

#### Comparing the advantages and disadvantages of a DBS technique

<u>ADVANTAGES</u>	<u>DISADVANTAGES</u>
The stimulations of DBS are adjustable. It can be programmed noninvasively to alter stimulation in the brain to maximize therapy and minimize side effects.	The implantation of a foreign body carries a risk for infection with it. Thus, certain amount of preoperative care needs to be taken.
Unlike the other surgical or biological methods, the effects of DBS can be reversed. The system can be turned off and taken out if a cure for PD using this method works out.	Equipment failures, such as fractures or erosion, and battery replacement require additional or re-surgery.
DBS is relatively safer than other surgical procedures.	Other devices like anthitheft devices, refrigerator door magnets, etc. may interfere with the system, this may spontaneously turn the system on and off.
With STN and GPi stimulation, all the cardinal features of PD liketremor, bradykinesia, rigidity as well as dyskinesia and motor fluctuations can improve over a period of time.	DBS vitally requires the time and effort on the part of the patient and the surgical therapy team for programming and medication adjustments that are required for optimal control of symptoms.

Nevertheless, in the Western economies, deep brain stimulation therapy continues to expand. Due to this, the implications of hardware-related complications cannot be overlooked. Such complications will without a doubt be reflected in over a period of time in hospital, long-term use of antibiotics, repeat surgery to remove or replace devices, and the associated loss of patient benefit.

### Prognosis of DBS

Even after the surgical process, a considerable number of patients still need to take medication. Many patients experience considerable drop of their PD symptoms and are able to greatly reduce their medications. The amount of this drop varies from patient to patient but can be significantly reduced in most patients. The reduction in dose of medication results in a significant improvement in side effects such as dyskinesias (involuntary movements caused by long-term use of levodopa). In some cases, the stimulation itself can subdue dyskinesias without a reduction in medication.

### Future Prospects of DBS<sup>[2]</sup>

Current DBS systems includes a quadripolar electrode implanted into the brain, in-line extensions running behind the ear, and an internal pulse generator (IPG) implanted either on top of or deep into the pectoralis fascia.

Depending on the current model, IPGs have an ability to accommodate either one or two electrodes. After this, the IPG is programmed transcutaneously via a PDA-like device with a magnet. The patient is given a controller with which they can use to turn the device on and off. Some IPGs can also be programmed to allow the patient to change the voltage within a particular defined set limit. It is likely that some technological features of this therapy will be improved in the near future.

In the future, there is a need to develop ways of simplifying the process of programming and adjusting stimulation factors, which is now being developed with artificial neural networks for spinal cord stimulator programming. The identification of the ideal surgical candidates and the most responsive clinical symptoms in each condition, as well as the expansion of surrogate electrophysiologic and imaging markers contribute to enhanced results and lessen the amount of postoperative time spent for programming.

The ability to program DBS devices through remote access, telephone lines or via the internet might possibly be very useful. A technology being used for cardiac pacemakers as well.

Another area of latest advance that still requires research relates to the power source for DBS. As currently used for movement disorders, the lifespan of the batteries used in regular IPGs is in the order of 5 years. However, for other applications (e.g., anterior capsule DBS for obsessive compulsive disorder), the power necessary to control the patients' symptomatology is significantly higher. Under these circumstances, the frequent replacement of the batteries is of significant concern and needs to be looked upon at. Rechargeable batteries are now present for the treatment of pain syndromes with spinal cord stimulation. The number of occasions the patients need to recharge the IPG changes according to the usage of the device.

Another area of interest would be the development of miniaturized pulse generators that would fit within a drilled out channel in the skull. This would be a significant advancement in the case of DBS for cervical dystonia, where there is a high occurrence of lead fracture due to the dystonic neck movements and postures associated with the disease. Improvements in battery technology will be necessary.

In addition to new developments in pulse generators, newer designs in the electrode collections, geometry, and orientation of active contacts also play an important part in optimizing the therapeutic efficiency and minimizing the hostile effects that are associated with DBS.

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