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Electromagnetic Therapy for Neurological and Neurodegenerative Diseases: ii. Deep Brain Stimulation

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Keywords:

Medical treatment of Parkinson's disease is highly successful early in the disease. However, the majority of patients experience significant complications in later stages when medications no longer adequately control motor symptoms. Deep brain stimulation offers a powerful therapeutic alternative. It involves the surgical implantation of one or more electrodes into specific areas of the brain, modulating or disrupting abnormal patterns of neural signaling within the targeted region. Outcomes are often dramatic with improvements in motor function and reductions in motor complications. Emerging indications for this surgical approach continue to be investigated in parallel with expansions of the therapeutic scope, advancements in neurosurgical techniques, and the precision of stimulation delivery. This article focuses on the nature and purpose of deep brain stimulation, its application to the treatment of neurodegenerative diseases including Parkinson's disease and other movement disorders, dystonia, essential tremor, cognitive behavior, dyskinesia (particularly the levodopa-induced variety), and epilepsy (particularly the focal type). The risks, benefits, and prognosis after treatment with this procedure are also reviewed. New research vistas and prospects are outlined [1-5].

Keywords: Cognitive impairment; Deep brain stimulation; Dementia; Dyskinesia; Dystonia, Essential tremor; Functional impairment; Levodopa-induced dyskinesia; Parkinson's disease

Abbreviations: AFAR: Automated Facial Affect Recognition; BDI-2: Beck Depression Inventory- Edition 2; BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale; BRAIN®: Brain Research through Advancing Innovative Neurotechnology; CBT: Cognitive Behavioral Therapy; CT: Computed Tomography; DaT: Dopamine Transporter scan with Iodine-123 Ioflupane functional imaging; DBS: Deep Brain Stimulation; DVA: (U.S.) Department of Veterans Affairs; EEG (or EKG): Electroencephalography; EM: Electromagnetic (field); EMA: Ecological Momentary Assessment; ERP: Exposure & Response Prevention; ET: Essential Tremor; FDA: (U.S.) Food & Drug Administration; fMRI: functional MRI: FSIQ: Full-Scale Intelligence Quotient; GAI: General Ability Index; GP: Globus Pallidus; GPi: GP-internus; HDE: Humanitarian Device Exemption; IC: Informed Consent; INS: Implantable Neurostimulator; IOCDF: International Obsessive-Compulsive Disorder Foundation; IPG: Implantable Pulse Generator; L-DOPA: Levodopa; LFP: Local Field Potentials; LID: Levodopa-Induced Dyskinesia; MCI: Mild Cognitive Impairment; MDRS-II: Mattis Dementia Rating Scale-Second Edition; MPTP: (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine); MRI: Magnetic Resonance Imaging; NDD: Neurodegenerative Disease; NIH: (U.S.) National Health Institutes; NINDS: (U.S.) National Institute for Neurological Disorders and Stroke; OCD: Obsessive-Compulsive Disorder; PACU: Post- Anesthesia Care Unit; PBS: Peripheral Brain Stimulations; PD: Parkinson's Disease; PI: Principal Investigator; Provoc: Provocation OC task; QOL: Quality of Life; SMA: Supplementary Motor Area; SNC: Substantia Nigra pars Compacta; STN: Subthalamic Nucleus; SWEDD: Scans Without Evidence of Dopaminergic Effect; T: Tesla (a unit of magnetic field); TRBG: Tremors Rigidity Bradykinesia and Gait and Postural Problems; TRS: Tremor Rating Scale; TSST: Trier Social Stress Test; VIM: Ventral Intermediate Nucleus of the Thalamus WAIT-IV: Wechsler Adult Intelligence Test-Fourth Edition; Diseases/disorders cited: Anxiety; Epilepsy; Cerebral palsy; Coagulation abnormalities; Cognitive impairment; Dementia; Depression; Dyskinesia; Dystonia, Epilepsy; Essential tremor; Functional impairment; Heart disease; Hypertension; Levodopa-induced dyskinesia; Obsessive-compulsive disorder; Parkinson's disease; Neurodegenerative diseases; Parkinson's disease, Respiratory disease; Dugs listed: Amantadine; Aripiprazole; Botulinum; Citalopram; Clomipramine; Escitalopram; Fluoxetine; Fluvoxamine; Haloperidol; Levodopa; Paroxetine; Quetiapine; Risperidone; Sertraline; Ziprasidone

Introduction

In a companion article (Part I), I elaborated on Peripheral Brain Stimulations (PBS) for the treatment of neurological and neurodegenerative diseases. In this article, I will focus on Deep Brain Stimulations (DBS). Strong electric currents may cause a localized lesion in the nervous tissue instead of a functional reversible stimulation. This property has been used for neurosurgical

procedures in a variety of treatments such as Parkinson's Disease (PD), focal epilepsy, and psychosurgery. Sometimes, the same electrode is used to probe the brain for finding defective functions before passing the lesioning current (electrocoagulation). PD is a multi-system Neurodegenerative Disease (NDD) with a long premotor phase and variable non-motor manifestations. In the early and mid-stages of the disease, motor dysfunction is pivotal and a major contributor to disability. An effective pharmacotherapy (Levodopa) is available to control the cardinal motor symptoms because the motor functions of PD link strongly with nigrostriatal dopaminergic denervation. Thus, Levodopa continues to be the backbone of pharmacotherapy ever since its introduction for clinical use in PD more than four decades ago. However, this dopaminergic therapy wanes off after the initial few years and motor complications such as unpredictable motor fluctuations and Levodopa-Induced Dyskinesia (LID) emerge and worsen over time. These clinical complications become progressively difficult to treat pharmacologically, leading to electromagnetic (EM) stimulation as a viable therapy such as, importantly, DBS. After a brief history of the development and modeling of brain circuits for movements, I will outline the pioneering work of Benabid who arrested tremors and demonstrated that thalamic stimulation was safer than surgical inactivation, heralding the clinical success of DBS. I will also consider the work of others to reverse other more debilitating symptoms. Also presented will be the DBS system, its programming to different symptoms, and its tuning for given patients. DBS treatment is also detailed for various NDDs (PD and other movement disorders, dystonia, Essential Tremor (ET), dyskinesia, and cognitive impairment. Levodopa-Induced Dyskinesia (LID) is specifically considered. After a discussion of the challenges in the pharmacological treatment of LID and the earlier surgical treatments of LID, the benefits and risks of DBS are outlined as well as the prognosis following this procedure. Current and future research as well as sample clinical trial protocols (both teaching and research trials) are presented and discussed. Prospects of LID will also be discussed [6-12].

History of development and modeling of brain circuits for movement

Understanding the brain circuitry underlying movement-related symptoms of PD and other movement disorders contributed significantly to the development of DBS. It can be traced back several decades:

1947: Development of the stereotactic frame apparatus to target specific brain areas based on the knowledge of brain anatomy and function known at the time and refined through trial-and- error.

The 1950s: Various movement disorders including PD, ET, and dystonia were-treated surgically by inactivating or lesioning brain regions involved in motor control. Surgical targets for PD and ET included parts of the thalamus as well as the globus pallidus (GP). Overall, surgical lesions improved motor symptoms for many patients, though sometimes at the expense of irreversible deficits in other functions.

The 1960s: Several reports noted that high-frequency stimulation of target regions mimicked surgical lesions, while lower-frequency stimulation worsened motor symptoms.

The 1970s: With the advent and wide adoption of Levodopa (L-DOPA) as treatment for PD, interest in ablative surgery for PD waned. Neurophysiologists were also learning more about brain circuits for motor control in animal models. As part of the movement-related circuit, the subthalamic nucleus (STN) was understood to modulate the GP, sending signals through the thalamus to the Supplementary Motor Area (SMA) - a brain area important for planning and coordinating movement. By this time, researchers knew that the loss of dopamine-producing neurons in the basal ganglia contributed to PD, but how such changes disrupted motor circuit activity and function was still not clear, in part because no animal model of the disease was available.

