

2025

The role of functional neurosurgery in Parkinson's disease: a focus on deep brain stimulation

<https://hdl.handle.net/2144/52357>

"Downloaded from OpenBU. Boston University's institutional repository."

BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

**THE ROLE OF FUNCTIONAL NEUROSURGERY IN PARKINSON'S DISEASE:
A FOCUS ON DEEP BRAIN STIMULATION**

by

NEVAEH BRUMFIELD

B.S., Spelman College, 2024

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2025

© 2025 by
NEVAEH BRUMFIELD
All rights reserved

Approved by

First Reader

Gwynneth Offner, Ph.D.
Associate Professor of Medicine

Second Reader

Karen Symes, Ph.D.
Associate Professor of Biochemistry and Cell Biology

DEDICATION

I dedicate this work to my mentors at Boston University Chobanian & Avedisian School of Medicine, whose guidance and belief in me have shaped my academic journey, and to my wonderful family, whose unwavering love and support have been my foundation through it all.

**THE ROLE OF FUNCTIONAL NEUROSURGERY IN PARKINSON'S DISEASE:
A FOCUS ON DEEP BRAIN STIMULATION**

NEVAEH BRUMFIELD

ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms that significantly impair quality of life. While pharmacologic therapies such as levodopa remain the first-line treatment, their efficacy diminishes over time, and long-term use is often associated with adverse effects such as motor fluctuations and dyskinesias. Deep brain stimulation (DBS), a functional neurosurgical technique, has emerged as a powerful intervention for advanced PD, particularly for patients whose symptoms are refractory to medication. This thesis explores the clinical role and optimization of DBS by comparing it to pharmacologic therapies and lesional procedures, and by evaluating surgical approaches (awake vs. asleep) and target nuclei (subthalamic nucleus [STN] vs. globus pallidus internus [GPi]). The analysis draws upon standardized motor and non-motor assessment tools, complication profiles, and quality-of-life outcomes. Findings suggest that DBS consistently provides superior motor benefits compared to pharmacological and lesional treatments, particularly in terms of reducing tremors, bradykinesia, and medication burden. STN targeting offers greater potential for medication reduction, while GPi may be preferable in patients with pre-existing psychiatric vulnerabilities.

Additionally, emerging evidence supports the safety and efficacy of asleep DBS, offering similar long-term outcomes to traditional awake surgery with improved patient comfort. Finally, the thesis emphasizes the importance of individualized treatment planning, incorporating factors such as patient age, disease duration, brain atrophy, and baseline symptom profile to enhance DBS outcomes. These insights contribute to a growing body of evidence supporting DBS as a personalized, adaptable treatment modality for managing advanced Parkinson's disease.

TABLE OF CONTENTS

DEDICATION	iv
ABSTRACT	v
TABLE OF CONTENTS	vii
LIST OF TABLES	viii
LIST OF FIGURES	ix
LIST OF ABBREVIATIONS	x
INTRODUCTION	1
Background.....	1
Clinical and Research Interest.....	3
Specific Aims	5
Awake vs Asleep DBS Intervention -Impact of Procedural Approaches.....	24
Target Selection – STN vs GPi	28
Improving Candidate Selection and Treatment Planning in Advanced PD	42
Clinical and Societal Impact of Deep Brain Stimulation in Parkinson’s Disease	43
CONCLUSION	46
BIBLIOGRAPHY	48
CURRICULUM VITAE	54

LIST OF TABLES

Table 1. Standardized assessment tools for evaluating balance and posture in Parkinson's disease.....	7
Table 2. Standardized assessment tools for evaluating hand and arm function in Parkinson's disease	8
Table 3. Standardized assessment tools for evaluating walking and gait function in Parkinson's disease	9
Table 4. Comparative overview of awake versus asleep DBS techniques.....	24
Table 5. Mean pre- and post-operative UPDRS-III subdomain scores following subthalamic nucleus (STN) and globus pallidus internus (GPi) deep brain stimulation in Parkinson's disease	31
Table 6. Clinical predictors of favorable response to deep brain stimulation in Parkinson's disease.....	36

LIST OF FIGURES

Figure 1. Changes of motor scores and levodopa equivalent daily dose.....	4
Figure 2. Schematic representation of sequence of events leading to levodopa-induced dyskinesia (LID).....	11
Figure 3. Mechanism of deep brain stimulation (DBS) in Parkinson's disease.....	14
Figure 4. Schematic representation of basal ganglia circuitry in the normal and parksonian state.	20
Figure 5. Changes in UPDRS motor sub-scores comparing STN and GPi DBS targets over 12 months.	30

LIST OF ABBREVIATIONS

DBS	Deep Brain Stimulation
ET	Essential Tremor
FUS.....	Focused Ultrasound
GPi.....	Globus Pallidus
LID	Levodopa Induced Dyskinesia
PD.....	Parkinson's Disease
PPT	Purdue Pegboard Test
QoL.....	Quality of Life
RF	Radiofrequency
STN.....	Subthalamic Nucleus
TUG	Timed Up and Go Test
UPDRS	Unified Parkinson's Disease Rating Scale
6MWT	Six-Minute Walk Test

INTRODUCTION

Background

Parkinson's disease (PD) is a progressive neurodegenerative disease that primarily affects motor function. It is caused by the degeneration of dopaminergic neurons within the substantia nigra pars compacta (National Institute of Neurological Disorders and Stroke, 2023), a region of the midbrain essential for communication between the basal ganglia and motor cortex. This dysfunction leads to a range of motor and non-motor symptoms, including resting tremor, bradykinesia, cognitive decline, and mood disturbances. These non-motor symptoms often contribute more to reduced quality of life than the motor symptoms alone.

Current treatments of PD are primarily pharmacological, with levodopa - a dopamine precursor – serving as the gold standard (Poewe et al., 2010). Levodopa provides *initial* symptom control in the early stages of PD, however, chronic use of levodopa is associated with complications such as motor fluctuations and levodopa-induced dyskinesias (LID) (Freitas et al., 2018). As the disease progresses the long-term efficacy of medical therapy becomes limited (less effective) thus calling for surgical interventions such as deep brain stimulation (DBS).

DBS is a functional neurosurgery technique which modulates dysfunctional neural circuits through electrical stimulation to improve symptom control. The modern era of DBS began in the late 1980s with the pioneering work of Dr. Alim-Louis Benabid, a French neurosurgeon and physicist (Blomstedt and Hariz, 2010). While performing intraoperative thalamotomy for tremor, Benabid discovered that high-frequency electric

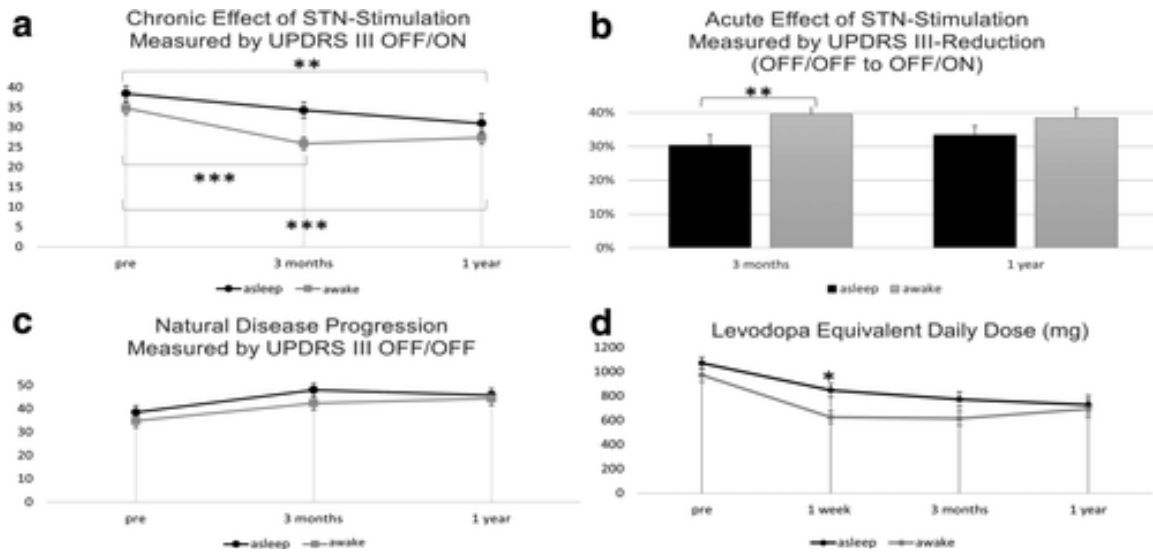
stimulation of the thalamus produced the same therapeutic effect as lesioning, without permanently damaging brain tissue (DeLong and Benabid, 2014). This observation laid the foundation for DBS as a reversible, adjustable and less destructive alternative to traditional ablative procedures. In 1997, the U.S. FDA approved DBS for essential tremor, followed by approval for PD in 2002, specifically targeting the subthalamic nucleus (STN) and globus pallidus internus (GPi) (National Institute of Neurological Disorders and Stroke, 2023). Over the following decades, DBS has expanded globally, evolving in precision and safety with advancements in imaging, targeting, and device programming.

Functional neurosurgery provides an alternative to traditional neurosurgery by focusing on structurally intact yet dysfunctional regions in the brain rather than focusing on structural lesions; this grants *restoration* of the region that is misfiring functionally. Functional neurosurgery refers to a specialized branch of neurosurgery focused on modulating neural activity in structurally intact but functionally impaired brain regions. Unlike conventional neurosurgery, which targets lesions such as tumors or vascular malformations, functional neurosurgery intervenes in circuits responsible for disorders like movement abnormalities, epilepsy, chronic pain, and certain psychiatric conditions (Chen et al., 2024). Techniques include deep brain stimulation (DBS), ablative procedures (e.g., thalamotomy, pallidotomy), and neuromodulatory interventions, such as vagus nerve stimulation. The central goal is not to remove pathology, but rather to restore or rebalance dysfunctional neural networks, often through electrical, thermal, or focused energy-based approaches. In Parkinson's disease, this approach has transformed the

therapeutic landscape by targeting subcortical structures to relieve disabling motor symptoms without compromising surrounding brain integrity. DBS involves the implantation of electrodes into specific target regions (such as the subthalamic nucleus (STN) or the globus pallidus internus (GPi)) allowing reversible and adjustable modulation of symptoms without causing permanent damage to the brain tissue. The STN and GPi are key nodes in the basal ganglia –thalamocortical circuit and play a central role in modulating motor output. By targeting these structures, DBS aims to restore the balance between excitatory and inhibitory signaling disrupted in PD. However, clinical outcomes vary widely depending on factors such as surgical approach, target selection, and patient-specific factors - highlighting the need for individualized treatment planning and further investigation into predictors of therapeutic response.

Clinical and Research Interest

Recent innovations in DBS technique have introduced asleep implantation procedures under general anesthesia, offering improved patient comfort compared to traditional awake surgeries, which rely on intraoperative neurophysiological feedback. However, whether asleep DBS compromises targeting accuracy, clinical efficacy, and long-term outcomes remains under investigation.



