Deep Brain Stimulation for Refractory Neurological Disorder Management

Subjects: Neurosciences

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Deep brain stimulation (DBS) has been extensively studied due to its reversibility and significantly fewer side effects. DBS is mainly a symptomatic therapy, but the stimulation of subcortical areas by DBS is believed to affect the cytoarchitecture of the brain, leading to adaptability and neurogenesis. The neurological disorders most commonly studied with DBS were Parkinson's disease, essential tremor, obsessive-compulsive disorder, and major depressive disorder.

DBS movement disorder brain stimulation electrical stimulation IPG Parkinson's disease tremor symptomatic neurosurgery neurology

1. Introduction

Deep brain stimulation (DBS), according to the National Institute of Neurological Disorders and Stroke (NINDS), is a surgical method used to manage various neurological conditions that do not effectively respond to conventional therapy. It comprises a neurostimulator surgically implanted battery-powered gadget, which resembles a cardiac pacemaker, that provides electrical stimulation to the appropriate location to block aberrant nerve signals [1]. The first studies with electrical stimulation of the cortex were designed at the end of the 19th century. Still, the main devices were only developed in the mid-20th century, following the scientific and technological achievements of the information age (**Table 1**).

Table 1. Timeline of the deep brain stimulation development.

Year	Description
1874	Electrical stimulation of the human cortex was performed by American physician Robert Bartholow
1947	The stereotactic frame was developed for human neurosurgery. Ernest A. Spiegel developed a stereotactic frame, which was followed in 1949 by the arc-based Leksell frame
1948	J. Lawrence Pool performed the first chronic DBS implantation using an electrode connected to an induction coil
1952	The first stereotactic atlas with coronal photographs of the brain was published
1954	Acute thalamic DBS to target chronic pain. It is considered one of the first functional applications for DBS

Year	Description
	Acute DBS used in pre-lesion targeting for psychiatric disorder
1958	The first definitive cardiac pacemaker was implanted. The first temporary transcutaneous cardiac pacing device was made in 1952
1960	Acute DBS is used to identify lesion targets in essential tremor
	Frequency-dependent effects of DBS reported
1961	The first human intraoperative microelectrode recordings
1963	José Manuel Rodríguez Delgado used a “stimoceiver” to inhibit the aggressive behavior of a bull
1968	Medtronic implantable pulse generator. Also, the first spinal cord stimulator was commercially available
1970s	Computed tomography is used for stereotactic targeting
	Radiofrequency control on an “external” transmitter on DBS systems
1972	The first chronic DBS implant for PD
1973	Thalamic DBS for denervation pain
1977	Periventricular DBS for pain
1980s	MRI is used for stereotactic targeting
	The first fully intracranial DBS devices were available. Also, the long-lasting implantable lithium batteries greatly extend implant life and the maintenance of the device
1980	DBS for multiple sclerosis tremor
1987	DBS of the ventral intermediate nucleus of the thalamus was effective in the management of tremor in individuals with PD
	DBS therapy for the management of tremors was successfully reported by Alim-Louis Benabid
1990	Refinement of battery-driven pacemakers
	DBS reverses motor symptoms in MPTP-induced parkinsonism in monkeys
1994	DBS of the subthalamic nucleus is used in the management of tremors in patients with PD
1997	The FDA approves DBS of the ventral intermediate nucleus of the thalamus for the management of essential tremors
1999	DBS of the anterior limb of the internal capsule was first used to manage obsessive-compulsive disorder