1972: Russian neurophysiologist Natalia Bekhtereva (former U.S.S.R.) suggested that brain stimulation might itself be used as a treatment for movement disorders instead of permanent lesions.

mid-1970s: Mahlon DeLong used electrical stimulation to meticulously characterize the functions of neurons in different brain areas as animals performed movements, leading to a model of basal ganglia circuit organization with parallel, functionally segregated circuits involved in movement and other complex functions.

1975: Medtronic began a neurological division building on its early use of modified pacemakers for neurologica indications [13-16].

The 1980s: Technological advances made chronic stimulation suitable for broad clinical application. Moreover, medical treatment with L-DOPA soon eclipsed neurosurgery as the preferred therapy for PD. Also reports described how a few people succumbed to Parkinson's-like symptoms after taking an illicit drug, the cause being an impurity known as MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), which selectively killed some of the same neurons lost in PD.

1983: (U.S.) National Health Institutes (NIH) scientists developed an MPTP-induced animal model of PD and used it to understand how the disease leads to motor symptoms. It was also used to probe the effects of inactivating parts of the basal ganglia circuit.

The mid-1980s: DeLong lesioned the STN in MPTP-treated monkeys and achieved dramatic results: a rapid reduction in PD-like motor symptoms, including tremor, rigidity, and reduced voluntary movement. The similar results could be obtained using high-frequency stimulation in the STN. These findings provided

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the scientific rationale for therapy targeting the STN. Meanwhile, medical device technology had advanced rapidly in the years since L-DOPA's introduction, and improved electrical pulse generators had developed alongside the first implantable cardiac pacemakers. Investigators supported by the (U.S.) National Institute for Neurological Disorders & Stroke (NINDS) were among the first to use an implanted device for deep brain stimulation in the thalamus as a treatment for chronic pain. Around this time, the limitations of L-DOPAwere becoming apparent, and neurosurgeons began exploring the use of DBS.

1994: Swiss neurosurgeons Jean Siegfried and Bodo Lippitz reported that chronic stimulation in the globus pallidus internus (GPi) improved symptoms in three patients with advanced PD.

1997: The (U.S.) Food & Drug Administration (FDA) approved Medtronic's device for VIM-DBS to treat essential tremor and tremor associated with PD.

2002: The FDA approved DBS in the STN or GPi to treat motor symptoms in advanced PD.

2003: The FDA granted a Humanitarian Device Exemption (HDE) allowing the use of DBS in the GPi and STN for dystonia.

2009: A pivotal clinical trial jointly supported by NINDS, the Department of Veterans Affairs (DVA), and Medtronic demonstrated that DBS for PD was superior to treatment with L-DOPA.

2009: The FDA approved DBS through an HDE.

2016: The FDA allowed DBS treatment for PD patients who had been diagnosed for at least four years but who experience troublesome off periods or dyskinesia [17-25].

Deep Brain Stimulation Becomes A Clinical Success

During a series of surgeries to treat patients with PD and other motor disorders who were not helped by L-DOPA, French neurosurgeon Alim-Louis Benabid observed that applying high-frequency stimulation to the Ventral Intermediate nucleus of the thalamus (VIM) caused the patients' tremor to cease. The treatment's effectiveness was subsequently demonstrated, showing that thalamic stimulation was safer than surgical inactivation. However, while DBS in the thalamus reduced or arrested tremors, it did not reverse other symptoms reported by patients as even more debilitating, including rigidity and akinesia (slowed or reduced voluntary movements). Neurosurgeons, therefore, began to try DBS in other areas. In 1994, Jean Siegfried and Bodo Lippitz reported that chronic stimulation in the internal segment of the GP (GPi) improved symptoms in three patients with advanced PD. Benabid's team also applied DBS to the subthalamic nucleus (STN) in patients with PD. Stimulating the STN improved tremor, rigidity, and akinesia that yielded their best results in patients yet. This successfully bridged basic and clinical neuroscience research. with growing evidence for the safety of DBS and results suggesting earlier intervention in PD may be beneficial, the FDA expanded approval beyond advanced stages of PD. Researchers further examined the use of DBS to alter basal ganglia circuit activity to treat psychiatric disorders such as Obsessive-Compulsive Disorder (OCD). DBS devices targeting other brain areas are now also either approved or/and under development for additional neurological disorders, including epilepsy and chronic pain. Further innovations are emerging with advances in neuroscience and technology. For example, while traditional DBS delivers constant stimulation, newer adaptive devices can self-tune stimulation in response to certain features of a person's brain activity or behavior. One such closed-loop device is approved for the treatment of medically refractory epilepsy, PD, and other disorders. Nonetheless, questions remain about exactly how DBS works, and new directions are likely to emerge through research on the mechanisms that underlie its benefits. In the Appendix, I summarize the conclusions and recommendations of the Expert Consensus Report on Deep Brain Stimulation for Parkinson's Disease [26-35].

Nature and Purpose of Deep-Brain Stimulation

Deep Brain Stimulation (DBS) is a surgical procedure used to treat most common disabling symptoms of neurological disorders, including debilitating motor symptoms of Parkinson's Disease (PD) such as tremor, rigidity, stiffness, slowed movement, and walking problems. The procedure is also used to treat ET, dystonia, LID, and focal epilepsy (epilepsy that originates in just one part of the brain). At present, the procedure is solely used for individuals whose symptoms cannot be adequately controlled with medications. However, only individuals who improve to some degree after taking medication for Parkinson's benefit from DBS. Figure 1 shows inside view an electrode inserted deep in the brain.

DBS system

The DBS system consists of three components: the lead, the extension, and the implantable pulse generator (IPG). The lead (also called an electrode)-a thin, insulated wire-is inserted through a small opening in the skull and implanted into the brain. The tip of the electrode is positioned within the specific brain area depending on the disorder. The extension is an insulated wire that is passed under the skin of the head, neck, and shoulder, connecting the lead to the IPG. The IPG is a surgically implanted, battery-operated medical device (the battery pack) that is similar to a heart pacemaker and has the approximate size of a stopwatch. It delivers electrical stimulation to specific areas in the brain that control movement, blocking the abnormal nerve signals that cause symptoms. The IPG is usually implanted under the skin near the collarbone; in some cases, it may be implanted lower in the chest or under the skin over the abdomen. Once the

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system is in place, and after a period of healing post-surgery, the device is programmed and tuned to sets of parameters that work best for each person over several visits with a neurologist. The therapy works by delivering electrical pulses from the IPG along the extension wire and the lead and into the brain. These pulses change the brain's electrical activity pattern at the target site to reduce motor symptoms [36-40].

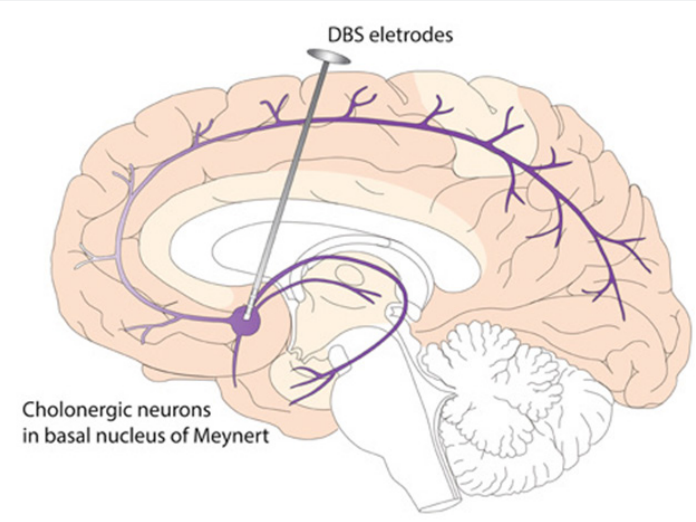

Figure 1: Pictorial showing a deep brain stimulation electrode inserted deep in the brain.