Changes of motor scores and levodopa equivalent daily dose (significance level $p < 0.05$). a. Chronic effects of STN-stimulation. b. Acute effects of STN-stimulation. c. Natural disease progression. d. Levodopa equivalent daily dose. Adapted from Blasberg et al. (2018)

Figure 1. Changes of motor scores and levodopa equivalent daily dose

Figure 1 compares awake and asleep DBS across several clinical dimensions, including both acute and chronic motor effects (measured by UPDRS III), disease progression, and levodopa daily dose reduction. Notably, both approaches yield substantial and sustained motor benefits over one year, although minor differences in early acute response and medication adjustment suggest that surgical variables may influence treatment trajectories (Blasberg et al., 2018). These findings underscore the need to evaluate not only surgical technique, but also target selection and patient-specific predictors to optimize outcomes and tailor DBS to the individual with advanced PD.

Specific Aims

DBS has become a cornerstone in the management of PD for patients who experience motor complications inadequately controlled by pharmacological therapy. However, several critical questions remain regarding its optimization and comparative effectiveness. This thesis aims to evaluate the role of DBS in PD by addressing key clinical and surgical variables that influence outcomes.

First, it will compare DBS to pharmacological therapy and lesional procedures in terms of motor and non-motor symptom control, complication rates, and long-term functional outcomes. Second, it will examine the impact of procedural approaches – specifically asleep vs awake DBS intervention- on surgical precision, patient safety, and overall comfort. These aims are guided by the following research questions: How do asleep and awake DBS procedures compare in terms of surgical accuracy, safety, and patient-centered outcomes? What are the relative advantages and limitations of each approach? Additionally, this thesis will assess how the selection of the target nucleus – subthalamic nucleus (STN) vs globus pallidus internus (GPi)- influences motor symptom improvement, medication reduction, cognitive side effects, and overall quality of life. Finally, this work will identify clinical and demographic predictors of favorable response to DBS such as age, disease duration, brain atrophy, and baseline symptom profile. These aims will guide a comprehensive evaluation of how DBS compares to standard treatments, how target selection and surgical approach influence outcomes, and which patient-specific factors predict optimal response, with the overarching goal of improving candidate selection and treatment planning in advanced PD.

COMPARING DEEP BRAIN STIMULATION TO PHARMACOLOGICAL THERAPY AND LESIONAL PROCEDURES

Motor Symptom Assessment as a Basis for Treatment Comparison

To meaningfully compare the motor outcomes of pharmacological therapy, lesional procedures, and deep brain stimulation (DBS), standardized assessment tools must be applied. The following instruments offer quantifiable insights into tremor, bradykinesia, posture, dexterity, and gait, which are experienced with advanced PD: the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), Timed Up and Go (TUG), and Purdue Pegboard Test (PPT) (Opara et al., 2017). These instruments form the foundation for evaluating the relative efficacy of each intervention and are critical when determining treatment effectiveness and selecting optimal therapeutic strategies.

Tables 1 through 3 present commonly used assessments grouped by motor function category: balance and posture, hand and arm function, and gait. Instruments such as the UPDRS, TUG, PPT, and Six-Minute Walk Test (6MWT) are frequently used in both clinical and research settings to measure outcomes before and after DBS intervention.

Table 1. Assessment of balance and posture in Parkinson's disease.

Name	Abbrev.	Author/Year
Unified Parkinson's Disease Rating Scale part III	UPDRS	Fahn & Elton, 1987
Timed Up and Go Test	TUG	Podsiadło & Richardson, 1989
Berg Balance Scale	BBS	Berg, 1992
Tinetti Balance and Gait Assessment Tool	TBGAT	Tinetti, 1987
Brunel Balance Assessment	BBA	Tyson & DeSouza, 2002
Functional Reach Test	FRT	Behrman et al. 2002
Activity Specific Balance Confidence	ASBC	Powell 1995; Talley, 2008
Balance Evaluation Systems Test	BESTest	Horak et al., 2009
Balance Evaluation Systems Mini Test	MiniBESTest	Franchignoni et al. 2012; King & Horak, 2013

Table 1. Standardized assessment tools for evaluating balance and posture in Parkinson's disease. Common tests include the UPDRS Part III, Timed Up and Go (TUG), and Berg Balance Scale, each providing quantifiable insight into postural instability and gait impairment. *Adapted from Opara et al. (2017).*

Table 2. Assessment of hand and arm function in Parkinson`s disease

Name	Abbrev.	Author/Year
Unified Parkinson`s Disease Rating Scale part II and III	UPDRS	Fahn& Elton, 1987
Purdue Pegboard Test	PPT	Tiffin, 1948
Nine-Hole Peg Test	NHPT	Kellor et al.,1971
Jebsen and Taylor test	JTT	Jebsen & Taylor, 1969, 1971
Pig-Tail Test	PTT	- (?) -
Frenchay Arm Test	FAT	Wade et al.,1983
Action Research Arm Test	ARAT	Lyle, 1981; van der Lee, 2002
Wolf Motor Function Test	WFMT	Wolf et al., 1989, 1991
Fugl-Meyer Motor Assessment Scale	FMAA	Fugl-Meyer et al.,1975
Södring Motor Evaluation	SMES	Södring,1994
Finger-Tapping Test	FTT	Shimoyama et al.,1990

Table 2. Standardized assessment tools for evaluating hand and arm function in Parkinson`s disease. These include the Purdue Pegboard Test (PPT), Nine-Hole Peg Test (NHPT), and Action Research Arm Test (ARAT), used to assess fine motor control, dexterity, and bradykinesia. *Adapted from Opara et al. (2017).*

Table 3. Assessment of walking in Parkinson's disease

Name	Abbrev.	Author/Year
Unified Parkinson's Disease Rating Scale part II and III	UPDRS	Fahn & Elton, 1987
Timed 10-Metre Walk Test	10MT	Bohannon et al., 1996
Timed 20-Metre Walk Test	20MT	Cunningham et al. 1982
Two-Minute Walk Test	2MWT	Butland et al., 1982
Six-Minute Walk Test	6MWT	Balke, 1963
Functional Ambulation Category	FAC	Holden, 1984
Emory Functional Ambulation Profile	E-FAP	Wolff et al., 1999

Table 3. Standardized assessment tools for evaluating walking and gait function in Parkinson's disease. These include timed walk tests (10MT, 20MT), endurance measures (2MWT, 6MWT), and functional ambulation scales (FAC, E-FAP). Such instruments are widely used in clinical practice and research to assess progression and therapeutic outcomes, including after DBS. *Adapted from Opara et al. (2017).*

Pharmacological Therapy

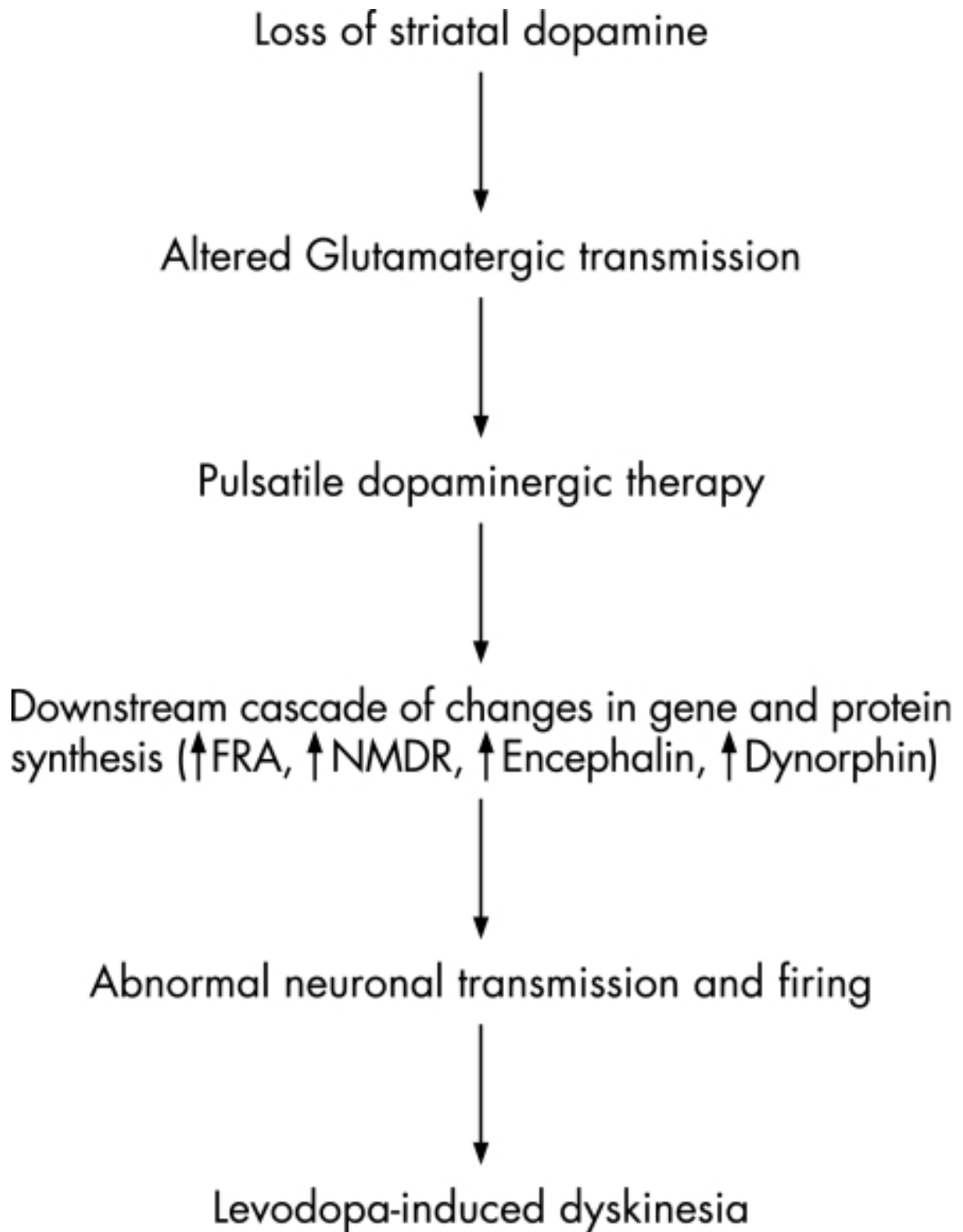
Pharmacological therapy remains the first-line approach for managing motor symptoms in PD. According to the 2021 American Academy of Neurology (AAN) guidelines, levodopa is the most effective initial treatment, providing the greatest symptomatic benefit (Pringsheim et al., 2021). In contrast, monoamine oxidase B (MAO-B) inhibitors offer only mild-to-moderate improvements, while dopamine agonists, though effective in some patients, are associated with a higher risk of neuropsychiatric complications, including impulse control disorders (Kulisevsky, 2022).

These guideline-based efficacy assessments are reinforced by long-term clinical outcome data. In the PD MED randomized controlled trial, which followed over 500

patients for a median of 4.5 years, no significant difference in mobility or overall quality of life was observed between dopamine agonists and dopamine reuptake inhibitors (MAO-B or COMT inhibitors) used as adjuncts to levodopa (Gray et al., 2022).

However, MAO-B inhibitors demonstrated modest advantages over COMT inhibitors, including better Parkinson's Disease Questionnaire (PDQ-39) mobility scores and higher EuroQol 5-dimension (EQ-5D) quality-of-life ratings. Additionally, while not statistically significant, there were trends suggesting lower rates of dementia and mortality in the MAO-B and dopamine agonist groups compared to COMT users (Gray et al., 2022). These findings highlight both the relative efficacy and the limitations of adjunctive pharmacological strategies, especially in the context of long-term disease progression.