Year	Description
	Visser-Vanderwalle reported the effective use of DBS of the medial thalamus in three patients with Tourette's syndrome
	Globus pallidus internus DBS for the management of refractory dystonia
	Implantable pulse generators with dual-channel technology, which was developed after the creation of dual chamber cardiac pacing in 1998
2000s	DBS therapy is refined for treating essential tremors, PD, and dystonia
2002	US FDA approves DBS in PD
	Quadripolar electrodes are commercially available
2003	The US FDA approves DBS for dystonia
2004	Computer models of DBS
2005	DBS is used to treat depression
2007	DBS is used to treat minimally conscious states
2009	DBS of the bilateral anterior limb of the internal capsule for the management of obsessive-compulsive disorder received a humanitarian device exemption from the FDA
	Rechargeable DBS batteries are available
2010	Sin Alzheimer's pilot trial evaluates the DBS of the fornix
2011	Close-loop stimulation for epilepsy management
	DBS device capable of simultaneous stimulation and recording activities of the local field potential signal processing.
2013	DBS of the subcallosal cingulate gyrus in an anorexia pilot trial
	A closed-loop, responsive DBS system was introduced to treat epilepsy. These devices need to have neural activity sensitivity, leading to a decreased number of side effects and a longer battery life
2015	The emergence of directional DBS leads can lead to an adjustment of the electrical field along the lead axis
2018	The US FDA has approved DBS as an add-on treatment for drug-resistant epilepsy in adults
2020	The US FDA approves a DBS device capable of neurosensitivity and directional leads [2]
	Wireless devices with three Tesla MRI compatibility

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such as substance-related and addictive disorders, aggressive behavior, eating disorders, major depressive disorder, obsessive-compulsive disorder, and refractory Gilles de la Tourette syndrome [3].

DBS implantation was based on lesioning operations performed in the last century to improve neurological symptoms, which resulted in a high percentage of undesired side effects [4]. DBS was considered a safer

Abbreviations: DBS, deep brain stimulation; MRI, magnetic resonance imaging; PD, Parkinson's disease; US FDA, US Food and Drug Administration.

alternative when compared to lesioning procedures due to fewer adverse events, leading to active research and further investigation of neuromodulation approaches for various neurological disorders [5].

Although DBS has been extensively used in managing tremor in individuals with PD, the exact mechanism of action for improving the symptoms in the neural circuitry is not fully understood. It is believed that stimulating the main nerve tracts while inhibiting the nearby neurons may facilitate the movement (**Figure 1**). The zones of uncertainty and cerebellar-thalamic pathways, which decrease tremor and increase dopamine, are also implicated [6]. Moreover, the nosological entity with adequate stimulation parameters and the cytoarchitecture of the brain structure (typically subcortical) are probably related to the efficacy of DBS therapy [7]. In this way, some authors proposed that the leads of DBS can inhibit the structures rich in cell bodies or disinhibit a specific collection of axons, leading to the synchronization of an abnormal pattern, which can facilitate movement or inhibit unusual neuronal activity [8]. Some individuals show a progressive improvement in motor symptoms, suggesting a possible change in the cytoarchitecture of the central nervous system and neuroplasticity [9].