Brain parts targeted

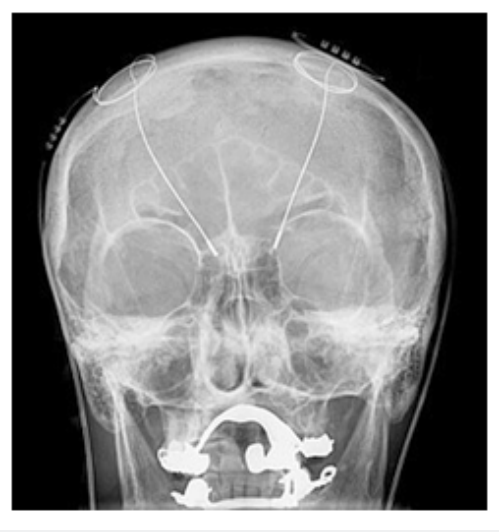

Figure 2: DBS-probes are shown in an X-ray of the skull (Bright white areas around the maxilla and the mandibles represent metal dentures that are unrelated to the DBS device).

Before the procedure, a neurosurgeon uses noninvasive diagnostic imaging-either Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) scanning-to identify and locate the exact target in the brain for the surgery. Most surgeons use microelectrode recording-which involves the insertion of a tiny wire that monitors the activity of nerve cells-to more specifically identify the precise brain area that will be stimulated (Figure 2). for PD treatment, DBS targets parts of the brain that play a role in the control of movement-the thalamus (which relays and integrates sensory and motor information), subthalamic nucleus (which helps direct movement preparation), or globus pallidus (which helps regulate intended movement). DBS for dystonia

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specifically targets the GPi (involved in the regulation of voluntary movement), while DBS for ET targets the thalamus. Different areas of the brain may be targeted for individuals with epilepsy who do not respond well to other therapies [41-45].

Deep brain stimulation treatment for neurodegenerative diseases

DBS is an approved surgical procedure for those neurological conditions that do not respond well to other treatments. It uses electrical stimulation to regulate electrical signals in neural circuits to and from identified areas in the brain to improve movement symptoms. Thus, if DBS causes unwanted side effects or newer, more promising treatments develop in the future, the IPG can be removed and the DBS procedure halted. Also, stimulation from the IPG is easily adjustable-without further surgery-if the person's condition changes. Some people describe the pulse generator adjustments as programming. DBS involves minimal permanent surgical change to the brain. Although minimally invasive, it is nonetheless a surgical procedure that carries some associated risk. There is a low chance the placement of the stimulator may cause bleeding or infection in the brain. Complications may include bleeding and swelling of brain tissue, headaches, seizures, and temporary pain following the surgery. Below are applications to various neurodegenerative diseases (NDDs)

Parkinson's Disease and Other Movement Disorders

Parkinson's disease (PD) is a neurodegenerative disorder that leads to resting tremor, rigidity, slowness of movement, and postural instability. These symptoms are caused by degeneration of neurons in the substantia nigra pars compacta (SNc), one of a group of brain structures known as the basal ganglia and part of a circuit crucial for coordinating purposeful movement. This circuit relies on the chemical messenger (or neurotransmitter) dopamine, which is produced by SNc neurons. As PD progresses and these neurons are lost, reduced dopamine results in abnormal circuit activity and motor symptoms. The molecular precursor to dopamine, L-DOPA (or Levodopa), is used to treat PD. However, people in the later stages of the disease experience off periods when this medication does not work well. Also, L-DOPA treatment can itself trigger uncontrolled involuntary movement; a condition called dyskinesia. DBS is used to treat the most commonly debilitating motor symptoms of PD such as tremors, rigidity, bradykinesia, and gait and postural problems (acronym TRBG) including slowed movement, stiffness, and problems walking. It is used only for individuals whose symptoms cannot be adequately controlled with medication. However, only people who improve to some degree after taking medication for Parkinson's benefit from DBS. A variety of conditions may mimic PD but do not respond to medication or DBS. DBS can offer symptomatic relief in later stages of PD and may reduce requirements for L-DOPA treatment and exposure to its side effects. DBS is also used to treat other movement disorders, including ET, which causes involuntary shaking (often in the hands) that worsens during movement, and dystonia, which causes involuntary muscle contractions and slow, repetitive movements or abnormal postures. Rigidity, tremor, and dopamine-induced dyskinesia in people with PD are treated with stimulation in the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi) (FDA approval, 2002). These same sites are stimulated for the treatment of dystonia (granted by a special FDA approval called a Humanitarian Device Exemption (HDE) in 2003). DBS in the Ventral Intermediate nucleus of the thalamus (VIM) is used to treat ET and tremor as a primary symptom of PD (FDA approval, 1997).

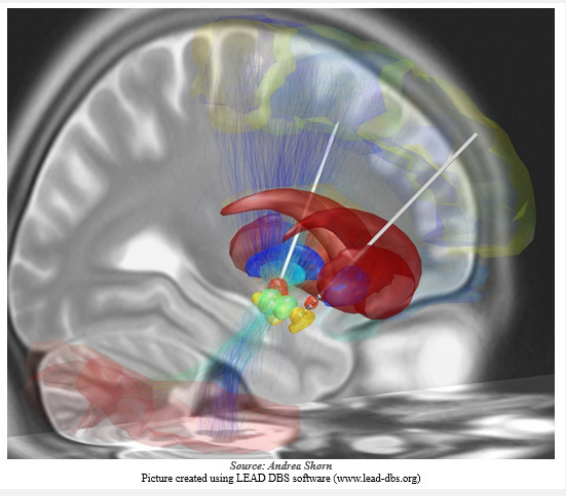

Figure 3: Reconstruction of a bi hemispheric deep brain stimulation electrodes surgically placed in the subthalamic nucleus for Parkinson's disease.

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Most people with PD still need to take medicine after undergoing DBS, but many of them experience a considerable reduction of their motor symptoms and may be able to reduce their medications. The degree of reduction varies by individual but can lead to a significant improvement in side effects such as dyskinesia (involuntary movements caused by long-term use of Levodopa). In some cases, the stimulation itself can suppress dyskinesia without a reduction in medication. DBS does not improve cognitive symptoms in PD and may even worsen them. Therefore, it is not generally used if there are signs of dementia. It must be emphasized that DBS is palliative and does not slow the progression of the neurodegeneration. Figure 3 depicts a reconstruction of bihemispheric DBS electrodes that have been surgically placed into the most common target structure for treatment of PD, the subthalamic nucleus STN (in orange color). Other subcortical structures include the red nucleus (green), the substantia nigra (yellow), the internal (cyan) and external (blue) pallidum and the striatum (red).

Dystonia

For individuals with dystonia, DBS may reduce the disorder's characteristic involuntary muscle contractions that cause such symptoms as abnormal posture, repetitive movements, or twisting. DBS has been shown to reduce both the severity of symptoms caused by dystonia and the level of disability they may cause. People with dystonia may respond better to DBS than medication; therefore, DBS may be an appropriate option for people who have found little or no improvement of symptoms after botulinum toxin injections (often the most effective treatment for some dystonia). DBS may be quicker to reduce symptoms of dystonia that migrates from place to place in the body than dystonia that remains fixed in a single body site, although both groups are likely to see improvement.

Essential Tremor

DBS targeting the thalamus can improve the involuntary movement of the arms, hands, and head that is associated with ET.

