Review Article

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Review Article on Deep Brain Stimulation (DBS) for advanced Parkinson's Disease (PD) and its outcome.

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Introduction:

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized primarily by bradykinesia, resting tremor, rigidity, and postural instability. In addition to motor manifestations, non-motor symptoms including cognitive impairment, autonomic dysfunction, sleep disturbance, depression, and sensory abnormalities substantially contribute to morbidity.

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The condition is typically associated with a PD is the second most common neurodegenerative disease worldwide and results mainly from degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), leading to depletion of dopamine within the striatum.[1–3] Parkinson's disease global prevalence is estimated at over 1% in adults over 60, with an annual incidence ranging from 5 to more than 300 per 100,000 person-years depending on age.[3]

The pathophysiology of PD is closely linked to dysfunction of the cortico-basal ganglia-thalamo-cortical circuitry. The basal ganglia are composed of interconnected subcortical nuclei including the striatum (caudate nucleus and putamen), globus pallidus externa (GPe), globus pallidus interna (GPi), subthalamic nucleus (STN), substantia nigra pars compacta (SNc), and substantia nigra pars reticulata (SNr). These nuclei regulate motor planning and execution through complex excitatory and inhibitory neurotransmitter pathways.[2–5] Within the basal ganglia, glutamate serves as the principal excitatory neurotransmitter, while gamma-aminobutyric acid (GABA) mediates inhibitory transmission. Dopamine from the SNc modulates striatal neuronal activity through D1 and D2 receptors. Activation of D1 receptors facilitates the "direct pathway," whereas activation of D2 receptors suppresses the "indirect pathway."[3–6]

In the normal motor circuit, cortical glutamatergic projections excite the striatum. The direct pathway consists of inhibitory GABAergic projections from the striatum directly to the GPi/SNr. Inhibition of GPi/SNr reduces their tonic inhibitory output to the thalamus, thereby disinhibiting thalamocortical projections and facilitating movement. Conversely, the indirect pathway projects from the striatum to the GPe, then to the STN, and finally to the GPi/SNr. Activation of this pathway increases inhibitory output from the GPi/SNr to the thalamus, thereby suppressing movement.[2–5] A third pathway, termed the "hyperdirect pathway," directly connects the cerebral cortex to the STN through glutamatergic projections. This pathway provides rapid excitatory input to the STN, which subsequently activates the GPi/SNr and transiently suppresses motor

activity. The STN therefore occupies a central position in the regulation of basal ganglia output and motor control.[1 2]

In PD, degeneration of nigrostriatal dopaminergic neurons disrupts the physiological balance between the direct and indirect pathways. Reduced dopaminergic stimulation of D1 receptors decreases activity within the direct pathway, while loss of dopaminergic inhibition of D2 receptor-bearing neurons enhances indirect pathway activity. The net effect is excessive activation of the STN and GPi/SNr, leading to increased inhibitory GABAergic output to the thalamus and diminished thalamocortical excitation. This abnormal circuitry manifests clinically as bradykinesia and rigidity.[3–8] In addition to altered firing rates, PD is associated with abnormal neuronal synchronization and oscillatory activity within the basal ganglia network, particularly in the beta frequency range. These electrophysiological abnormalities are believed to contribute significantly to motor impairment and form the physiological basis for deep brain stimulation (DBS). High-frequency DBS targeting the STN or GPi modulates pathological network activity, restores functional circuit balance, and improves motor symptoms in appropriately selected patients.[6 8]

History of Deep Brain Stimulation Surgery for Parkinson's Disease

The development of deep brain stimulation (DBS) for Parkinson's disease (PD) evolved from earlier stereotactic lesioning procedures performed during the mid-twentieth century. Before the advent of levodopa therapy, ablative surgeries such as thalamotomy and pallidotomy were widely used for the treatment of tremor and rigidity in PD. These procedures targeted deep motor nuclei of the basal ganglia and thalamus using stereotactic techniques developed in the 1940s and 1950s.[9 10] During stereotactic lesioning surgeries, investigators observed that electrical stimulation of deep brain structures could transiently suppress tremor. Early studies demonstrated that low-frequency stimulation often aggravated tremor, whereas high-frequency stimulation produced effects similar to those of lesioning.[9] These findings laid the physiological foundation for chronic therapeutic stimulation of deep nuclei.