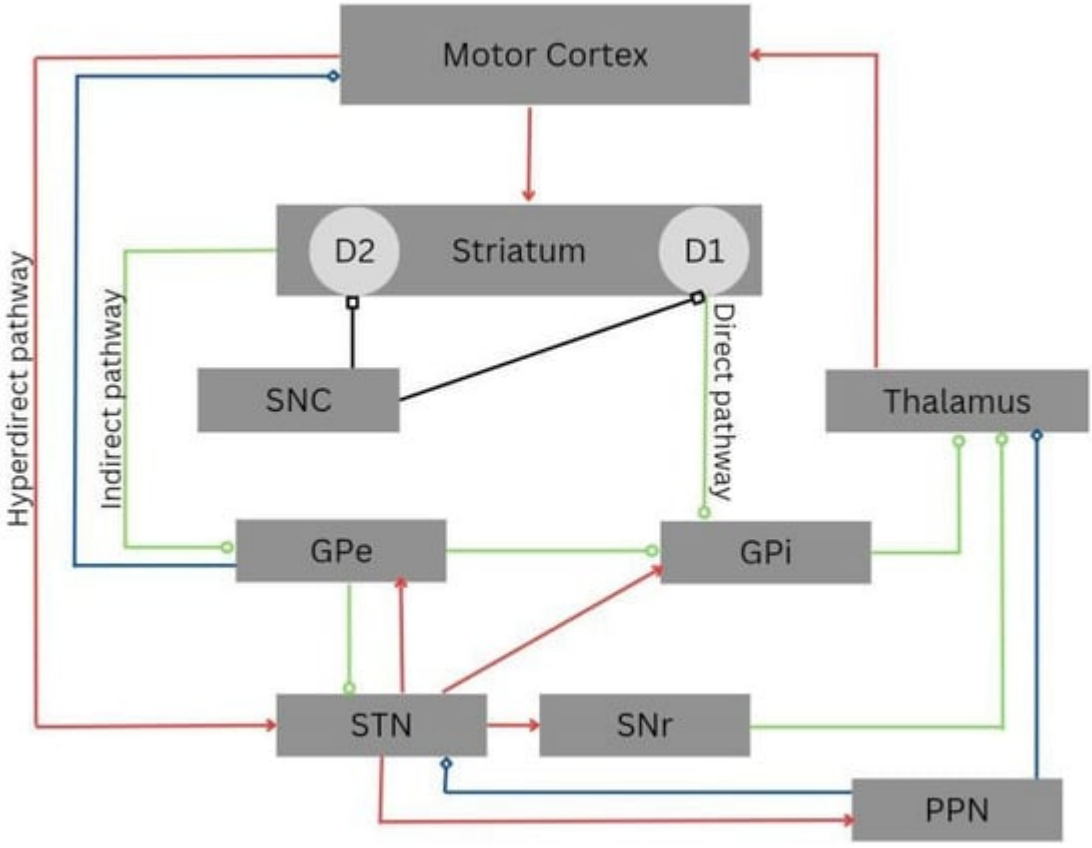

Figure 1. Cortico-basal-ganglia-thalamo-cortical circuitry. The direct, indirect, and hyperdirect pathways are indicated. Green lines denote inhibitory connections (GABAergic), red lines denote excitatory connections (glutamatergic), black lines denote dopaminergic pathways, and blue lines denote mixed cholinergic connections. Notably, the pedunculopontine nucleus (PPN) exhibits anatomic projections to the striatum and cortex. Abbreviations: D1, dopamine receptor D1; D2, dopamine receptor D2; GPe, external globus pallidus; GPi, internal globus pallidus; PPN, pedunculopontine nucleus; SNC, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.

2. Surgical Techniques

The surgical procedure for implanting DBS devices involves several key elements and can vary in approach and technique. A meticulous preoperative airway assessment is necessary since the patient's head will be immobilized in a stereotactic headframe during the DBS procedure. Monitored anesthesia care with sedation is the most commonly used anesthesia technique during lead implantation for most patients. This leads to minimal effects of anesthetic agents on neuronal background and spike activity during microelectrode recording localization [10].

The primary components of a fully implanted DBS system include the precise implantation of an intracranial electrode, which involves surgically placing an intracranial electrode into the specific target area within the brain where stimulation is intended. The implant lead extension connects the intracranial electrode to the power-generating and programming sources. An internal pulse generator that generates electrical pulses for stimulation is implanted under the skin, typically in the chest or abdomen [11].

The surgical procedure for DBS can differ among medical facilities and centers. The most common approach for implanting the device is general anesthesia. On the other hand, local anesthetics are applied for device maintenance that does not involve lead manipulations such as battery changes [12]. A Leksell stereotactic frame is sometimes securely attached to the patient's head under local anesthesia. This frame is used for precise targeting during the surgery. After securing the frame, stereotactic imaging is performed to aid in planning the electrode's target and trajectory. Various software packages are available for this purpose, and they can employ coordinate frame-based, frameless, or robotic stereotaxic procedures [13].

Overall, the choice of approach and surgical technique may depend on the specific patient, the target area within the brain, and the preferences and expertise of the medical facility performing the procedure.