Dyskinesia (see the section below on levodopa-induced dyskinesia)

Cognitive impairment

As will be seen in the section below on clinical trial protocols, cognitive impairment may limit patient selection for DBS. During selection, patients need to have sufficient mental capabilities to understand the procedure, its benefits, and limitations. They also need to cooperate with the medical team throughout the process of selection, surgery, and post-surgical follow-up. On the other hand, certain aspects of cognitive performance may decline after DBS, namely when the therapeutic target is the widely used STN. While DBS is generally considered as safe from the cognitive standpoint in well- selected PD patients, especially when looking at measures of global cognition, there is nonetheless a clear risk of post-surgical cognitive decline. The decline seems greater whenever the STN is used, although data concerning other targets is scanter. Post-surgical decline in VF is the most consistently reported cognitive adverse effect in patients undergoing subthalamic DBS. In some studies, intriguing and disturbing dementia cases have been detected a few months after the surgical procedure. It would be important to also explore and assess what these post-surgical cognitive changes imply in terms of quality of life (QOL) and daily functioning.

Epilepsy

Brain stimulation for focal epilepsy (seizures that originate in just one part of the brain) may reduce the number of seizures over time. It is not a single therapy, but it is used along with anti-epileptic drugs.

DBS has been approved as an add-on therapy for adults with focal epilepsy. Another form of treatment, called neurostimulation, uses an implanted monitor in the skull and tiny wires to give small pulses of stimulation to the brain when electrical activity in the brain looks like a seizure.

Levodopa-Induced Dyskinesia

Pharmacological management challenges of levodopa-induced dyskinesia

In ~ 50% of cases, LID emerges after nearly 5 years of Levodopa (LD) therapy, increasing to ~ 90% after a decade. The underlying pathophysiological mechanisms are largely irreversible once they are established. The pharmacological strategies aimed at delaying the emergence of LID and its suppression once it has emerged have their own inherent limitations, namely

The inexorable progression of the neurodegeneration underlying PD (this contributes both to progressive worsening of parkinsonian symptoms as well as LID).

The successful control of dyskinesia by manipulation of dopaminergic treatment is possible on the majority of occasions only at the cost of a poorer control of parkinsonian symptoms (that is, the anti-parkinsonian effects of dopaminergic treatment are coupled with dyskinesia), and Following the demonstration in clinical trials of this latter result has incited some PD patients to delay Levodopa therapy. The parkinsonian symptoms, rather than LID, affect functioning and quality of life (QOL) more, particularly in earlier stages of PD. However, in the view of many movement disorder neurologists, delaying the initiation of Levodopa to prolong its therapy and prevent the emergence of motor complications are unacceptable to most patients. Thus, patients initiated on Levodopa early on have better QOL compared to Levodopa-sparing therapies, which have their particular adverse effects and cost. Moreover, the occurrence of clinically significant and disabling LID is unaffected by delaying Levodopa treatment as the severity of neurodegeneration plays a more important role in this type of LID. Thus, pharmacological

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interventions targeting the dopaminergic mechanisms underlying LID are unlikely to remain successful for prolonged periods because the control of LID achieved by this strategy is at the cost of poorer control of parkinsonian symptoms. Therapies addressing the nondopaminergic mechanisms, with the exception of Amantadine, are yet to show promising and clinically relevant results. Functional neurosurgery, particularly DBS, is currently the standard of care for patients with moderately advanced stages of PD in whom LID has a dose-limiting effect on dopaminergic treatment.

On earlier surgical treatments of levodopa-induced dyskinesia

In the 1950s, surgical treatments consisted of ablative surgeries for the control of parkinsonian symptoms. They had their origin in the serendipitous observation that tremors were relieved by ligation of the anterior choroidal artery to control bleeding. That interest dwindled as Levodopa yielded robust symptomatic improvement. However, in the early 1990s, surgery re-emerged as a treatment of the motor complication of Levodopa. Later, surgery shifted from ablation of the GPi (pallidotomy) to thalamotomy as tremor control was thought to be better with the latter. The concept of DBS also evolved from serendipity. During intra-operative stimulation for clinical localization before thalamotomy, it was noted that tremors were suppressed by high-frequency stimulation. The current era of neurostimulation for movement disorders was ushered in by Benabid's report of the efficacy of chronic thalamic stimulation to control tremor in PD. Then, with the rapidly increasing popularity of DBS, ablative surgeries limited by concerns on irreversibility and adverse effects when done bilaterally are again facing a diminished interest; however, they still have a role in selected patients where DBS is contraindicated or financially not feasible, particularly in resource-poor countries.

Benefits and Risks of Deep Brain Stimulation

Advantages: DBS involves minimal permanent surgical changes to the brain. If DBS causes unwanted side effects or more promising treatments develop in the future, the IPG can be removed and the DBS procedure can be halted. Also, stimulation from the IPG is easily adjustable-without further surgery-if the person's condition changes.

Risks

Although minimally invasive, DBS is nonetheless a surgical procedure. It, therefore, carries some associated risk. There is a low chance that the placement of the stimulator may cause bleeding or infection in the brain. Complications of DBS such as bleeding and swelling of brain tissue may result from mechanical stress from the device but are generally reversible. Other complications may include headache, seizures, and temporary pain following surgery. Also, the hardware may erode or break down with use, requiring surgery to replace parts of the device. Side effects of the stimulation may include numbness or tingling sensations, behavioral changes, as well as balance or speech problems.

Prognosis following the procedure

Most individuals still need to take medication after undergoing DBS. Many PD patients experience a considerable reduction of their motor symptoms after DBS and can reduce their medications. People with dystonia may respond better to DBS than medications in reducing involuntary muscle contractions. DBS targeting the thalamus can improve the involuntary movement of the hands, arms, and head that is associated with involuntary tremors. DBS for epilepsy may reduce the number of seizures over time. However, DBS does not improve cognitive symptoms in PD and indeed may worsen them, so it is not generally used if there are signs of dementia. DBS changes the brain firing pattern but does not slow the progression of the neurodegeneration.

Current and Future Research

The mission of the (U.S.) National Institute of Neurological Disorders & Stroke (NINDS) is to seek fundamental knowledge of the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. The NINDS is a component of the (U.S.) National Institutes of Health (NIH), the leading supporter of biomedical research in the world. The NINDS supports research on DBS to determine its safety, reliability, and effectiveness as a treatment for neurological disorders. NINDS-supported research on brain circuitry was critical to the development of DBS. Researchers are continuing to study DBS and to develop ways of improving it. In one NINDS clinical study, researchers are monitoring the progress of participants who will receive DBS over two years for either PD, dystonia, or ET. Participants will return periodically for examination and answering questions, their DBS placement will be evaluated with MRI, and their neurostimulator will be programmed. The monitoring will include tests of movements, thinking, and memory.

Other NINDS researchers are collecting data on the physiology and effectiveness of DBS therapy and motor and cognitive function in people with either PD, dystonia, or ET who do not respond to other treatment. Data will include the change in motor symptoms measured before and three months after treatment. Intra-operative electrode recordings will investigate the neurophysiological mechanisms of DBS and explore the neural circuits essential for motor and cognitive processing in the basal ganglia. NINDS-supported researchers are developing and testing improved IPGs and new devices and conducting studies to better understand and optimize the therapeutic effect of neurostimulation on neural circuitry and brain regions affected in neurological diseases. Several research directions combine other tools, such as complex imaging of the brain with DBS.

The Brain Research through Advancing Innovative Neurotechnology (BRAIN®) Initiative spurs research to unlock

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the mysteries of the brain and accelerate the development of research and technologies to treat neurological disorders such as PD, essential tremor, and dystonia. For example, in one project aimed at treating ET, researchers are using DBS devices that are capable of recording and stimulating simultaneously to continuously monitor brain activity and deliver stimulation only when necessary to control tremor. This work may provide proof-of-concept for a first of its kind DBS system to treat ET.