Although these medications are foundational in early PD management, their long-term use often yields variable outcomes, and complications such as motor fluctuations and LID frequently emerge.



Schematic representation of sequence of events leading to levodopa-induced dyskinesia (LID). FRA, Fos-related proteins; NMDA, *N*-methyl-D-aspartate. *Adapted from Thanvi et al., (2007)*

Figure 2. Schematic representation of sequence of events leading to levodopa-induced dyskinesia (LID).

The term dyskinesia refers to any “involuntary movements other than tremor” where the PD patient commonly displays chorea (Zesiewicz et al., 2007)- a symptom which occurs when dopamine derived by levodopa seeps into the brain. One major limitation of long-term pharmacological treatment in Parkinson’s disease is the development of levodopa-induced dyskinesia (LID). As depicted in figure 2, the pathogenesis of LID begins with the progressive loss of striatal dopamine, which alters glutamatergic transmission in motor pathways. Chronic pulsatile levodopa therapy, rather than restoring normal physiological dopamine signaling, results in intermittent stimulation of dopamine receptors. While the etiology of LID is currently unknown, evidence suggests that irregular or intermittent activation of dopamine receptors may play a role in the underlying pathology (Zesiewicz et al., 2007). Some variables which may increase the potential risk of LID include younger age disease onset, disease severity, and high levodopa dosage (Thanvi et al., (2007).

The modest and sometimes diminishing returns of pharmacologic add-ons underscore the need for individualized treatment plans, particularly when motor symptom control plateaus. A comprehensive comparative study of pharmacological treatments for PD is the PD MED trial, a large, pragmatic, open-label randomized controlled trial involving over 1,600 patients newly diagnosed with PD (Gray et al., 2014). The trial compared initial treatment with levodopa, dopamine agonists, and MAO-B inhibitors

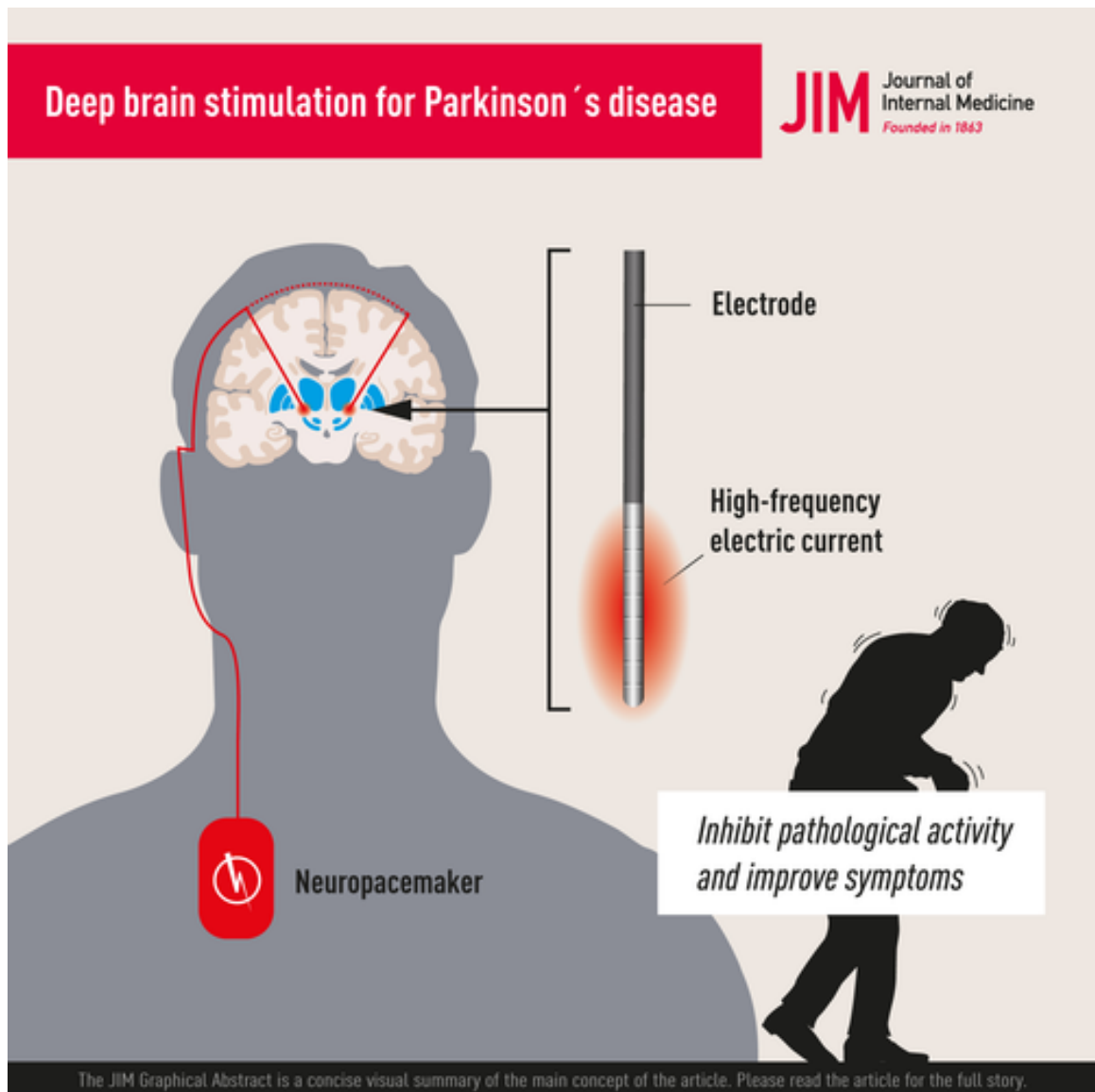
over a long-term follow-up. Patients in the levodopa group demonstrated better mobility, higher quality of life scores, and lower rates of treatment discontinuation compared to those receiving dopamine agonists or MAO-B inhibitors. Although levodopa was associated with a modest increase in dyskinesia, these side effects were non-disabling in most cases. The results reaffirm levodopa as the gold standard for initial pharmacologic therapy, supporting early initiation in appropriate patients rather than delaying its use due to concerns about motor complications.

In early PD, levodopa remains the most effective agent for motor symptom relief, providing rapid and consistent benefit. Dopamine agonists offer good initial motor control and may modestly improve certain non-motor symptoms such as sleep and mood. MAO-B inhibitors, though less potent for motor control, are generally well tolerated and can aid in addressing fatigue and depressive symptoms (Pringsheim et al., 2021). However, as PD progresses, the limitations of pharmacological therapy in managing both motor and non-motor domains often lead to the consideration of surgical options such as DBS, particularly in patients with symptom profiles less responsive to medication alone.

While pharmacologic treatments are foundational in early-stage PD care, their long-term use is constrained by significant adverse effects. Levodopa, despite its efficacy, is associated with the development of motor complications such as wearing-off phenomena and levodopa-induced dyskinesias (Pringsheim et al., 2021). Dopamine agonists carry a particularly high risk of neuropsychiatric complications, including impulse control disorders (e.g., gambling, hypersexuality), hallucinations, and excessive daytime sleepiness. These effects can be especially disabling in elderly patients. Even

MAO-B inhibitors, though well tolerated, can lead to insomnia and rarely interact dangerously with serotonergic antidepressants. These cumulative risks often drive patients toward DBS, which offers sustained motor benefit without the dose-dependent toxicity seen in chronic drug therapy (Pringsheim et al., 2021).

Deep Brain Stimulation



Mechanism of deep brain stimulation (DBS) in Parkinson's disease. A surgically implanted neurostimulator delivers high-frequency electrical impulses to targeted brain

structures such as the subthalamic nucleus (STN) or globus pallidus internus (GPi), aiming to inhibit abnormal neural activity and improve motor symptoms.

Adapted from the Journal of Internal Medicine (Hariz and Blomstedt, 2022)

Figure 3. Mechanism of deep brain stimulation (DBS) in Parkinson's disease.

Due to the long-term complications associated with pharmacological treatments, such as levodopa-induced dyskinesia, functional neurosurgery has emerged as a critical therapeutic alternative. DBS, an effective surgical intervention, has been shown to outperform medical therapy in patients with PD who experience motor fluctuations (Blasberg et al., 2018).

As illustrated in figure 3, DBS involves the surgical implantation of a neurostimulator, which delivers high-frequency electrical impulses to targeted regions of the brain, most commonly the STN or the GPi (Hariz and Blomstedt, 2022). These regions are central nodes in the basal ganglia-thalamocortical circuit and play a critical role in regulating motor output. The goal of DBS is to modulate aberrant neural firing patterns associated with Parkinson's disease without causing permanent structural damage to the brain (Lozano et al., 2019). High-frequency stimulation inhibits pathological activity within these circuits, thereby improving motor symptoms such as tremor, rigidity, and bradykinesia. The ability to adjust stimulation parameters postoperatively offers a level of flexibility that makes DBS a superior alternative to lesional procedures in many advanced PD cases.

While DBS is typically considered in advanced stages of PD, emerging evidence supports its earlier use for sustained motor benefit. In a pioneering pilot trial, patients with early-stage PD who received STN-DBS plus optimized medication demonstrated slower disease progression and reduced medication burden over five years compared to

those managed with medication alone (Hacker et al., 2020). The motor gains persisted throughout the study period, highlighting that timely intervention may enhance long-term outcomes and delay the need for polypharmacy—an insight that informed subsequent FDA-approved trials targeting early PD cohorts. These findings suggest that earlier DBS implantation may offer a strategy to maintain motor control and reduce treatment complexity more effectively than delaying until advanced disease stages.

DBS has shown benefit in select pain subtypes, particularly dystonic and central pain, while other types respond better to pharmacological or rehabilitative interventions (Cattaneo and Jost, 2023). A multimodal treatment approach- often including levodopa, MAO-B inhibitors, botulinum toxin, or physiotherapy- remains essential for comprehensive pain management.

DBS alleviates motor symptoms and certain non-motor symptoms in PD by delivering high-frequency electrical stimulation to specific brain regions, most commonly the STN or GPi. The therapeutic effect depends heavily on precise electrode placement and the functional connectivity of the target, making stimulation targeting a critical factor in clinical outcomes.

DBS yields robust improvements in motor function for patients with Parkinson's disease, particularly those with advanced or medication-refractory symptoms. A meta-analysis reviewed 44 studies and found that DBS significantly reduced motor symptom severity (Fasano et al., 2021), as measured by the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III). Specifically, patients who received DBS stimulation experienced range of 30-50% improvement in UPDRS-III scores. These findings

confirm that DBS can dramatically alleviate hallmark motor features of Parkinson's disease, such as tremor, bradykinesia, and rigidity, beyond the capabilities of pharmacologic therapy alone. Moreover, the sustained effect across both targets underscores DBS as a powerful tool for restoring motor function in appropriately selected patients (Fasano et al., 2021).

While the motor benefits of DBS are well established, growing evidence also highlights its impact on non-motor symptoms, which can be equally debilitating and significantly affect quality of life.