The surgical procedure for DBS involves the following steps: The patient is positioned semi-recumbent, and the scalp is prepared by clipping the hair and applying betadine solution to ensure sterility. Then, a coronally oriented incision is typically made, spanning Kocher's point bilaterally on the scalp. However, alternative incision techniques can be used. The scalp is opened to expose the skull's frontal bone. A hole, or trephination, is made approximately 1 cm anterior to the coronal suture and at least 2 cm lateral from the midline of the skull. The dura mater is coagulated and carefully incised. Special care is taken to minimize cerebrospinal fluid loss. A guide cannula is inserted into the brain, typically about 1.0 to 1.5 cm above the intended target area. Microelectrode recording is used to identify the electrophysiological characteristics of the target structure and determine its dorsal-ventral boundaries. This helps with the precise placement of the macrolectrodes. Once a suitable tract is identified, the microelectrodes are removed, and a permanent macroelectrode is inserted into the target structure [14].

Stimulation tests are conducted at each electrode contact point to evaluate for adverse effects and clinical efficacy. This ensures that the stimulation is effective and safe. The proper placement of the DBS electrode is verified through intra-operative fluoroscopy [15]. If placement is confirmed, the electrode is affixed to the skull. The incision is closed, completing the surgical procedure. These steps ensure the precise placement of the DBS electrode in

the intended target area within the brain while minimizing complications. It is a delicate and highly specialized procedure performed by neurosurgeons with expertise in DBS. In some DBS centers, microelectrodes are advanced through the cannula for recording or stimulation. The microelectrode stimulation can define the anatomical location of the electrode, which can be further assessed with directional leads and changing the voltage and current. This is important for the evaluation of possible side effects related to the localization of the leads, such as paresthesia, muscle contractions, and flashes of light [16]. Also, during the insertion of the DBS lead, fluoroscopy can be used to confirm the location of the lead in a two-dimensional view (**Table 2**).

Table 2. Stimulus-induced side effects in DBS surgical procedures.

Adverse Event	DBS Target	Region Related to the Side Effect	Correctional	Reference
Dyskinesias	GPe, GPi, STN	Excessive modulation of the indirect pathway	Decrease frequency. Removal of leads	[17]
Dysphonia, dysarthria	STN, GPi	Internal capsule and associate circuits of basal ganglia	If possible, change the hemisphere	[18]
Muscle contractions	STN, GPi, VOP	Corticospinal tract of the internal capsule	Move posterior	[19]
Mood changes, risky behavior	GPi, STN	Associative and limbic circuits of the basal ganglia	Move dorsal	[20]
Oculomotor disturbances	GPi, STN	Internal capsule for conjugate eye deviation Third nerve medial to STN for ipsilateral eye movements	Move medial; Move lateral	[21]
Paresthesia	Vim, STN, VOP, PPN	Lemniscal fibers	Move anterior	[22]
Phosphenes	GPi	Optic tract	Move medial	[23]
Sadness, depression	STN	Ventromedial STN, substantia nigra pars reticularis	Move dorsal	[24]
Verbal fluency, working memory	GPi, STN	Associative circuits of the basal ganglia	Move dorsal	[25]
Weight gain	STN, GPi	Normalization of energy metabolism	Increase physical activity	[26]

Abbreviations: DBS, deep brain stimulation; GPe, globus pallidus externus; GPi, globus pallidus internus; PPN, pedunculopontine nucleus; STN, subthalamic nucleus; Vim, ventral intermediate nucleus of the thalamus; VOP, posterior ventral oral nucleus.