Sample Clinical Trial Protocols

(A) Nih teaching protocol for Dbs therapy in movement disorders

Objective-Being a teaching protocol, no research questions are addressed prospectively. The main goals are

a. To provide training in DBS management procedures to fellows and other trainees in all aspects of DBS treatment of medically refractory PD, dystonia, ET, and other indications, including patient selection, physiology, and programming and management after DBS placement.

b. To provide care for patients treated with DBS whose surgery was performed at NIH or another facility and who could participate in other research protocols at the NIH,

c. To maintain a cohort of patients treated with DBS who can participate in other NIH protocols addressing the efficacy of functional surgery and the relevant physiology.

d. To use physiology and efficacy data related to DBS therapy and motor and cognitive function in these patient populations. All the data collected will be an outcome of standard-of-care and all analyses will be retrospective.

e. All treatments under this protocol will be based on the current standard-of-care for DBS therapy.

f. Subjects may be enrolled in the study for its teaching value or to support participation in other DBS protocols or for both reasons.

Study population – It consists of

a. Patients 18 years and older with confirmed medically refractory PD, dystonia, ET.

b. Other indications will be added with subsequent amendments if FDA approval of DBS is so extended.

c. Patients will be offered DBS as a therapeutic option.

Eligibility

a. Patients will be evaluated for their eligibility for the procedure and the risk/benefit balance for surgical therapy assessed.

b. After the evaluation is completed, a decision will be made on recommending or denying the procedure.

c. If the procedure is recommended, patients will be referred for the surgical intervention to the NIH Surgical Neurology Branch or to collaborating surgeons in the community.

d. After surgery, patients will be followed in the NIH-DBS clinic and the DBS programming will be initiated and performed as outlined below.

e. Inclusion criteria - To participate in the study, candidates must meet all of the following criteria:

f. Be 18 years of age or older.

g. Can speak and understand sufficient English or Spanish to provide informed consent and complete study assessments validly.

h. Be able to provide informed consent.

i. Have a clinical diagnosis of idiopathic PD, primary dystonia, or ET:

j. The diagnosis of idiopathic PD will be based on the UK Brain Bank Criteria and confirmed by the Movement Disorders Neurologists in the NIH Parkinson Clinic.

k. The diagnosis of primary (generalized or segmental), hemidystonia, or cervical dystonia will be confirmed on clinical examination in the NIH Movement Disorders Clinic.

l. The diagnosis of ET will be confirmed on clinical examination in the NIH Movement Disorders Clinic (the diagnosis of ET will be based on bilateral, largely symmetric postural or kinetic tremor involving hands and forearms that is visible and persistent). Additional or isolated tremor in the head may be present but there should be the absence of abnormal posturing.

m. History of appropriate response to dopaminergic medication, with at least a 30% improvement in motor UPDRS with L-DOPA by history or in-clinic testing, for the PD patients, or:

n. Patients with tremor-dominant PD that do not respond to dopaminergic therapy and exhibit a tremor score of at least 2 for tremor severity on at least one side of the body on the motor UPDRS examination.

o. Unsatisfactory clinical response to maximal medical management (with trials of both higher and lower doses of drugs), including.

For PD patients

a. Benefit from dopaminergic medication but associated with insufficient duration of action or unacceptable side-effects; or

b. Intractable disabling motor fluctuations (severe off periods, dyskinesias, or freezing spells); or

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c. For ET and dystonia patients:

d. Intractable symptoms of ET or dystonia impacting at least 2 activities of daily living.

e. Interested in being evaluated to undergo DBS, if indicated, to treat medically refractory movement disorder; or

f. Patients already implanted with DBS for continued management.

Exclusion criteria: For those who have not had DBS, candidates will be excluded if they meet any of the following criteria:

Under 18 years.

Clinically significant medical disease that would increase the risk of developing pre- or postoperative complications, including but not limited to:

a. Uncontrolled systemic hypertension with values above 170/100.

b. Unstable heart disease.

c. Unstable respiratory disease.

d. Uncorrected coagulation abnormalities or need for therapeutic anticoagulation cannot be interrupted.

e. Intellectual impairment as determined by a score of less than 70 on the estimated General Ability Index (GAI), a composite score of the Wechsler Adult Intelligence Test-Fourth Edition (WAIT-IV) or equivalent to FSIQ less than 70 (which would render the participant unable to provide informed consent or to comply with the study procedures).

f. Evidence of secondary or atypical parkinsonism/dystonia/tremor as suggested by:

g. History of stroke.

h. Exposure to toxins, neuroleptics, or encephalitis.

i. Neurologic signs of upper motor neuron or cerebellar involvement, supranuclear gaze palsy, or orthostatic hypotension.

j. MR-imaging with evidence indicative of secondary diseases such as iron deposits in putamen, tumor, or stroke (which could cause the movement disorder).

k. Dementia as evidenced by formal neuropsychological evaluation, (MDRS-2) score, and clinical evaluations.

l. Unable to complete cognitive assessments and testing in English or Spanish.

m. Depression or anxiety as evidenced by self-report on the Beck Depression Inventory- 2 (BDI-2) (score above 20) and Beck Anxiety Inventory (BAI), respectively.

n. Unable to undergo MR-imaging because of implanted pacemakers, medication pumps, aneurysm clips, metallic prostheses (including metal pins and rods, heart valves or cochlear implants), shrapnel fragments, permanent eyeliner or small metal fragments in the eye that welders and other metalworkers may have, or if candidates are uncomfortable in small closed spaces (have claustrophobia), or cannot lie comfortably on their back for up to one hour.

o. Pregnant women.

p. Otherwise not eligible for DBS surgery (for example, known inability to undergo anesthesia).

q. For those who have had DBS-1: contra-indications for ongoing stimulation side effects of DBS despite stimulation parameter adjustment.

Post-op care

Patients will be followed-up for at least two years and then will have the option to transfer their care back to the neurologists in the community or continue care with the NIH Neurology team if care in the community is not available.

Outcome Measures: Clinically generated data on outcome measures include:

a. Change in motor symptoms, as measured by the UPDRS-III scale.

b. Changes in quality of life (QOL) for PD patients measured by UPDRS-II and other scales such as the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and the Tremor Rating Scale (TRS) before and 1 year after treatment.

c. Change(s) in levels of effective drug therapy before and after surgery.

d. Change(s) in behavior and performance of activities of daily living.

e. Complications of therapy as measured by the UPDRS-I, -II, and -IV scales before and after surgery and the SF-12 score.

f. Radiographic correlation of DBS electrode position and clinical changes.

g. Neurophysiological mechanisms of DBS and relevant basal ganglia physiology.

h. All data collected will be done as standard-of-care and all analyses will be retrospective.

Research protocols including the ones described in sections (B) and (C) below generally follow the NIH teaching protocol in section (A) above but extend it to answer the research questions respectively posed.

Dbs For Parkinson's Disease, Dystonia, And Essential Tremor

a. Description - The objective is to

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b. study normal human biology and disease pathogenesis,

c. collect physiology and efficacy data related to DBS therapy, and

study motor and cognitive function. During the surgery, the study investigators will do research procedures that include recording information from wires placed in the brain for surgery, stimulating small areas of the brain through the wires, and having participants do tests of movement, thinking, and reasoning.

Recruitment - Up to 200 people (18 years of age or older) with movement disorders that are FDA-approved indications for DBS, including PD, dystonia, and ET. Participants will have tests before and after surgery that are part of standard care for people having DBS surgery. Tests include brain imaging with MRI and CT scans, tests of thinking and memory, and evaluation of their movement disorders and response to DBS.

Inclusion criteria - To be eligible for entry into the study, candidates must meet all the following criteria:

Be 18 years of age or older.

Able to provide informed consent.

Have a clinical diagnosis of

Idiopathic PD based on the UK Brain Bank Criteria and confirmed by the Movement Disorders Neurologists in the NIH Parkinson Clinic.