A major breakthrough occurred in 1987 when Alim Louis Benabid and colleagues reported successful high-frequency stimulation of the ventral intermediate nucleus (VIM) of the thalamus in patients with Parkinsonian tremor.[11] This landmark study demonstrated that chronic electrical stimulation could effectively suppress tremor while avoiding the irreversible complications associated with bilateral thalamotomy. Subsequently, Benabid's group published long-term results confirming sustained tremor control with chronic VIM stimulation in PD and essential tremor.[12 13]

The success of thalamic DBS encouraged exploration of other basal ganglia targets implicated in PD pathophysiology. In the early 1990s, renewed understanding of basal ganglia circuitry highlighted the role of the subthalamic nucleus (STN) and globus pallidus interna (GPi) in motor dysfunction. Functional models proposed that overactivity of the STN and GPi contributed to the hypokinetic manifestations of PD through excessive inhibitory output to the thalamus.[14]

Building on these experimental and physiological insights, Pollak, Benabid, and colleagues pioneered STN stimulation in patients with advanced PD during the mid-1990s. Bilateral STN DBS was found to improve bradykinesia, rigidity, tremor, motor fluctuations, and levodopa-induced dyskinesia.[15] The procedure rapidly gained international acceptance because it provided substantial symptomatic improvement while permitting reduction of dopaminergic medication requirements.

Parallel advances were made with GPi DBS, particularly for dyskinesia and motor fluctuations. GPi stimulation emerged as an effective alternative target with a favorable neuropsychiatric profile in selected patients. By the late 1990s and early 2000s, randomized controlled trials established DBS as a superior therapy compared with best medical treatment for advanced PD with motor complications.[16]
Over the following decades, DBS technology continued to evolve with improvements in neuroimaging, stereotactic targeting, microelectrode recording, implantable pulse generators, and programming algorithms. Modern systems now offer directional leads,

rechargeable batteries, adaptive stimulation paradigms, and closed-loop technologies aimed at improving efficacy while minimizing adverse effects. DBS has become an established treatment modality for medically refractory PD and remains one of the most significant advances in functional neurosurgery.[9] [14]

Surgical Procedure of Deep Brain Stimulation and Device Programming

Deep brain stimulation (DBS) surgery for Parkinson's disease (PD) involves stereotactic implantation of electrodes into deep brain nuclei, most commonly the subthalamic nucleus (STN) or globus pallidus interna (GPi). Careful patient selection, neurological evaluation, neuropsychological assessment, and preoperative MRI are essential before surgery.[17]

On the day of surgery, a stereotactic frame or frameless navigation system is used for accurate targeting. Burr holes are created, and microelectrode recording (MER) may be performed to identify characteristic neuronal activity within the target nucleus. Intraoperative test stimulation helps assess symptom improvement and detect adverse effects. Once the optimal target is confirmed, permanent DBS leads are implanted and fixed to the skull.[18]

In a second stage, extension wires are tunneled subcutaneously and connected to an implantable pulse generator (IPG) placed in the infraclavicular chest wall. Postoperative imaging is performed to confirm lead position and exclude complications.[17] [19]

Programming of the IPG usually begins several weeks after surgery. Using an external programmer, clinicians adjust stimulation parameters including active contact, amplitude, pulse width, and frequency to maximize motor benefit while minimizing side effects. Initial programming commonly involves monopolar review of each contact to determine therapeutic and adverse-effect thresholds. Long-term follow-up is required because stimulation settings often need modification according to symptom progression and medication changes.[20]

Outcome of Deep Brain Stimulation in Parkinson's Disease

Deep brain stimulation (DBS) has become an established treatment for patients with advanced Parkinson's disease (PD) who experience disabling motor fluctuations, dyskinesia, or medically refractory tremor despite optimized pharmacological therapy. Numerous clinical studies have demonstrated significant improvement in motor symptoms, quality of life, and reduction of medication-related complications following DBS.[21] [22]