Following the initial procedure, the patient undergoes general anesthesia, and the intracranial electrodes are connected to extension wires. These wires are placed under the skin, behind the ear, and down to the chest through a tunnel. An additional incision is made below the clavicle to create a pocket for the internal pulse generator. Then, the extension wires are connected to the internal pulse generator, and the system's impedances are checked to ensure proper function [27]. Patients are usually admitted for observation for one night after the

procedure. After, an outpatient appointment is scheduled within eight weeks of the procedure for device activation and programming, ensuring the DBS system is optimized for their specific needs. When treating Parkinson's disease, programmers often begin with a monopolar configuration to stimulate the brain. In this configuration, a contact electrode is the cathode with a negative voltage. In contrast, the outer casing of the implantable pulse generator serves as the anode with a positive voltage. If adverse effects arise at higher voltages, a bipolar stimulation configuration can be used. In this configuration, one contact serves as the cathode and another as the anode, limiting current spread into adjacent brain regions that cause side effects. This technique is useful in ensuring that therapy remains within the therapeutic range and does not induce any side effects (**Figure 2**) [28].

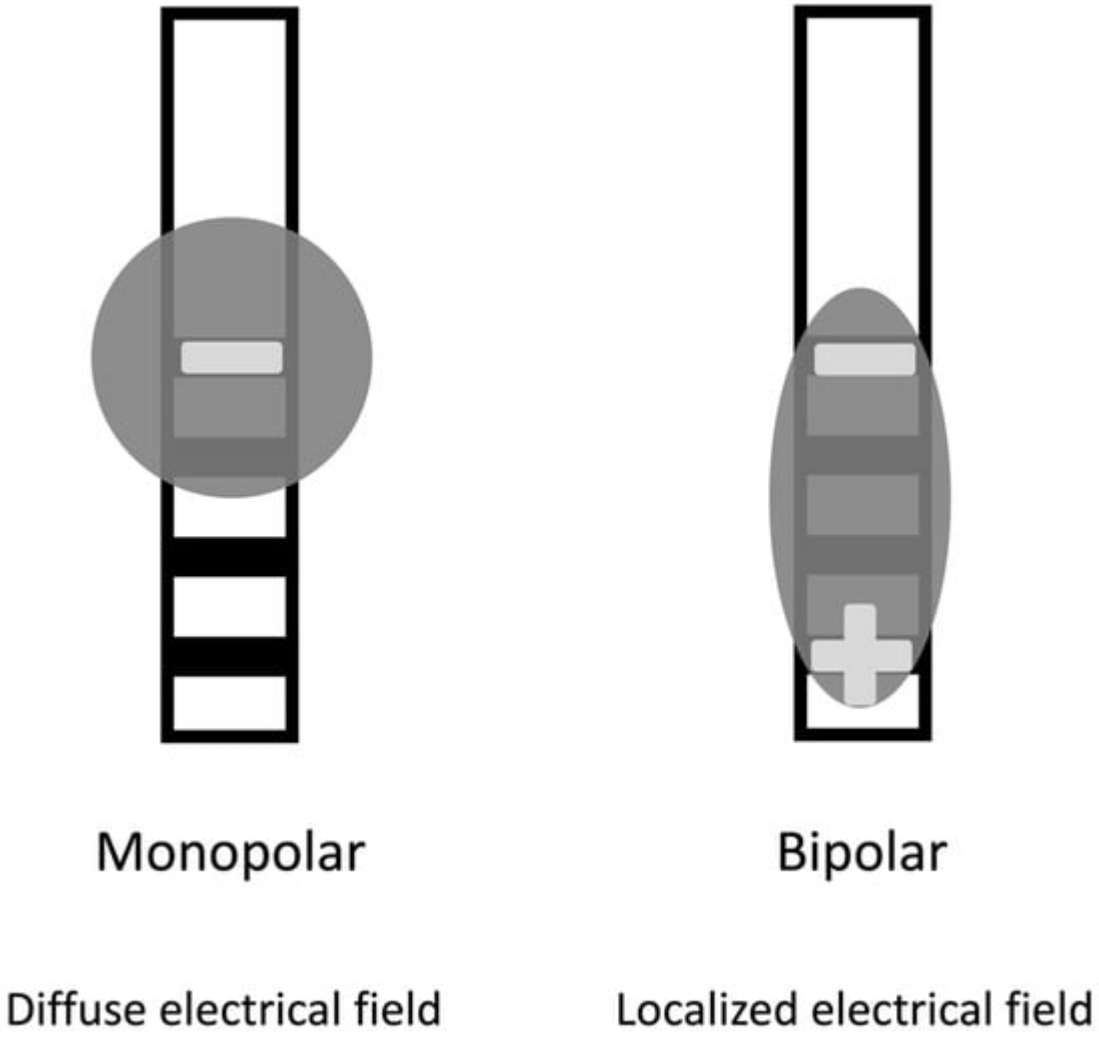

Figure 2. Modes of stimulation. The monopolar (cathodic) stimulation has a spreading negative current in all directions. In the bipolar, the electrode has both anodic and cathodic contact points, with a narrower and more intense flow of current between them.

The implantable pulse generators contain a battery, power module, central processing unit, program memory, and a microprocessor. They are the DBS system's active components and control the devices' functions, including activation, deactivation, pulsing parameters, internal diagnostics, and communication with external devices. Features of implantable pulse generators for deep brain stimulation are described in **Table 3** [29].

Table 3. Features of implantable pulse generators for deep brain stimulation.