A highly prevalent and often underrecognized non-motor symptom in PD is pain, which affects up to 85% of patients across disease stages (Cattaneo & Jost, 2023). Yet, despite its high prevalence, pain remains frequently overshadowed by motor symptoms, often receiving less clinical attention than motor impairments. The pathophysiology of pain is complex, involving dopaminergic, serotonergic, and glutamatergic dysfunction, and its clinical expression varies from musculoskeletal and dystonic pain to central neuropathic pain. Pharmacological therapies such as levodopa and MAO-B inhibitors have demonstrated efficacy for musculoskeletal and central pain types, while botulinum toxin is the treatment of choice for dystonic pain. Additionally, non-pharmacologic strategies including physiotherapy and yoga can reduce pain severity by improving motor control and flexibility. DBS, while primarily aimed at motor symptom control, has shown particular benefit for dystonic and central pain, subtypes which are less responsive to conventional therapies (Cattaneo and Jost, 2023). In contrast, lesional procedures like pallidotomy may offer pain relief through motor improvement yet lack the

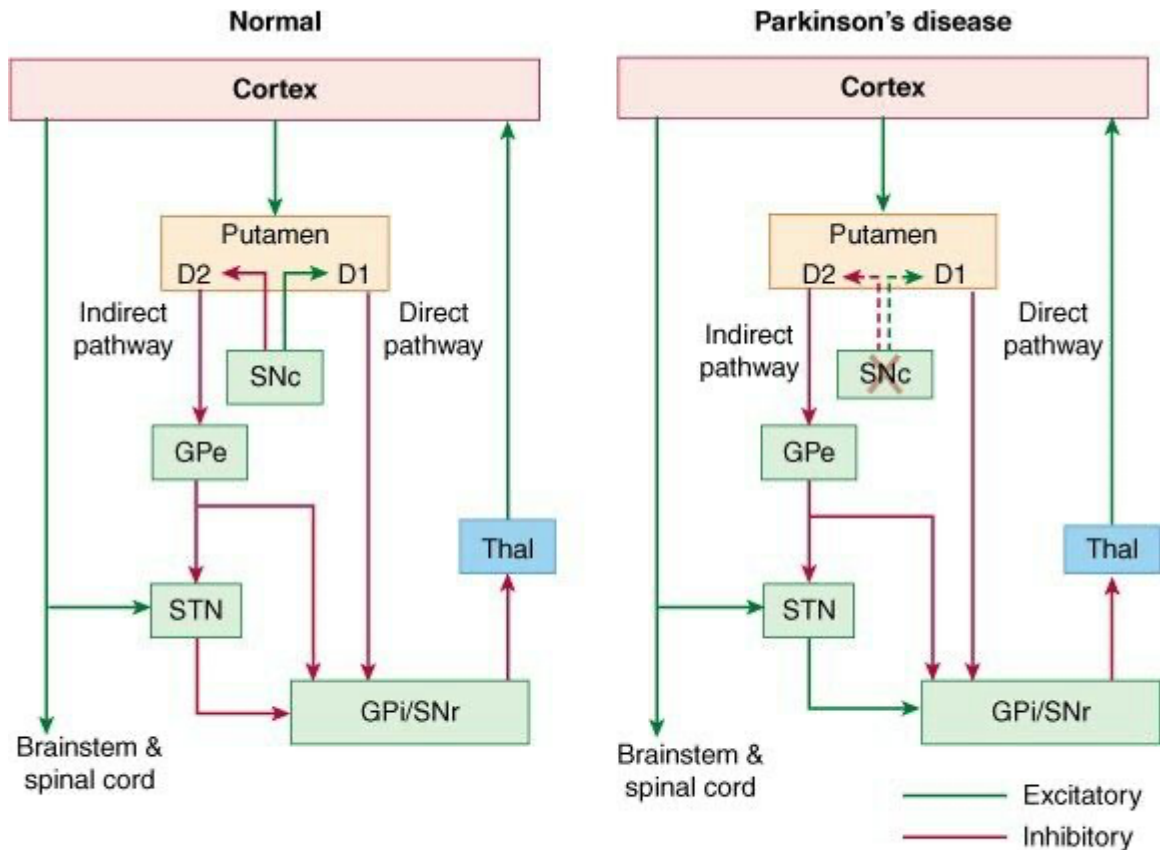
programmable flexibility and non-motor benefits observed with DBS. These findings underscore the need for a multimodal treatment approach, with DBS offering unique advantages in specific pain phenotypes unresponsive to other modalities.

Movement disorders such as PD arise from dysfunction within parallel basal ganglia–thalamo–cortical loops, particularly the motor circuit. Abnormal firing patterns in the basal ganglia, characterized by excessive synchronization and pathological oscillations, disrupt output to the thalamus and motor cortex, resulting in hallmark motor symptoms such as akinesia, rigidity, and gait disturbances (DeLong and Wichmann, 2015). Both ablative procedures and DBS work by disrupting these pathological rhythms, effectively releasing downstream structures to resume more physiologic function.

A key mechanistic insight has emerged from studies showing that neuronal burst firing, not just tonic spiking, underlies the generation of these pathological oscillations. In a pivotal intraoperative study, researchers recorded from the subthalamic nucleus (STN) in PD patients and the ventral intermediate nucleus (VIM) in essential tremor patients (Scherer et al., 2022). They found that single-neuron bursts were tightly phase-locked to local field potential oscillations, with STN bursts preceding beta oscillations 64% of the time. These findings suggest that bursts may initiate or sustain the network-level oscillatory dynamics that disrupt motor function, rather than merely responding to them. This micro-level synchronization supports the theory that DBS exerts therapeutic effects by desynchronizing aberrant burst-related oscillations, ultimately restoring more normal network activity. These results also support emerging adaptive DBS (aDBS) paradigms,

where burst detection may serve as a feedback signal to guide real-time, closed-loop stimulation.

The therapeutic effects of DBS involve multiple overlapping mechanisms. High-frequency stimulation can induce depolarization blockade, preventing neurons at the stimulation site from firing in a pathological manner. It also causes antidromic and orthodromic axonal activation, altering information flow within and beyond the target nucleus. Additional mechanisms include synaptic inhibition, short-term depression, and modulation of neurotransmitter release, all of which contribute to circuit-level rebalancing (Kopell and Greenberg, 2008). Rather than simply silencing neural activity, DBS appears to “reset” maladaptive network dynamics by disrupting aberrant signals, promoting a more physiological firing pattern, and breaking feedback loops that perpetuate motor dysfunction (DeLong and Wichmann, 2015). These effects extend beyond the stimulation site, suggesting DBS acts as a network therapy rather than a focal intervention.



Source: Watts RL, Standaert DG, Obeso JA: *Movement Disorders, 3rd Edition*: <http://www.accessphysiotherapy.com>

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

Schematic representation of basal ganglia circuitry in the normal and Parkinsonian state, showing alterations in direct and indirect pathways and the resulting over-inhibition of the thalamus. (*Adapted from Watts RL et al., 2012*)

Figure 4. Schematic representation of basal ganglia circuitry in the normal and Parkinsonian state.

The pathological motor symptoms of Parkinson's disease arise from imbalances within the basal ganglia circuitry, as illustrated in Figure 4. Under normal conditions, dopaminergic input from the substantia nigra pars compacta (SNc) enhances activity in the direct pathway (via D1 receptors) and suppresses the indirect pathway (via D2 receptors), facilitating smooth and purposeful movement. In Parkinson's disease, degeneration of SNc neurons leads to reduced dopaminergic tone, resulting in

overactivity of the indirect pathway and underactivity of the direct pathway. This imbalance increases inhibitory output from the GPi/SNr to the thalamus, which suppresses thalamocortical excitation and manifests clinically as bradykinesia and rigidity. DBS modulates these dysfunctional circuits by interrupting pathological firing patterns, particularly in the STN or GPi, thereby reducing excessive inhibition of the thalamus and restoring more physiologic motor output. This circuit-level intervention reinforces the rationale for DBS as a neuromodulatory, not destructive, strategy.

While DBS is often favored for its reversibility and safety compared to lesional procedures (such as pallidotomy), stimulation-related complications can occur beyond surgical risks such as hemorrhages or infection. A spectrum of movement disorders that may be induced by stimulation includes dystonia, dyskinesias, freezing of gait, and hemiballism (Baizabal-Carvallo and Jankovic, 2016). Importantly, these symptoms are not due to hardware failure or disease progression, but rather arise from imprecise targeting or overstimulation of nearby or interconnected circuits. Many of these effects are reversible through adjustment of stimulation parameters, underscoring the critical role of individualized programming and follow up care. This reinforces the notion that even technically successful DBS implantation may require careful, ongoing optimization to avoid iatrogenic complications and ensure maximal benefit.

A compelling clinical example involves a patient who developed stimulation-induced hemiballism, a violent and involuntary flinging of the limbs, shortly after DBS activation (Baizabal-Carvallo and Jankovic, 2016). This rare but striking complication was not attributable to disease progression or electrode misplacement, but rather to

excessive spread of stimulation into adjacent structures, likely the internal capsule.

Notably, the hemiballism resolved completely following reprogramming of the stimulation settings, without the need for surgical revision.

Such cases highlight the delicate balance between therapeutic efficacy and adverse effects in DBS and demonstrate how even well-placed electrodes can produce unintended consequences depending on stimulation intensity, field spread, and individual neuroanatomy. Together, these observations reinforce the principle that optimal DBS outcomes depend not only on surgical precision, but also on adaptive, patient-specific programming that responds to evolving clinical needs, making long-term follow-up and multidisciplinary care essential components of effective DBS management.

Lesional Procedures

Lesional procedures, such as pallidotomy and thalamotomy, remain important surgical options in regions where DBS is unavailable or unaffordable. Thalamotomy was one of the earliest surgical treatments for PD, introduced prior to levodopa. This procedure involves creating a lesion in the VIM of the thalamus, whose region is associated with tremor circuitry. By disrupting the abnormal neuronal signals within the VIM, thalamotomy was found to be effective at alleviating tremor thus making it a viable option for unilateral tremor-dominant PD (Groiss et al., 2009). Pallidotomy targets the internal segment of the globus pallidus (GPi), a major output nucleus of the basal ganglia implicated in Parkinsonian motor symptoms. Although the procedure was first introduced in the mid-20th century, it experienced a resurgence in the 1990s as a response to LID and medication-refractory motor fluctuations. This renewed interest was driven by

improved imaging and intraoperative techniques that enhanced both targeting precision and safety. A landmark study demonstrated that unilateral posteroventral pallidotomy produced substantial improvements in tremor, rigidity, bradykinesia, and dyskinesias, with minimal adverse effects, re-establishing the procedure as a viable alternative in advanced Parkinson's disease (Lozano et al., 1995). By lesioning the overactive GPi, pallidotomy reduces excessive inhibitory output to the thalamus, thereby helping to restore more physiological motor control.

A 2024 systematic review comparing traditional radiofrequency (RF) versus newer focused ultrasound (FUS) pallidotomy found that both modalities produced similar motor benefits, with comparable UPDRS III score improvements (Guidera et al., 2024). However, RF pallidotomy was associated with a 14% failure rate and significantly higher rates of cognitive adverse effects, whereas FUS had a slightly higher failure rate (24%) but lower risk of cognitive decline (Guidera et al., 2024). These findings support the adoption of FUS pallidotomy when available, offering equivalent motor efficacy with improved cognitive safety over RF lesioning.