Subthalamic nucleus (STN) DBS and globus pallidus interna (GPi) DBS are the two most widely used targets in PD. Both targets provide substantial improvement in tremor, rigidity, bradykinesia, and dyskinesia. STN DBS is often associated with greater reduction in dopaminergic medication requirements, whereas GPi DBS may offer better control of dyskinesia and a comparatively favorable neuropsychiatric profile in selected patients.[22] [23]

Randomized controlled trials have shown that DBS combined with best medical therapy produces superior motor outcomes compared with medical therapy alone. Significant reduction in "off" time and improvement in activities of daily living have been consistently reported. Improvements in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores are commonly observed after surgery.[21] [24]

In addition to motor benefits, DBS may improve quality of life, sleep, and certain aspects of non-motor symptoms. However, cognitive decline, speech disturbance, gait freezing, balance impairment, mood changes, and neuropsychiatric complications may occur in some patients during long-term follow-up. Careful patient selection and postoperative programming are therefore essential to optimize outcomes.[23] [25]

Long-term studies have demonstrated sustained motor improvement for many years after DBS, although progression of non-dopaminergic features of PD may limit functional independence over time. Despite disease progression, DBS remains one of the most effective surgical therapies for advanced PD and significantly reduces motor complications and medication burden in appropriately selected patients.[26]

Surgical and Brain Risks[27]

- **Brain Bleeding:** Bleeding inside the skull or brain tissue (hemorrhage) can cause weakness, numbness, or a stroke.
- **Confusion:** Temporary mental confusion or trouble focusing often occurs right after the procedure.
- **Seizures:** Uncontrolled brain activity may happen during or right after wire placement.
- **Infection:** Swelling, pain, or fluid leakage can occur at the surgery site on the head or chest.

Hardware and Device Complications[27]

- **Lead Movement:** The thin wire placed in the brain can shift or move out of place.
- **Broken Parts:** The wires or the battery device under the skin can break, fracture, or malfunction.
- **Skin Erosion:** The implanted pulse generator in the chest can rub against or wear through the skin.

Conclusion:

Deep brain stimulation (DBS) has revolutionized the surgical management of advanced Parkinson's disease (PD) and remains one of the most effective therapeutic options for patients with disabling motor complications refractory to optimized medical therapy. Advances in the understanding of basal ganglia circuitry and the pathophysiology of PD have established the scientific basis for DBS targeting of structures such as the subthalamic nucleus and globus pallidus interna. By modulating abnormal neuronal activity within the cortico–basal ganglia–thalamo–cortical network, DBS significantly improves tremor, rigidity, bradykinesia, motor fluctuations, and levodopa-induced dyskinesia. Modern DBS surgery combines high-resolution neuroimaging, stereotactic navigation, electrophysiological mapping, and sophisticated implantable pulse generator technology to achieve precise and individualized therapy. Careful patient selection, meticulous surgical technique, and long-term postoperative programming are essential determinants of successful outcomes. Although DBS does not halt disease progression, it substantially enhances quality of life, functional independence, and daily activities in appropriately selected patients.

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) plays a vital role in Parkinson's disease research as a powerful chemical tool used to create reliable animal models that mimic human parkinsonism. It acts as a selective neurotoxin that damages dopamine-producing brain cells, helping scientists study how the disease develops and test new treatments.[28]

Long-term studies have demonstrated sustained motor benefits and reduction in medication burden following DBS. Nevertheless, progression of non-dopaminergic symptoms, cognitive decline, gait disturbance, and neuropsychiatric complications may influence long-term functional outcomes. Ongoing technological innovations including directional leads, adaptive stimulation, and closed-loop systems continue to improve therapeutic precision and safety. Overall, DBS represents a major milestone in functional neurosurgery and continues to play a pivotal role in the multidisciplinary management of Parkinson's disease.

Conflict of Interest:

None of the coauthors declared any conflict of interest.

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