Primary dystonia (generalized or segmental), hemidystonia, or cervical dystonia confirmed on clinical examination in the NIH Movement Disorders Clinic, or

ET based on bilateral, largely symmetric postural or kinetic tremor involving hands and forearms that is visible and persistent. Diagnosis must be confirmed on clinical examination in the NIH Movement Disorders Clinic. (Note: The diagnosis of ET with additional or isolated tremor in the head may be present but abnormal posturing should be absent).

History of appropriate response to dopaminergic medication, with at least a 30% improvement in motor UPDRS with L-DOPA by history or in-clinic testing for PD patients or patients with tremor-dominant PD that do not respond to dopaminergic therapy and that exhibit a tremor score of at least 2 for tremor severity on at least one side of the body on the motor UPDRS examination.

Unsatisfactory clinical response to maximal medical management (with trials of both higher and lower doses of drugs), including:

Benefit from dopaminergic medication but associated with insufficient duration of action or unacceptable side-effects, or

Intractable disabling motor fluctuations (severe off periods, dyskinesias, or freezing spells), or

Intractable symptoms of ET or dystonia impacting at least 2 activities of daily living.

Agree to undergo DBS if indicated to treat medically refractory movement disorder.

Exclusion criteria - candidates will be excluded if they meet any of the following criteria

Clinically significant medical disease that would increase the risk of developing pre- or post-operative complications, including but not limited to uncontrolled systemic hypertension with values above 170/100.

Active heart disease needing immediate intervention.

Active respiratory disease needing immediate intervention.

Uncorrected coagulation abnormalities or the need for therapeutic anticoagulation cannot be interrupted.

Current or pre-existing life-threatening respiratory disease, such as respiratory failure or ARDS.

Cognitive impairment on Full-Scale Intelligence Quotient (FSIQ) portion of the Wechsler Adult Intelligence Test (WAIT), which would render the participant unable to provide informed consent or to comply with the study procedures (FSIQ less than 70).

Evidence of secondary or atypical parkinsonism/dystonia/tremor as suggested by:

History of CVA.

Exposure to toxins, neuroleptics, or encephalitis.

Neurologic signs of upper motor neuron or cerebellar involvement, supranuclear gaze palsy, or orthostatic hypotension.

a. MR-imaging with evidence indicative of secondary diseases such as iron deposits in putamen, tumor, or stroke, which could cause the movement disorder.

b. Features atypical of idiopathic Parkinson s disease.

c. Dementia as evidenced by:

d. Formal neuropsychological evaluation.

e. Mattis Dementia Rating Scale (DRS-2) score.

f. Clinical evaluations.

g. Depression or anxiety as evidenced by self-report on the Beck Depression Inventory (BDI)-2 (score above 20).

h. Unable to undergo MR-imaging because of implanted pacemakers, medication pumps, aneurysm clips, metallic prostheses (including metal pins and rods, heart valves or cochlear implants), shrapnel fragments, permanent eyeliner or small metal fragments in the eye that welders and other metalworkers may

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have or, if candidates are uncomfortable in small closed spaces (have claustrophobia), or cannot lie comfortably on their back for up to one hour.

i. Pregnant women.

j. Patients with tremor-dominant PD with Scans Without Evidence of Dopaminergic Effect (SWEDD) will be excluded based on clinical and historic information, including the dopamine transporter (DaT) scan with Iodine-123 Ioflupane functional imaging obtained during routine clinical evaluation of PD as needed.

Treatment

a. Participants will have 1-2 outpatient visits before surgery to check eligibility.

b. Eligible subjects will be admitted to the hospital for surgery for about a week.

c. Participants will return for outpatient visits 1, 2- and 3-months surgery. Each visit will last about two hours.

d. All study visits will take place at the NIH Clinical Center in Bethesda, MD.

e. The duration of the study for participants is 3 months.

f. At the end of this surgical study, participants will have the option of continuing post-DBS therapy and care at the NIH (for 2 years) under a related protocol or returning to their own physicians for DBS management and follow-up.

Adaptive Dbs for Obsessive-Compulsive Disorder

Recruitment - Potential participants are referred by their treating clinicians, who will be made aware through direct clinician-clinician letters and emails. Subjects will also learn of the study through consumer advocacy groups such as the International Obsessive-Compulsive Disorder Foundation (IOCDF) and local support group meetings. Enrollment Upon eligibility screened by the Principal Investigator (PI), or his duly appointed representative, and execution of an Informed Consent (IC) that includes decision-making capacity (understanding, appreciation, reasoning, and ability to express a choice). The IC process includes discussions with the patient's family and referring clinician. Medical records will be carefully reviewed to determine the adequacy of past treatments including Cognitive-Behavioral Therapy (CBT).

Eligibility criteria

Inclusion criteria: - These include:

a. A signed informed consent before any specific study procedures being performed.

b. Male or female between ages 21 and 70.

c. At least a five-year history of treatment-refractory OCD that causes substantial subjective distress and impairment in functioning.

d. Y-BOCS minimum score of 28.

e. Failed an adequate trial of at least three of the following:

f. SSRIs: Citalopram; Escitalopram; Fluoxetine; Fluvoxamine; Paroxetine; Sertraline.

g. Failed an adequate trial of Clomipramine.

h. Failed augmentation of one or more of the aforementioned drugs with at least one of the following antipsychotics: Aripiprazole; Haloperidol; Quetiapine; Risperidone; Ziprasidone.

i. Failed an adequate trial of CBT for OCD, defined as 25 hours of documented exposure and response prevention (ERP) by an expert therapist.

j. Stable psychotropic medical regimen for the month preceding surgery.

Exclusion criteria

a. Inability or refusal to give informed consent.

b. Lifetime diagnosis of psychotic disorders such as schizophrenia.

c. Alcohol or substance abuse/dependence within 6 months, excluding nicotine.

d. Deemed at high risk of suicidal behavior or impulsivity (per clinical opinion assessments).

e. Any neurological/medical condition that makes the subject a poor candidate (in the opinion of the surgeon).

f. Pregnancy (confirmed by serum pregnancy test on females of childbearing age (or plans to become pregnant in the next 24 months).

g. Need for diathermy.

Control exclusion criteria

a. Inability or refusal to give informed consent.

b. Lifetime diagnosis of mental illness.

Screening

The purpose of the screening evaluations is to demonstrate that the potential subject is in a stable clinical situation, including a stable medical regimen, and is severely symptomatic. Potential subjects meeting inclusion/exclusion criteria and willing to participate in the study as demonstrated by signing the informed consent will be enrolled and undergo screening consisting of:

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a. Two baseline evaluations spaced approximately over 1-month period.

b. Diagnostic and screening ratings are completed, followed by complete medical, neurological and neurosurgical evaluations. (The raters will be trained and certified in the use of the clinician-administered scales of the study.)

c. The final selection of candidates will be made by consensus of the multi-disciplinary investigating team.

Treatment

If the potential subject continues to meet the above inclusion/exclusion/control exclusion/screening criteria, he/she will proceed to treatment (surgery to implant the DBS system).

a. Phase 1a – Subject will undergo a single-stage DBS surgery, in which bilateral deep brain leads will be implanted under conscious sedation, followed by implantation of a single Implantable Neuro Stimulator (INS), Activa PC+S, under general anesthesia according to the following procedure:

b. A stereotactic head frame will be applied on the morning of surgery, and an intraoperative stereotactic reference CT will be performed. The initial target point within the ventral striatum will be chosen based on the subject's specific anatomy and intraoperative CT that is fused with the preoperative 3T MRI scan. The surgical trajectory will also be planned to avoid prominent vessels and ventricles.

c. The subject will be positioned and prepped. Conscious sedation will be initiated by the anesthesiologist.

d. Following incision and burr hole placement, a burr hole electrode locking mechanism will be secured to the skull with two screws.

e. The coordinates for the ventral striatum target will be set.

f. The Model 3387 DBS electrode (Medtronic Inc., Minneapolis, MN, USA) will be inserted through the guide tube to the target point. An intra-operative CT will be obtained to confirm the position of the DBS electrode. Sedation will be withdrawn.