Focused ultrasound (MRgFUS) thalamotomy emerges as an effective lesional treatment for unilateral medication-resistant tremor in both essential tremor (ET) and PD. VIM-targeted MRgFUS provides significant tremor relief in approximately 70–90% of patients at one year, with minimal side effects, such as transient paresthesia or balance issues, and no lasting cognitive decline (Fernandez et al., 2023). Compared to RF lesioning, which can carry cognitive and neurologic risks, MRgFUS offers a non-invasive option without hardware implantation—making it a valuable alternative for selected

patients. While long-term bilateral outcomes require further study, MRgFUS strengthens the argument for tailored, patient-centered selection among surgical interventions.

Awake vs Asleep DBS Intervention -Impact of Procedural Approaches

When considering procedural approaches it is relevant to consider the technical divergence between awake and asleep DBS surgery, which primarily centers on the use of microelectrode recording (MER) versus image-guided targeting. Awake DBS procedures incorporate MER and intraoperative stimulation testing to refine lead placement using real-time neurophysiological feedback. This procedural method enables a personalized approach to lead placement, facilitating more effective and clinically optimal outcomes.

In contrast, asleep DBS relies solely on high-resolution imaging, typically intraoperative CT or MRI, to directly visualize anatomical targets such as the STN or GPi. According to Kochanski et al. (2008), while MER offers the advantage of functional confirmation, modern imaging techniques have achieved lead placement accuracy comparable to that of MER-guided approaches, making asleep DBS a technically viable alternative in appropriate candidates.

Table 4 outlines the key clinical, technical, and experiential differences between awake and asleep DBS approaches.

Feature	Awake DBS	Asleep DBS
Anesthesia	Local anesthesia	General anesthesia
Intraoperative monitoring	MER, real-time symptom feedback	Imaging-based targeting (CT/MRI); no patient feedback

Patient experience	Requires cooperation; can cause anxiety/fatigue	More comfortable; avoids intraoperative stress
Target accuracy	Enhanced by live testing and MER	High, if using intraoperative imaging; depends on image quality
Lead placement verification	Physiologic response and patient input	Imaging-based confirmation only
Postoperative programming	Often easier due to precise intraoperative feedback	May require more adjustments post-op
Use case preference	Younger, cognitively intact patients; centers with MR expertise	Older, anxious, or cognitively impaired patients
Complication rate	Slightly higher risk of anxiety-related issues	May have higher risk of inaccurate targeting if imaging fails
Adoption trend	Declining in some centers	Increasing with improved imaging and navigation tools

Table 4. Comparative overview of awake versus asleep DBS techniques. Awake DBS allows real-time physiologic feedback and intraoperative testing, while asleep DBS offers improved patient comfort via imaging-guided targeting under general anesthesia. Each approach has specific advantages and limitations, making patient selection and institutional expertise critical.

A core technical distinction between awake and asleep DBS surgery lies in the method of target localization. Awake procedures typically employ MER to capture neuronal firing patterns of the STN, paired with intraoperative macrostimulation to evaluate symptom suppression and side effects in real time. In contrast, asleep DBS relies on high-resolution, image-guided targeting using fused

preoperative MRI and intraoperative CT, omitting physiological feedback. These approaches are directly compared in matched cohorts and found that the awake, MER-guided group exhibited greater short-term motor improvement and better control of axial symptoms such as speech and freezing at three months postoperatively (Blasberg et al., 2018). However, by twelve months, both groups achieved similar motor outcomes, medication reduction, and complication rates. These findings suggest that while awake MER-based targeting may offer superior early precision, image-guided asleep DBS can achieve comparable long-term efficacy when surgical planning is optimized.

Conventionally, the standard procedure of DBS surgery is performed with the patient in an awake condition. It allows the operating team to interact with the patient and test for stimulation effects and side effects intraoperatively to ensure optimal electrode placement. Technically, it is also possible to perform DBS surgery with the patient asleep during general anaesthesia, which is usually applied to patients not eligible for awake surgery, that is, in cases of unbearable motor or non-motor off-medication symptoms, severe anxiety, cardiovascular or respiratory problems or other general medical limitations (Blasberg et al., 2018). Asleep surgery may lead to reduction of stress and pain for the patient, shorten the operation's duration, and might increase the number of patients eligible and willing for DBS.

Asleep DBS maintains accuracy with possibly lower complication rates and better patient comfort since the procedure avoids the stress and duration of awake surgery. Despite initial skepticism, studies now suggest that asleep DBS can match awake DBS in terms of targeting accuracy while offering several safety and patient-experience advantages. Asleep procedures are associated with a trend toward fewer intraoperative complications, including lower risks of hemorrhage and infection, likely due to shorter surgical duration and reduced patient movement (Kochanski et al., 2008). Additionally, the elimination of intraoperative testing minimizes psychological stress and discomfort, improving procedural tolerance for patients with high anxiety or cognitive decline. These benefits must be balanced against the absence of real-time physiological confirmation available during awake surgery.

Although asleep DBS has emerged as a promising alternative to traditional awake surgery, offering improved patient comfort and reduced procedural anxiety, concerns persist regarding the lack of intraoperative neurophysiological confirmation and limited long-term outcome data. Despite the emerging evidence which suggests comparable motor outcomes to awake procedures, questions regarding long-term efficacy, targeting accuracy, and patient selection continue to drive debate within the neurosurgical community. Future research must address whether image-guided targeting alone can ensure consistent long-term symptom relief, especially in complex cases with anatomical variation or narrow therapeutic windows (Kochanski and Sani, 2008). While asleep DBS offers clear advantages in

terms of patient comfort and procedural efficiency, awake DBS remains the gold standard where maximal targeting precision and intraoperative adaptability are required.

Both awake and asleep DBS approaches demonstrate efficacy in managing motor symptoms of Parkinson's disease when paired with appropriate surgical planning. Awake DBS facilitates intraoperative neurophysiological feedback, which may enhance initial targeting precision and early postoperative outcomes. Conversely, asleep DBS offers improved patient comfort and reduced operative stress, with emerging evidence indicating comparable long-term motor benefits when imaging-guided targeting is utilized. The choice between approaches should be informed by patient-specific factors, such as cognitive status, anxiety levels, and comorbidities, as well as institutional protocols and surgical expertise. With the ongoing integration of technologies including directional leads, robotic guidance, and adaptive stimulation, the procedural distinction between awake and asleep DBS may become increasingly procedural rather than outcome-determinative. Tailoring the surgical approach to the individual patient remains essential to optimizing therapeutic outcomes.

Target Selection – STN vs GPi

Target selection in DBS plays a critical role in determining the clinical outcomes for patients with PD. While both the STN and the GPi are approved and widely used targets, they differ in how they modulate motor circuitry and influence specific symptom

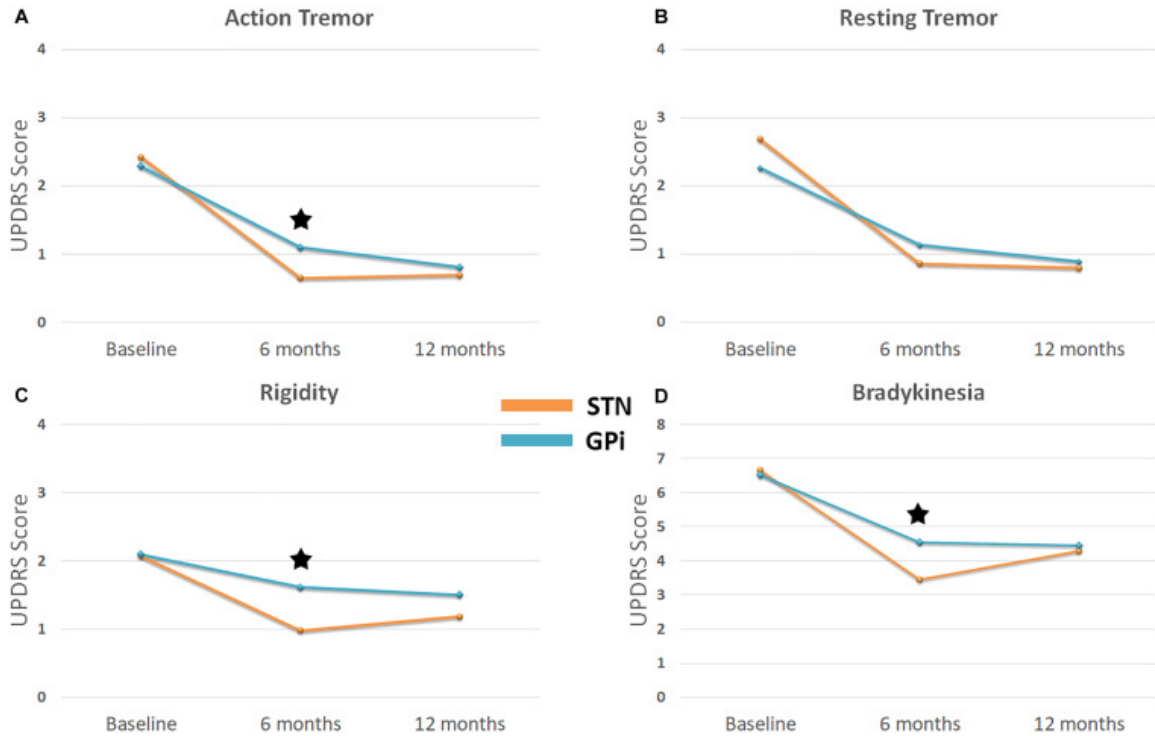
domains. These differences have significant implications for individualized treatment planning, especially when considering each patient's symptom profile, medication tolerance, cognitive status, and risk for mood or behavioral complications. For instance, STN stimulation is often associated with greater medication reduction and more pronounced improvement in bradykinesia and rigidity, whereas GPi stimulation may offer a more favorable neuropsychiatric profile and better tolerance in patients with preexisting cognitive vulnerability. As such, choosing the optimal target is not a one-size-fits-all decision, it must be guided by a nuanced evaluation of the patient's motor and non-motor symptom burden, treatment history, and overall clinical trajectory.

Motor outcomes

When evaluating DBS targets for motor symptom control, both the STN and GPi demonstrate substantial efficacy. Tremor outcomes in 56 PD patients were analyzed and it was found that both targets significantly improved action and rest tremors, with no statistically significant difference between groups at 12 months postoperatively (Wong et al., 2020). A meta-analysis encompassing STN and GPi stimulation found both targets to be equally effective in reducing action and rest tremors, with nearly identical effect sizes (STN = 0.38, GPi = 0.35) and no significant intergroup difference (Wong et al., 2020).

These findings suggest that while tremor suppression is a key benefit of DBS, it does not distinguish between targets. Therefore, tremor control cannot be the sole criterion when selecting a DBS target. Instead, decision-making should incorporate additional motor outcomes, such as rigidity and bradykinesia response, along with non-

motor factors like cognitive impact, medication reduction potential, and quality-of-life measures.