Model	No. of Chambers	Weight (g)	Size (mm)	Rechargeable Cell	Frequency Range (Hz)	Pulse Width (μs)	Temporal Fractionation	Current Fractionation	Directional Lead	Magnetic Resonance Safety	Local Field Potential
St. Jude (Abbott) Infinity 5 [a]	2	49	56 × 50 × 13	No	2–240	20–500	Multi-stim set	Coactivation	Yes	Conditional: more than 1.5T requires specific conditions	No
St. Jude (Abbott) Infinity 7 [a]	2	58	67 × 50 × 14	No	2–240	20–500	Multi-stim set	Coactivation	Yes	Conditional: more than 1.5T requires specific conditions	No
Boston Scientific Vercise PC [b]	2	55	71 × 50 × 11	No	2–255	10–450	Areas	Multiple independent current controls	Yes	Unsafe failure of the equipment	No
Boston Scientific Vercise Gevia [b]	2	26	51 × 46 × 11	Yes	2–255	20–450	Areas	Multiple independent current controls	Yes	Conditional	No
Boston Scientific Vercise Genus P8/P16 [b]	1 or 2	58	72 × 50 × 12	No	2–255	20–450	Areas	Multiple independent current controls	Yes	Conditional	No
Boston Scientific Vercise Genus R16 [b]	2	27	52 × 46 × 11	Yes	2–255	20–450	Areas	Multiple independent current controls	Yes	Conditional	No
Medtronic Activa PC [c]	2	67	65 × 49 × 15	No	2–250	60–450	Interleaving	No	No	Conditional, certain requirements	No
Medtronic Activa	2	40	54 ×	Yes	2–250	60–450	Interleaving	No	No	Conditional, 1.5T MRI	No

Model	No. of Chambers	Weight (g)	Size (mm)	Rechargeable Cell	Frequency Range (Hz)	Pulse Width (µs)	Temporal Fractionation	Current Fractionation	Directional Lead	Magnetic Resonance Safety	Local Field Potential
RC [c]			54 × 9								
Medtronic Activa SC [c]	1	44	55 × 60 × 11	No	3–250	60–450	Interleaving	No	No	Conditional, but not eligible for full-body MRI	No
Medtronic Perpcept PC [c]	2	61	68 × 51 × 12	No	2–250	20–450	Interleaving	No	No	Conditional, 3T, and 1.5T MRI	Yes

[a] https://www.neuromodulation.abbott/us/en/parkinsons/infinity-for-deep-brain-stimulation.html, accessed on 15 October 2023. [b] https://www.bostonscientific.com/en-US/products/deep-brain-stimulation-systems.html, accessed on 15 October 2023. [c] https://www.medtronic.com/us-en/patients/treatments-therapies/deep-brain-stimulation-parkinsons-disease/about-dbs-therapy/dbs-products.html, accessed on 15 October 2023.

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