Test stimulation will be performed to

a. Assess stimulation-induced side effects.

b. Monitor acute changes in behavior to assess anxiety, arousal, and mood.

c. If there are no side effects, the lead will be secured to the skull with the burr hole cap. The free end of the leads will be left out and the incision will be closed.

The headframe will be removed, and general anesthesia will be induced. The pulse generator will then be implanted and connected to the brain lead via extension cables.

If no complications occur, it is expected that the subject will be observed overnight in a Post Anesthesia Care Unit (PACU) and a regular room setting before discharge the following day.

Post-operative follow-up and care

The subject will return to the neurosurgery clinic for post-operative evaluation according to normal clinical protocol (suture removal/wound surveillance). One to two weeks after surgery, the subject will return to the clinic for a routine post-operative examination. Psychiatric measures may be collected at an affiliated psychiatric clinic to establish post-surgical baseline and recording completed. One week after the recording visit, the DBS device will be programmed. Post-surgical 1.5 rs-fMRI scans will also be performed to ensure safety. Participants will be asked to keep their current medications constant for the first 6 months post-surgery. However, clinical circumstances that mandate changes will be allowed. Provocation tasks The Provocation OC task (Provoc) and the Trier Social Stress Test (TSST) will be used to start OC-related distress and distress unrelated to OCD (e.g., performance anxiety), respectively. Three sessions will be videotaped with Automated Facial Affect Recognition (AFAR) system concurrent to recording of local field potentials (LFPs) from VS and scalp electroencephalography (EEG).

Ambulatory Recording: Behavioral states will be assessed using both Ecological Momentary Assessment (EMA) analysis and patient-initiated reports. Subjects will be given a customized Apple Watch and iPhone to log subject-perceived states at various times throughout the day. Subjects will be notified throughout the day to perform a 3-minute, 5-point Likert rating of their OCD-related distress, mood and anxiety levels. Additionally, the system will allow manual labeling of OCD compulsions by the user. CBT augmentation: Starting at 6-months, subjects will receive a two-month (15 sessions) CBT course. Subjects already receiving stable CBT will be allowed to continue it during the study. Participants will be encouraged at study visits to actively confront OC triggers while refraining from ritual engagement. Subjects, especially those who are still habitually avoiding, will be allowed to derive maximal clinical benefit by receiving a two-month refresher course of CBT before entering the double-blind discontinuation phase at 9 months.

Blinded discontinuation: The purpose of the one-month blinded discontinuation period is to confirm clinical benefit. The decision whether to reinstate active DBS at the end of the discontinuation will be based on clinical considerations in discussion with the subject and significant others. The benefits and discomforts will be carefully weighed in arriving at a long-term plan. Long-term follow-up: After the 18 months of the study, the device will remain implanted in those subjects who are doing well clinically. For subjects who are not responsive, it will be explanted, if the surgical risks of explanation are deemed acceptable by the treatment team. The follow-up management

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will be arranged on a case-by-case basis, depending on the geographic location and desires of the subject. DBS therapy management by the investigating team will be guaranteed for at least two years if subjects continue to receive DBS therapy and do not arrange alternative management during that period. Subjects will be encouraged to enroll and participate in long-term follow-up studies to monitor the continued safety of this system. Only subjects who complete their 6-month visit will be allowed to participate in the long-term follow-up study with active stimulation. Attempts will be made to collect all device-related adverse events in all willing participants at 6-month intervals after they exit the study. Subject participation is anticipated to continue for a minimum of 18 months.

Prospects

Novel targets such as the Centro median/perifascicular nucleus of thalamus and the caudal zone incerta are being explored for treating motor complications of PD. Neurostimulation for PD is witnessing several technological advances including robot-assisted DBS and the use of intraoperative magnetic resonance imaging. Conventional cylindrical electrodes currently in use stimulate neurons around the entire circumference of the lead. Directional DBS leads are currently under trial. These carry radially segmented electrodes capable of delivering stimulation in directions orthogonal to the lead. These could theoretically deliver more focused stimulation, minimizing stimulation-related adverse effects. Closed loop neurostimulation (adaptive DBS) is another evolving concept wherein local field potential recorded by the implanted electrodes provide ongoing feedback to regulate current delivery. The current era is also witnessing a fascinating resurrection of the interest in neurorestorative therapies in PD, which had faced a setback following discouraging results from the initial trials of human embryonic mesencephalic transplants. In spite of improvement in imaging markers of nigrostriatal dopaminergic innervation in many participants, overall improvement in motor functions, particularly in older patients and those with more advanced disease, was not satisfactory. Graft-induced dyskinesias, concerns on tumorigenesis and spread of alpha-synuclein pathology to grafted tissue, practical difficulties in the procurement of donor tissue, and importantly, ethical concerns contributed to the initial desperation. With a better understanding of the underlying neurobiology and refined protocols, newer clinical trials have been initiated recently. Newer sources of stem cells, like parthenogenetic stem cells (derived from unfertilized oocytes) or autologous mesenchymal-derived stem cells devoid of ethical concerns, offering additional advantages such as lesser risk of teratoma formation and rejection and wider availability are also evolving. Disease progression and degree of neurodegeneration being one of the major determinants of LID, these neurorestorative therapies could be a viable option to treat LIDs in the future.

Summary and Conclusions

Deep brain stimulation offers a powerful therapeutic alternative to pharmacologic treatment especially during the advanced stages of Parkinson's disease when medications wane off. Better understanding of the brain's electrical circuits combined with technological advances and surgical precision has resulted in dramatic improvements in motor function and reductions in motor complications. Emerging indications for this surgical approach continue to be investigated in parallel with expansions of the therapeutic scope to dystonia, essential tremor, dyskinesia, levodopa-induced dyskinesia, focal epilepsy, and cognitive impairment. Advancements in neurosurgical techniques and better precision of the stimulation delivery have also greatly aided. The risks, benefits, and prognosis after treatment with this procedure are now also better appreciated. Nonetheless, questions remain about exactly how deep brain stimulation works. New directions are likely to emerge through research on the mechanisms that underlie its benefits. However, notwithstanding these impressive advances, it must be remembered that this is a symptomatic treatment that can significantly improve on the current patient's condition but does not alter the course of the patient's disease. A real treatment still rests with the identification and eradication of the root cause(s) of the diseases that have eluded us so far.

Appendix

The expert consensus report on deep brain stimulation for Parkinson's disease

Surgical treatment of Parkinson's disease (PD) was described as early as 1940 and, until recently, had focused on ablative procedures of the thalamus and globus pallidus pars interna (GPi). These surgical treatments (especially pallidotomy) rose to prominence in the era before levodopa (LD) but later re-emerged as popular approaches in the 1990s. They were rapidly replaced in the late 1990s by deep brain stimulation (DBS), mainly as a result of concerns for adverse effects resulting from bilateral lesions as well as the irreversible effects resulting from poorly placed lesions. Furthermore, a new target, the subthalamic nuclei (STN) was identified to be an effective target quickly becoming the most common site for DBS electrode placement. Since its approval by the Food and Drug Administration (FDA) for PD in 2002, more than 70,000 patients have undergone DBS surgery, according to Medtronic Inc. Despite the widespread use of this treatment, several aspects of DBS therapy remain controversial. The purpose of this consensus workshop and its resulting report was to bring together many of the leading experts in the field to address certain issues involving the procedure that remain unresolved.