Changes in UPDRS motor sub-scores comparing STN and GPi DBS targets over 12 months. Line graph illustrates outcomes for (A) action tremor (B) rest tremor (C) rigidity and (D) bradykinesia for STN DBS versus GPi DBS. Blue line represents STN DBS and orange line represents GPi DBS. Baseline represents UPDRS item scores before surgery. UPDRS item 20 applicable to contralateral arm was used for assessment of rest tremor, item 21 for action tremor, item 23 for rigidity and summation of items 23, 24, and 25 for bradykinesia. Scores at 6 and 12 months after DBS were obtained in during OFF medication – ON stimulation state. *Denotes a statistically significant difference between the two groups. *Adapted from Wong et al., (2020).*

Figure 5. Changes in UPDRS motor sub-scores comparing STN and GPi DBS targets over 12 months.

Supporting these findings, motor outcomes for both STN and GPi have been compared across specific Unified Parkinson's Disease Rating Scale (UPDRS) subdomains. Figure 5 shows changes in action tremor, resting tremor, rigidity, and bradykinesia from baseline to 12 months post-implantation. While STN showed slightly

greater numerical reductions in some domains, particularly bradykinesia, these differences were not statistically significant long-term (Okun et al., 2020). This further reinforces the notion that both targets are effective for motor symptom control, and that target selection should be individualized based on non-motor considerations and patient-specific risk profiles.

Motor Symptom	Target	Pre-DBS Mean Score	Post-DBS Mean Score	% Improvement
Tremor	STN	7.4	2.4	67.6%
Bradykinesia	STN	14.1	7.5	46.8%
Rigidity	STN	10.5	5.0	52.4%
Axial Symptoms	STN	6.7	4.9	26.9%
Tremor	GPI	6.9	3.3	52.2%
Bradykinesia	GPI	13.3	9.4	29.3%
Rigidity	GPI	10.1	6.4	36.6%
Axial Symptoms	GPI	6.2	5.6	9.7%

Table 5. Mean pre- and post-operative UPDRS-III subdomain scores following subthalamic nucleus (STN) and globus pallidus internus (GPi) deep brain stimulation in Parkinson's disease. While both targets led to substantial improvements in tremor, rigidity, and bradykinesia, STN-DBS demonstrated greater overall efficacy across all domains. Improvement in axial symptoms was modest for both targets, with minimal benefit observed in GPi-DBS. *Adapted from Fasano et al., (2021).*

As illustrated in Table 5, DBS outcomes vary meaningfully depending on the selected target. Patients receiving STN-DBS demonstrated consistently greater improvements across all major motor domains when compared to those receiving GPi-DBS. Tremor reduction was most pronounced in the STN group, with a 67.6% decrease in

symptom severity, compared to 52.2% in the GPi cohort. Similarly, bradykinesia and rigidity improved by 46.8% and 52.4% in STN-DBS recipients, respectively, outperforming GPi stimulation, which produced 29.3% and 36.6% improvements. The most notable disparity, however, emerged in axial symptoms (e.g., gait, balance, and postural control), where STN provided a modest 26.9% benefit while GPi showed only a 9.7% improvement. These data highlight the superior motor efficacy of STN stimulation overall, particularly for bradykinesia and rigidity, although neither target offers robust benefit for axial impairments.

The pattern of symptom-specific response reinforces the need to align surgical targets with individualized motor phenotypes. Ultimately, understanding these differences supports more personalized DBS planning, allowing clinicians to optimize outcomes based on the specific constellation of symptoms affecting each patient.

Medication reduction

STN-DBS consistently shows superior outcomes in reducing dopaminergic medication burden compared to GPi stimulation. In a cohort of LRRK2-G2019S PD patients, those who underwent STN-DBS experienced more substantial reductions in levodopa equivalent daily dose than those who received GPi-DBS (Leaver et al., 2021). This aligns with broader findings that STN targeting allows for more aggressive medication tapering, which may be particularly beneficial in patients with medication-induced dyskinesias or side effects. However, this benefit must be balanced against potential psychiatric risks that may emerge with rapid pharmacologic withdrawal.

Cognitive and psychiatric side effects

While DBS provides substantial motor benefits in PD, its psychiatric side effects (particularly suicidality) warrant careful consideration during target selection. A review of suicidality outcomes found that early reports indicated suicidal ideation in up to 16% of DBS patients, with suicide attempts and completions ranging from 0–6% and 1.5–4.6%, respectively (Foncke et al., 2006). More recent studies suggest lower incidence rates (~0.5%), but the risk remains elevated compared to the general PD population. Notably, STN stimulation appears more strongly associated with suicidality than GPi stimulation, possibly due to rapid dopaminergic withdrawal or inadvertent stimulation of adjacent limbic circuits. These findings underscore the importance of preoperative psychiatric screening, gradual medication tapering, and multidisciplinary follow-up—especially when STN is the chosen target in patients with a history of mood or behavioral disorders.

While STN-DBS offers motor and medication advantages, it may carry a higher risk of psychiatric complications compared to GPi-DBS. One study reported that a patient in the STN group developed stimulation-related depression, and two required surgical lead revisions (Leaver et al., 2021). In contrast, no cases of psychiatric symptoms or hardware complications were reported in the GPi cohort. These findings reinforce the view that STN's proximity to limbic circuitry and its sensitivity to stimulation parameters may increase the likelihood of mood disturbances. Consequently, GPi may represent a safer target for patients with baseline psychiatric vulnerability or those at risk for mood destabilization.

Quality of life

DBS significantly improves quality of life in Parkinson's disease, with both STN and GPi targets producing durable benefits. A longitudinal study noted a 15.6 % quality of life (QoL) improvement at 4 months following unilateral DBS, with STN outperforming GPi at 4 and 18 months (Cernera et al., 2020). When using staged bilateral implantation, patients experienced a 25.3 % increase in QoL after the first lead, but no further benefit from the second, and scores declined only slightly after 18 months, remaining above baseline at five years. These data indicate that target-specific differences in QoL are most pronounced in the short term, with STN offering more rapid improvement, while bilateral DBS provides sustained long-term benefit regardless of target. This supports personalized target selection based not only on motor needs but on patient-valued outcomes like daily living and well-being.

These observed differences in quality-of-life outcomes may not be solely attributable to surgical targets, but also to how stimulation interfaces with broader motor networks. The PD MED trial consisted of 245 PD patients who underwent STN-DBS. Within the trial, postoperative imaging was utilized to localize electrode placement and correlate connectivity from stimulation sites with clinical outcomes. It was determined that STN-DBS was the most effective when stimulation sites were functionally connected to the primary motor cortex, supplementary motor area, and cerebellum. The patients whose electrodes had strong connectivity to these areas displayed greater motor improvement; poorer outcomes were associated with connectivity to non-motor regions, such as the prefrontal cortex (Gray et al., 2014). This study provides supporting evidence that DBS outcomes depend on connectivity rather than solely anatomical accuracy.

Predictors of Favorable Response to DBS

While DBS offers substantial benefits for motor symptom control in PD, patient outcomes vary widely. Not all individuals experience the same degree of motor improvement, medication reduction, or quality-of-life gains. As such, identifying reliable predictors of favorable response is critical for optimizing patient selection and tailoring surgical planning. A growing body of evidence suggests that both clinical factors—such as age at surgery, disease duration, baseline symptom profile, and levodopa responsiveness—and neuroanatomical variables like brain atrophy and structural connectivity influence DBS efficacy. This section explores these key predictors to better define which patients are most likely to achieve meaningful therapeutic benefit from DBS.

Classical predictors include younger age, robust levodopa response, and shorter disease duration. These factors correlate with improved motor outcomes and reduced postoperative complications. However, motor symptom laterality also appears to play a role. In a five-year follow-up, patients with right-predominant symptoms experienced significantly higher apathy, depression, and cognitive decline post-DBS compared to those with left-sided dominance (Beric et al., 2023). These findings suggest that hemispheric asymmetry may affect neuropsychiatric trajectories and should inform preoperative risk stratification.

Beyond clinical traits, neuroimaging studies show that the structural integrity of motor-related regions can influence DBS efficacy. One recent study found that lower gray matter volume in the medial superior frontal gyrus, SMA, and cingulum predicted

greater motor improvement and medication reduction after STN-DBS (Koivu et al., 2024). These anatomical predictors were independent of age or disease severity, highlighting the potential of morphometric biomarkers to guide treatment planning.

Favorable responses to DBS

While DBS offers substantial benefits for motor symptom control in PD, patient outcomes vary widely. Not all individuals experience the same degree of motor improvement, medication reduction, or quality-of-life gains. As such, identifying reliable predictors of favorable response is critical for optimizing patient selection and tailoring surgical planning. A growing body of evidence suggests that both clinical factors—such as age at surgery, disease duration, baseline symptom profile, and levodopa responsiveness—and neuroanatomical variables like brain atrophy and structural connectivity influence DBS efficacy. This section explores these key predictors to better define which patients are most likely to achieve meaningful therapeutic benefit from DBS.

Table 6 outlines key clinical predictors of favorable DBS outcomes in Parkinson’s disease, as identified by recent studies (Weaver et al.; Koivu et al.; Beric et al.).

Predictor	Favorable outcomes associated	Clinical implications
Younger age	Better motor improvement, fewer psychiatric complications	Consider earlier surgical referral before age-related decline
Shorter disease duration	Greater motor benefit and medication reduction	Ideal timing may be within 4-10 years of symptom onset
Good levodopa responsiveness	Strong predictor of DBS motor efficacy	Use UPDRS-III response as part of screening

Left-predominant symptoms	Lower rates of cognitive decline and apathy post-DBS	Factor in laterality during counseling and risk assessment
Tremor-dominant subtype	Greater tremor control with either STN or GPi targeting	Target-specific planning based on dominant symptom

Table 6. Clinical Predictors of Favorable Response to Deep Brain Stimulation in Parkinson's Disease. Summary of key patient characteristics associated with improved clinical outcomes following DBS, including motor improvement, medication reduction, and quality-of-life gains. These predictors assist in surgical candidacy decisions and preoperative counseling.

Clinical characteristics remain among the most practical and widely used predictors of DBS outcomes in Parkinson's disease. These traits are easily obtainable through standard neurological evaluation and have been correlated with both short- and long-term therapeutic responses. While classical factors such as younger age at surgery, shorter disease duration, and good levodopa responsiveness have long been associated with favorable motor outcomes, other features like baseline symptom lateralization and clinical subtypes (e.g., tremor-dominant vs akinetic-rigid) are emerging as relevant modifiers of response.

Younger patients consistently demonstrate greater motor improvement, lower complication rates, and more durable benefit following DBS. In multiple large cohort studies, age below 70 has been linked to enhanced motor response, greater reductions in medication burden, and fewer adverse neuropsychiatric effects post-surgery. For instance, in the EARLYSTIM study patients under 60 experienced greater improvements in quality of life and motor function compared to older cohorts (Schuepbach et al., 2013). Younger age also confers longer

hardware longevity and fewer comorbidities, which facilitate both perioperative management and long-term follow-up. However, this must be weighed against the increased duration of device dependency and potential for long-term complications such as hardware erosion or lead migration over decades.

On the other hand, advanced age is not an absolute contraindication. Several studies have demonstrated meaningful benefit in patients over 70 when carefully selected, especially when targeting the GPi to reduce psychiatric side effects. Thus, chronologic age should be interpreted in the context of physiologic status, cognitive reserve, and comorbidity burden, rather than as a strict cutoff.

Disease duration prior to surgery is another key predictor of DBS response. Shorter duration is generally associated with better outcomes, particularly for motor function and medication reduction. Patients who undergo DBS earlier in their disease course—typically within 4 to 10 years of symptom onset—are more likely to retain cognitive and limbic integrity, reducing the risk of neuropsychiatric side effects and enabling more robust plasticity post-stimulation.

However, overly early intervention can be premature. The EARLYSTIM trial showed improved quality of life in patients with relatively short disease duration (~7 years), but the ideal “window” for DBS remains debated. Too early may expose patients to unnecessary surgical risks, while too late may reduce benefit due to advanced degeneration or dementia.

Perhaps the strongest and most consistently validated predictor of DBS efficacy is levodopa responsiveness. If a patient's motor symptoms (especially bradykinesia and rigidity) improve substantially with dopaminergic therapy, they are more likely to experience similar or greater benefit from DBS. This is especially true for STN targeting.

Levodopa responsiveness acts as a proxy for the degree of preserved dopaminergic circuitry, and it helps predict the stimulation-responsive portions of the motor circuit. In contrast, patients whose symptoms are poorly responsive to levodopa—such as those with postural instability or freezing of gait—may derive less motor benefit from DBS.

Quantitatively, a 30–50% improvement on the Unified Parkinson's Disease Rating Scale (UPDRS-III) with levodopa is typically used as a benchmark for candidacy.

Motor symptom lateralization has emerged as a lesser-known, yet clinically relevant predictor. In a five-year follow-up, Beric et al. (2023) found that patients with right-predominant symptoms experienced significantly higher rates of apathy, depression, and cognitive decline following STN-DBS compared to those with left-sided dominance. This hemispheric difference may reflect variations in dominant hemisphere circuitry, particularly involving the limbic and prefrontal networks.

As such, symptom laterality could inform not just target selection (e.g., choosing GPi over STN) but also the order of lead implantation and postoperative monitoring strategies. Right-sided symptom dominance may necessitate more conservative programming or more frequent psychiatric evaluation.

PD patients can be broadly categorized into tremor-dominant (TD) and akinetic-rigid (AR) subtypes. Tremor-dominant patients often experience dramatic tremor control with either STN or GPi stimulation, even when tremor was refractory to medication. This is due to the strong link between the tremor network (including VIM and cerebellothalamic pathways) and DBS target connectivity.

In contrast, AR patients may show more modest motor benefit but potentially greater improvements in gait, rigidity, and bradykinesia, especially with bilateral stimulation. However, they may also be more prone to axial complications post-DBS, particularly if advanced disease has already led to postural instability. Therefore, baseline symptom profile not only predicts likely benefit but also shapes expectations and informs post-surgical goal setting.

While clinical and neuroanatomical predictors offer valuable guidance for patient selection and surgical planning, they are not definitive determinants of DBS outcomes. Individual variability remains substantial, and some patients who meet all “favorable” criteria may still experience suboptimal benefit or unexpected side effects. Conversely, patients with less ideal profiles—such as advanced age or poor levodopa responsiveness—may still derive meaningful symptomatic relief,

particularly when surgery is tailored to their specific clinical phenotype. Factors such as surgical technique, lead placement accuracy, stimulation programming, and post-operative follow-up play critical roles in determining treatment success. Additionally, disease heterogeneity and the evolving nature of Parkinson's pathology mean that no single factor can fully predict long-term response. These limitations underscore the need for a comprehensive, multidisciplinary evaluation that considers both measurable predictors and the broader clinical context of each patient.

Beyond clinical characteristics, neuroimaging has emerged as a powerful tool in identifying structural and network-level predictors of DBS efficacy. Morphometric studies have shown that preserved gray matter volume in specific motor-related regions may correlate with improved outcomes. Koivu et al. (2024) reported that lower baseline volume in the medial superior frontal gyrus, supplementary motor area (SMA), and cingulum was paradoxically associated with greater motor improvement and medication reduction following STN-DBS. This suggests that compensatory cortical reorganization may underlie stronger stimulation responses in patients with early cortical involvement. Additionally, connectomic approaches have demonstrated that DBS outcomes are not solely dependent on anatomical accuracy, but rather on the degree of functional connectivity between the stimulation site and key motor networks. Horn et al. (2022) found that stronger connectivity between the implanted STN and regions such as the primary motor cortex, supplementary motor area, and cerebellum

predicted greater clinical benefit. In contrast, lead placement resulting in unintended activation of prefrontal or limbic regions was associated with cognitive and psychiatric side effects. These findings support the integration of network-based targeting strategies and highlight the potential of neuroanatomical markers to refine patient selection and optimize electrode placement.

Improving Candidate Selection and Treatment Planning in Advanced PD

Findings concluded that the location of DBS implantation can significantly reduce brain volume, specifically in the “caudate, pallidum, putamen and thalamus ipsilateral to the implanted hemisphere” (Kern et al. 2020). This reduction demonstrates the importance of viewing patients holistically, as those experiencing brain atrophy would be at a greater risk. By shifting diagnosis from primarily clinical symptoms to include biological classifications of PD, the patients’ treatment plan can better be individualized; by doing so, it calls for improved diagnosis and outcome.

The complexity of individual patient anatomy and disease expression necessitates a personalized approach to DBS management. Neuromesodermal syndrome refers to a congenital disorder which involves both neural and mesodermal tissues. This syndrome illustrates how even optimally placed electrodes can produce unexpected adverse effects due to variable neural connectivity or heightened sensitivity to stimulation (Fomékong et al., 2022). These reversible complications were effectively managed through stimulation parameter reprogramming, including amplitude and voltage adjustments. This case series reinforces the critical role of ongoing postoperative monitoring and individualized stimulation protocols. Tailoring DBS settings to each patient’s evolving symptomatology

not only improves outcomes but also minimizes treatment-induced morbidity, positioning patient-specific programming as a central pillar in the long-term success of neuromodulatory therapies.

Clinical and Societal Impact of Deep Brain Stimulation in Parkinson's Disease

While DBS has revolutionized the management of advanced PD, its benefits remain disproportionately available to patients in high-income countries, tertiary care centers, and well-resourced urban settings. The clinical success of DBS, evident in improvements in motor function, reduction in medication burden, and enhanced quality of life, must be contextualized within broader issues of accessibility, cost, and healthcare infrastructure.

One of the most significant barriers to widespread DBS implementation is cost. The procedure involves not only the implantation surgery, which can exceed \$50,000 in the United States, but also the long-term financial burden of device maintenance, battery replacements, and frequent postoperative programming sessions. For patients without robust health insurance coverage or those in countries without national health systems that cover DBS, these costs are prohibitive. Even in systems where DBS is reimbursed, logistical barriers - such as limited surgical centers, geographic distance, or neurologist shortages - can delay or entirely prevent access.

Disparities in DBS utilization have also been observed across racial, socioeconomic, and geographic lines. Studies from the U.S. have shown that Black

and Hispanic patients are less likely to be referred for DBS, even after adjusting for disease severity and insurance status. Factors such as implicit bias in referral patterns, mistrust in surgical interventions, and differences in healthcare-seeking behavior may contribute to these gaps. Additionally, patients in rural or underserved areas may lack access to centers with DBS expertise, forcing difficult decisions about travel, cost, and follow-up care.

Beyond access, long-term support and programming represent a major challenge. Effective DBS therapy depends on postoperative management by specialized clinicians, often requiring repeated visits for device adjustments and symptom monitoring. For patients living far from movement disorder centers, this need for ongoing care may result in suboptimal outcomes or device underutilization. Telemedicine and remote DBS programming technologies are emerging to help bridge this gap, but they are not yet widely adopted.

Furthermore, global disparities are stark. While DBS is relatively common in North America and Western Europe, access in low- and middle-income countries (LMICs) is minimal. The lack of surgical infrastructure, device availability, and trained personnel in many LMICs renders DBS an impractical solution despite the high burden of Parkinson's disease worldwide. Collaborative efforts to reduce cost, train local providers, and implement scalable programming platforms are necessary to extend the benefits of DBS more equitably.

As DBS continues to evolve, with innovations such as adaptive stimulation, closed-loop systems, and improved surgical targeting, the need to address these inequities becomes more urgent. Technological progress alone will not expand access unless coupled with policy reforms, cost-reduction strategies, and public health initiatives aimed at increasing availability in underserved populations. A truly patient-centered and globally conscious approach to DBS must prioritize not only clinical efficacy but also equitable implementation.

Ethical Considerations in DBS

As the use of deep brain stimulation (DBS) expands, so too do the ethical considerations surrounding its implementation in Parkinson's disease (PD). While DBS is considered reversible and non-lesional, its impact on cognition, personality, and long-term autonomy raises important questions. Informed consent can be especially complex in PD patients with subtle cognitive decline, fluctuating capacity, or psychiatric comorbidities. Surgeons and neurologists must ensure that patients not only understand procedural risks, but also have realistic expectations about postoperative outcomes—particularly regarding non-motor symptoms, disease progression, and device maintenance.

The promise of symptom relief may also lead to coercive dynamics in family decision-making, especially when caregiver burden is high. Additionally, some patients experience shifts in mood, motivation, or identity after stimulation begins, prompting concerns about neuroethical issues such as authenticity and agency. The decision to deactivate the device, for instance, may not always be voluntary or straightforward.

Long-term dependency on specialized follow-up care also raises equity concerns, as patients in resource-limited settings may receive the device but lack ongoing programming access. These challenges underscore the need for robust preoperative counseling, multidisciplinary evaluation, and long-term care planning that prioritizes patient-centered and ethically sound practices.

CONCLUSION

Deep brain stimulation (DBS) has transformed the therapeutic landscape for Parkinson's disease by offering a reversible, adjustable, and effective intervention for patients who are no longer responsive to pharmacologic therapy. Through a comprehensive analysis of treatment outcomes, this thesis highlights DBS's superiority over both traditional medications and lesional procedures in managing motor complications and, in select cases, non-motor symptoms such as dystonia and central pain.

The comparative review of DBS targets demonstrates that both the subthalamic nucleus (STN) and globus pallidus internus (GPi) are viable and effective, with STN offering greater reductions in medication burden, while GPi is associated with fewer psychiatric complications. Similarly, procedural innovations—such as asleep DBS—have broadened the treatment landscape, allowing for improved patient comfort without sacrificing surgical precision. These findings underscore the importance of tailoring both target selection and procedural approach to the individual's symptom profile, cognitive reserve, and comorbidities.

Optimal DBS outcomes depend not only on technical accuracy, but also on thoughtful candidate selection and long-term programming. Predictive markers—ranging from clinical features to neuroimaging and genetics—may help refine surgical decisions and personalize care. Furthermore, emerging research into adaptive neuromodulation, directional leads, and connectivity-based targeting points to a future in which DBS is increasingly precise and responsive to real-time neural activity.

Deep brain stimulation has emerged as a cornerstone in the management of advanced Parkinson's disease, offering durable motor improvement, medication reduction, and improved quality of life for carefully selected patients. Its evolution—from lesion-based interventions to sophisticated network-targeted modulation—reflects both technological progress and a maturing understanding of Parkinsonian pathophysiology. Yet the complexity of patient response, variability in outcomes, and disparities in access highlight the importance of individualized, ethically sound, and equitable care. As DBS continues to advance in scope and sophistication, future efforts must balance innovation with accessibility and clinical rigor. In doing so, the field can move closer to delivering truly personalized neurosurgical care for Parkinson's disease.