The charge of this Expert Committee was to provide recommendations to patients, physicians, and other health care providers on several issues involving deep brain stimulation (DBS) for Parkinson's disease (PD). For this purpose, it organized

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and reviewed the literature on the subject. Its findings were:

Patients with PD (a) without significant active cognitive or psychiatric problems and (b) who have medically intractable motor fluctuations, intractable tremor, or intolerance of medication adverse effects are good candidates for DBS. Patients with atypical parkinsonism usually have less favorable outcomes and therefore are not generally considered good candidates for DBS. DBS surgery is best performed by an experienced neurosurgeon with expertise in stereotactic neurosurgery who is working as part of an inter-professional team. Surgical complication rates are extremely variable, infection being the most commonly reported complication. DBS programming is best accomplished by a highly trained clinician and can take 3 to 6 months to obtain optimal results. DBS improves levodopa-responsive symptoms, dyskinesia, and tremor. Benefits seem to be long-lasting in many motor domains. Sub-thalamic nuclei DBS may be complicated by increased depression, apathy, impulsivity, worsened verbal fluency, and executive dysfunction in a subset of patients. Both globus pallidus pars internus (GPi) and subthalamic nuclei (STN) DBS are effective in addressing the motor symptoms of PD. Ablative therapy is still an effective alternative and should be considered in a select group of appropriate patients.

Best results have been reported in patients with advanced PD and

a. excellent LD response,

b. younger age (although there are insufficient data to establish a clear age cutoff). The major concerns with age have been the associated co-morbidities, cognitive decline, higher incidence of LD-resistant symptoms, and higher overall risk of surgical complications. Advanced age may be associated with higher risk of frontal and related executive deterioration following STN DBS),

c. no or few axial LD-unresponsive motor symptoms,

d. no or very mild cognitive impairment, and

e. absence of or well-controlled psychiatric disease. (However, the rigid application of these criteria may lead to the exclusion of a substantial number of persons with PD. While there was consensus on their importance for the selection process, there was less agreement on how to accurately measure them or the cutoff values that should be respected for DBS eligibility.)

Disease duration is not a primary factor in dictating the selection of patients. There is currently no evidence of a neuroprotective effect of DBS to provide a clear rationale for earlier surgery. However, DBS may have a greater beneficial effect on quality of life for patients with less advanced disease. Operating on patients earlier than 5 years following diagnosis may lead to the inclusion of patients with atypical parkinsonism.

Disease severity has been correlated with clinical outcome but there remains no consensus on a specific severity measure and/or cutoff. (Disease severity that leads to disability is influenced by individual factors such as professional status and social function and should be considered.)

LD responsiveness is the single best outcome predictor. (Most centers use a formal LD challenge. A 30% improvement in the Unified Parkinson Disease Rating Scale III score is used as one useful - but not absolute - marker of LD responsiveness. Also, severe tremor resistance to LD therapy is an accepted exception.)

Dementia is the most frequent exclusion criterion for DBS surgery. There was no consensus on the type of testing to establish cognitive impairment or on the level of performance including mild cognitive impairment (MCI) that would exclude patients from receiving DBS.

Surgery is generally deferred in patients with unstable psychiatric conditions until their symptoms have been adequately managed. (The reported increased rate of suicide in patients with PD who have undergone STN DBS underscores the need for a more accurate preoperative psychiatric assessment and treatment of depression as well as the need for careful and detailed postoperative follow-up.) Although a source of debate, the best technique for performing DBS surgery is

a. An experienced surgeon with specific expertise in stereotactic (see Figure 4) and functional neurosurgery who should be working as part of an inter-professional team that includes a movement disorder neurologist, a neuropsychologist, a psychiatrist, and a neurophysiologist.

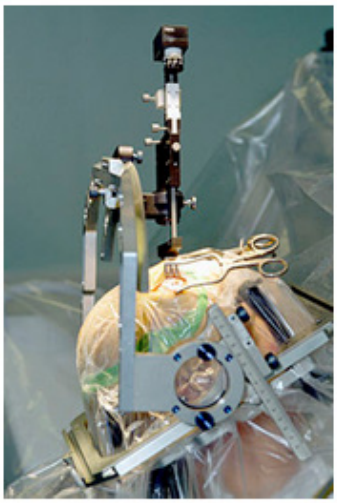

Figure 4: Insertion of electrode during surgery using a stereotactic frame.

b. Both frame-based and so-called frameless navigation techniques are acceptable as long as the surgeon is experienced

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with the chosen method.

c. There is no best means of targeting for DBS surgery. Acceptable imaging modalities for targeting include MRI, CT, ventriculography, and various combinations thereof.

d. Some form of intra-operative neurophysiological monitoring is useful for guiding proper lead placement (microelectrode recording, semi–microelectrode recording, microelectrode or macroelectrode stimulation, and/or tissue impedance monitoring);

e. Some form of postoperative brain imaging (CT or MRI) is performed to check the position of the implanted DBS leads and to evaluate for hemorrhage and pneumocephalus; and

f. The DBS leads may be implanted during one surgery or in two separate procedures. The extension cables and pulse generators may be implanted on the same day as the electrodes or days-to-weeks after, depending on the center's preference. (While of interest, the value of staging or doing unilateral-only implants in a subset of patients, particularly elderly patients or those with cognitive impairment, is currently not known.)

The rates of surgical complications are quite variable, including intracranial hemorrhage (0%-10%; 2% for most centers), stroke (0%-2%), infection (0%-15%), lead erosion without infection (1%-2.5%), lead fracture (0%-15% or less), lead migration (0%-19% or less), death (0%-4.4%), and hardware infection.

Hardware complications are not infrequent. (The absence of standardized reporting of adverse events makes it impossible to accurately determine the adverse event profile.) Most commonly reported hardware-related complications are infection, migration or misplacement of the leads, lead fractures, and skin erosion. MRI procedures are necessary for some patients for evaluation of new or existing intracranial pathology, assessments of DBS lead location in cases with limited benefit or adverse effects and performing additional DBS surgery. (Important considerations are heating – most important, magnetic field interactions and movements, induced currents, and operational/functional disruption of DBS components.)

DBS-programming is best accomplished by a highly trained clinician (eg, neurologist, neurosurgeon, nurse, physician assistant) who understands not only the technical aspects of DBS but also PD-related issues and pharmacological management. (Rigidity and tremor were the most frequent clinical signs targeted for improvement during the first programming session; however, measurement of motor speed and gait assessment may also be useful.) Optimization of DBS parameters is usually attained within 3 to 6 months during 4 to 5 programming sessions. Anti-PD medication reduction should be performed gradually, and excessive early reduction avoided.

Surgical outcomes on

(a) gait and speech are difficult to interpret because they are complex behaviors that may or may not be sensitive to LD or DBS. STN DBS can worsen speech and gait in some patients

(b) the number of falls increases with STN DBS compared with GPi DBS and medical therapy

(c) psychiatric and cognitive co-morbidities (especially depression, anxiety, apathy, psychosis, impulsivity prior to surgery, worsened verbal fluency, executive dysfunction, and processing speed) confound assessment of surgical results. Long-term improvements on motor fluctuations and tremors have been demonstrated for up to 5 years for both STN and GPi DBS.

DBS does not alter disease progression. Over time, patients who had DBS often develop LD-resistant symptoms, including freezing of gait, postural instability, and cognitive decline.

Although thalamotomy and pallidotomy have been largely abandoned and replaced by DBS, ablative therapies may yet have a role in patients with

a. an increased risk of infection,

b. limited access to centers specializing in DBS surgery,

c. not desiring implanted hardware, or

d. unwilling to commit to long-term programming. Potential disadvantages of ablative surgery include mistargeted lesions with permanent neurological deficit(s), suboptimal benefits requiring repeat procedures, and risk of bilateral lesions. For further particulars regarding the selection of experts, the organization of the workshop, its tenor, and findings, patient selection, and corresponding risk-benefit evaluation, refer to the original Report.

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