BIBLIOGRAPHY

- Baizabal-Carvallo, José Fidel, and Joseph Jankovic. "Movement Disorders Induced by Deep Brain Stimulation." *Parkinsonism & Related Disorders*, vol. 25, Apr. 2016, pp. 1–9. <https://doi.org/10.1016/j.parkreldis.2016.01.014>
- Benabid, Alim Louis, et al. "Deep Brain Stimulation of the Subthalamic Nucleus for the Treatment of Parkinson's Disease." *The Lancet. Neurology*, vol. 8, no. 1, Jan. 2009, pp. 67–81. [https://doi.org/10.1016/S1474-4422\(08\)70291-6](https://doi.org/10.1016/S1474-4422(08)70291-6)
- Blasberg, Fabian, et al. "Comparison of Awake vs. Asleep Surgery for Subthalamic Deep Brain Stimulation in Parkinson's Disease." *Neuromodulation: Technology at the Neural Interface*, vol. 21, no. 6, 2018, pp. 541–547. <https://doi.org/10.1111/ner.12766>
- Blomstedt, Patric, and Marwan I. Hariz. "Deep Brain Stimulation for Movement Disorders before DBS for Movement Disorders." *Parkinsonism & Related Disorders*, vol. 16, no. 7, Aug. 2010, pp. 429–433. <https://doi.org/10.1016/j.parkreldis.2010.04.005>
- Cattaneo, Carlo, and Wolfgang H. Jost. "Pain in Parkinson's Disease: Pathophysiology, Classification and Treatment." *Journal of Integrative Neuroscience*, vol. 22, no. 5, 5, Sep. 2023, p. 132. <https://doi.org/10.31083/j.jin2205132>
- Cernera, Stephanie, et al. "Long-Term Parkinson's Disease Quality of Life after Staged DBS: STN vs. GPi and First vs. Second Lead." *NPJ Parkinson's Disease*, vol. 6, Jul. 2020, p. 13. <https://doi.org/10.1038/s41531-020-0115-3>
- Chen, Wesley, et al. "Role of Functional Neurosurgery in Improving Patient Outcomes in Epilepsy, Movement Disorders, and Chronic Pain." *Missouri Medicine*, vol. 121, no.

- 2, 2024, pp. 149–155.
- DeLong, Mahlon R., and Alim-Louis Benabid. “Discovery of High-Frequency Deep Brain Stimulation for Treatment of Parkinson Disease: 2014 Lasker Award.” *JAMA: The Journal of the American Medical Association*, vol. 312, no. 11, Sep. 2014, pp. 1093–1094. <https://doi.org/10.1001/jama.2014.11132>
- DeLong, Mahlon R., and Thomas Wichmann. “Basal Ganglia Circuits as Targets for Neuromodulation in Parkinson Disease.” *JAMA Neurology*, vol. 72, no. 11, Nov. 2015, pp. 1354–1360. <https://doi.org/10.1001/jamaneurol.2015.2397>
- Freitas, Maria Eliza, et al. “Motor Complications of Dopaminergic Medications in Parkinson’s Disease.” *Seminars in Neurology*, vol. 37, no. 2, Apr. 2017, pp. 147–157. <https://doi.org/10.1055/s-0037-1602423>
- Gray, Richard, et al. “Long-Term Effectiveness of Adjuvant Treatment With Catechol-O-Methyltransferase or Monoamine Oxidase B Inhibitors Compared With Dopamine Agonists Among Patients With Parkinson Disease Uncontrolled by Levodopa Therapy: The PD MED Randomized Clinical Trial.” *JAMA Neurology*, vol. 79, no. 2, Feb. 2022, pp. 131–140. <https://doi.org/10.1001/jamaneurol.2021.4736>
- Groiss, S. J., et al. “Deep Brain Stimulation in Parkinson’s Disease.” *Therapeutic Advances in Neurological Disorders*, vol. 2, no. 6, Nov. 2009, pp. 20–28. <https://doi.org/10.1177/1756285609339382>
- Guidera, Jennifer A., et al. “A Systematic Review Comparing Radiofrequency versus Focused Ultrasound Pallidotomy in the Treatment of Parkinson’s Disease.”

- Stereotactic and Functional Neurosurgery*, vol. 102, no. 5, Aug. 2024, pp. 325–342.
<https://doi.org/10.1159/000539911>
- Hacker, Mallory L., et al. “Deep Brain Stimulation in Early-Stage Parkinson Disease: Five-Year Outcomes.” *Neurology*, vol. 95, no. 4, Jul. 2020, pp. e393–401.
<https://doi.org/10.1212/WNL.0000000000009946>
- Hariz, Marwan, and Patric Blomstedt. “Deep Brain Stimulation for Parkinson’s Disease.” *Journal of Internal Medicine*, vol. 292, no. 5, Nov. 2022, pp. 764–778.
<https://doi.org/10.1111/joim.13541>
- Kern, Drew S., et al. “Discrete Changes in Brain Volume after Deep Brain Stimulation in Patients with Parkinson’s Disease.” *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 91, no. 9, Sep. 2020, pp. 928–937. <https://doi.org/10.1136/jnnp-2019-322688>
- Kochanski, Ryan B., and Sepehr Sani. “Awake versus Asleep Deep Brain Stimulation Surgery: Technical Considerations and Critical Review of the Literature.” *Brain Sciences*, vol. 8, no. 1, Jan. 2018, p. 17. <https://doi.org/10.3390/brainsci8010017>
- Koivu, Maija, et al. “Clinical and Brain Morphometry Predictors of Deep Brain Stimulation Outcome in Parkinson’s Disease.” *Brain Topography*, vol. 37, no. 6, Nov. 2024, pp. 1186–1194. <https://doi.org/10.1007/s10548-024-01054-2>
- Kopell, Brian Harris, and Benjamin D. Greenberg. “Anatomy and Physiology of the Basal Ganglia: Implications for DBS in Psychiatry.” *Neuroscience & Biobehavioral Reviews*, vol. 32, no. 3, Jan. 2008, pp. 408–422.
<https://doi.org/10.1016/j.neubiorev.2007.07.004>

- Kulisevsky, Jaime. “Tratamiento Farmacológico de Los Síntomas Motores de La Enfermedad de Parkinson: Actualización y Recomendaciones de Un Experto.” *Revista de Neurología*, vol. 75, no. Suppl 4, Oct. 2022, pp. S1–10.
<https://doi.org/10.33588/rn.75S04.2022217>
- Leaver, Katherine, et al. “Clinical Profiles and Outcomes of Deep Brain Stimulation in G2019S LRRK2 Parkinson Disease.” *Journal of Neurosurgery*, vol. 137, no. 1, Jul. 2022, pp. 184–191. PubMed Central, <https://doi.org/10.3171/2021.7.JNS21190>
- Lozano, A. M., et al. “Effect of GPi Pallidotomy on Motor Function in Parkinson’s Disease.” *Lancet*, vol. 346, no. 8987, Nov. 1995, pp. 1383–1387. PubMed, [https://doi.org/10.1016/s0140-6736\(95\)92404-3](https://doi.org/10.1016/s0140-6736(95)92404-3)
- Lozano, Andres M., et al. “Deep Brain Stimulation: Current Challenges and Future Directions.” *Nature Reviews. Neurology*, vol. 15, no. 3, Mar. 2019, pp. 148–160.
<https://doi.org/10.1038/s41582-018-0128-2>
- Martínez-Fernández, Raúl, et al. “Prospective Long-Term Follow-up of Focused Ultrasound Unilateral Subthalamotomy for Parkinson Disease.” *Neurology*, vol. 100, no. 13, Mar. 2023, pp. e1395–1405.
<https://doi.org/10.1212/WNL.0000000000206771>
- Okun, Michael S., et al. “Cognition and Mood in Parkinson’s Disease in Subthalamic Nucleus versus Globus Pallidus Interna Deep Brain Stimulation: The COMPARE Trial.” *Annals of Neurology*, vol. 65, no. 5, 2009, pp. 586–595.
<https://doi.org/10.1002/ana.21596>

Opara, Józef, et al. “Motor Assessment in Parkinson’s Disease.” *Annals of Agricultural and Environmental Medicine*, vol. 24, no. 3, Sep. 2017, pp. 411–415.

<https://doi.org/10.5604/12321966.1232774>

Poewe, Werner, et al. “Levodopa in the Treatment of Parkinson’s Disease: An Old Drug Still Going Strong.” *Clinical Interventions in Aging*, vol. 5, 2010, pp. 229–238.

<https://doi.org/10.2147/cia.s6456>

Pringsheim, Tamara, Gregory S. Day, Don B. Smith, Alex Rae-Grant, Nicole Licking, Melissa J. Armstrong, Rob M.A. de Bie, et al. “Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary.” *Neurology*, vol. 97, no. 20, Nov. 2021, pp. 942–957.

<https://doi.org/10.1212/WNL.0000000000012868>

Pringsheim, Tamara, Gregory S. Day, Don B. Smith, Alex Rae-Grant, Nicole Licking, Melissa J. Armstrong, Rob M. A. de Bie, et al. “Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary: A Report of the AAN Guideline Subcommittee.” *Neurology*, vol. 97, no. 20, Nov. 2021, pp. 942–957.

<https://doi.org/10.1212/WNL.0000000000012868>

Scherer, Maximilian, et al. “Single-Neuron Bursts Encode Pathological Oscillations in Subcortical Nuclei of Patients with Parkinson’s Disease and Essential Tremor.”

Proceedings of the National Academy of Sciences of the United States of America, vol. 119, no. 35, Aug. 2022, p. e2205881119.

<https://doi.org/10.1073/pnas.2205881119>

- Schuepbach, WM Michael, et al. "Quality of Life Predicts Outcome of Deep Brain Stimulation in Early Parkinson Disease." *Neurology*, vol. 92, no. 10, Mar. 2019, p. e1109. <https://doi.org/10.1212/WNL.0000000000007037>.
- Thanvi, Bhomraj, et al. "Levodopa-Induced Dyskinesia in Parkinson's Disease: Clinical Features, Pathogenesis, Prevention and Treatment." *Postgraduate Medical Journal*, vol. 83, no. 980, Jun. 2007, pp. 384–388. <https://doi.org/10.1136/pgmj.2006.054759>
- Wong, Joshua K., Vyas T. Viswanathan, et al. "STN Versus GPi Deep Brain Stimulation for Action and Rest Tremor in Parkinson's Disease." *Frontiers in Human Neuroscience*, vol. 14, Oct. 2020, p. 578615. <https://doi.org/10.3389/fnhum.2020.578615>
- Wong, Joshua K., James H. Cauraugh, et al. "STN vs. GPi Deep Brain Stimulation for Tremor Suppression in Parkinson Disease: A Systematic Review and Meta-Analysis." *Parkinsonism & Related Disorders*, vol. 58, Jan. 2019, pp. 56–62. <https://doi.org/10.1016/j.parkreldis.2018.08.017>
- Zesiewicz, Theresa A., et al. "Levodopa-Induced Dyskinesia in Parkinson's Disease: Epidemiology, Etiology, and Treatment." *Current Neurology and Neuroscience Reports*, vol. 7, no. 4, Jul. 2007, pp. 302–310. <https://doi.org/10.1007/s11910-007-0046-y>

CURRICULUM VITAE

