

Deep brain stimulation in movement disorders

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ABSTRACT

Deep brain stimulation is an evidence-based therapy for movement disorders. In Parkinson's disease (PD), essential tremor (ET), and dystonia, DBS offers substantial and sustained benefits when patients are carefully selected and treatment is delivered within a multidisciplinary framework. This review summarizes the current state of DBS in movement disorders, focusing on established indications, optimal patient selection, target choice, and surgical strategies. For PD, the subthalamic nucleus (STN) and globus pallidus internus (Gpi) remain the main targets, each with distinct advantages depending on clinical phenotype, therapeutic goals, and risk profiles. In ET, ventral intermediate nucleus (VIM) of thalamus stimulation continues to provide the most reliable tremor control, while caudal zona incerta (cZI) and posterior subthalamic area (PSA) stimulation represent emerging alternatives. In dystonia, GPi stimulation remains the standard of care, with growing evidence supporting the use of STN in selected cases. The variability in outcomes underscores the importance of aligning expectations with symptom responsiveness, as axial, gait, and speech problems in PD or fixed and bulbar features in dystonia often remain refractory. Recent advances are reshaping the field, including directional leads, robotic and imaging-based guidance, tele-programming, and adaptive closed-loop systems that adjust stimulation in real time based on physiological markers. Novel targets are under exploration to address unmet needs such as freezing of gait and postural instability. Together, these developments highlight a transition toward increasingly precise, personalized, and network-informed interventions, with DBS continuing to expand its role in movement disorder therapy.

1. Overview

Deep brain stimulation (DBS) is widely recognized as a valuable option for various movement disorders. It is known to act through multiple mechanisms rather than a single process [1]. It exerts local and network-level effects, alters oscillatory activity, modulates synaptic plasticity, and may even promote neuroprotection and neurogenesis, reflecting its complex therapeutic nature.

DBS is primarily used in three key movement disorders: Parkinson's disease (PD), essential tremor (ET), and dystonia. It has been observed that a substantial number of patients who would greatly benefit from DBS often do not get referred for an evaluation at a DBS center in a timely manner, thus facing extended periods of disability, compromised functionality, and decreased quality of life (QoL). Conversely, there are cases where unsuitable candidates are referred to DBS as a last resort after other treatments have failed. Therefore, certain key factors have been identified as critical for ensuring successful outcomes for those undergoing DBS treatment, including careful selection of patients,

precise placement of the leads, careful device programming, and effective postoperative management.

In this review, an overview of basic concepts and current literature on DBS in movement disorders will be presented.

2. Deep brain stimulation for Parkinson's disease

PD is a complex neurodegenerative disorder primarily characterized by Parkinsonian symptoms due to the early degeneration of dopaminergic nigrostriatal pathways. While initial symptoms result from striatal dopamine loss, later features reflect broader extrastriatal pathology. PD remains the leading indication for DBS to alleviate motor symptoms, which vary widely across patients and evolve throughout disease progression.

While not all patients with PD are suitable for DBS, estimates suggest that approximately 10–20 % of PD patients could significantly benefit from this therapeutic approach. Although there are no strictly defined guidelines for determining who is eligible for DBS, a consensus exists

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within the medical community that helps guide clinical decisions (Table 1) [2]. Therefore, determining DBS eligibility requires a systematic evaluation of various factors.

2.1. Selection for surgery

2.1.1. Diagnostic certainty

DBS has been shown to offer considerable benefits to those diagnosed with idiopathic PD. However, it is important to note that, as of now, there is no evidence to support the effectiveness of DBS in treating conditions such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration and dementia with Lewy bodies, even though these disorders may present PD-like symptoms. Therefore, accurately diagnosing PD is a fundamental step in determining a patient's eligibility for DBS. This involves an in-depth neurological evaluation, examining the evolution and current manifestation of symptoms, response to dopaminergic medications, and the presence/absence of typical PD symptoms. Although a definitive diagnosis is achievable only through autopsy [3], imaging techniques can play a crucial role in supporting this diagnosis or distinguishing PD from other aforementioned similar conditions. For instance, standard MRI scans in idiopathic PD typically do not show significant abnormalities. In contrast, individuals with vascular parkinsonism might show multiple deep white matter lesions on MRI scans. Features indicative of MSA include disproportionate atrophy, pontine "hot cross bun" sign, or T2 hyperintense putaminal rim, while PSP might show midbrain atrophy, recognizable as the hummingbird or morning glory sign. Meanwhile, corticobasal syndrome may be associated with asymmetric cortical atrophy or T2 hyperintensities in the subcortical white matter of affected gyri [4]. Additionally, dopamine transporter (DAT) SPECT has an important role in the diagnostic process, especially when differential diagnosis remains challenging [5]. A normal DAT SPECT scan is considered a definitive exclusion criterion for PD. Since most atypical Parkinsonian syndromes become apparent within four to five years of symptom onset, offering DBS after this period may be prudent if there is still any diagnostic uncertainty [6].

2.1.2. Symptom severity

The decision to recommend DBS hinges on a detailed understanding of the symptomatology and the likelihood of these symptoms ameliorating in response to the intervention. This tailored approach ensures that DBS is considered for those anticipated to derive substantial symptomatic relief and improved QoL. Certain motor symptoms respond well to treatment, while others remain less responsive. Symptoms such

as tremor, bradykinesia, rigidity, dyskinesia, and motor fluctuations are typically responsive. In contrast, hypophonic speech, dysphagia, micrographia, freezing of gait (particularly in the "on" state), and pronounced balance difficulties are often unresponsive or only minimally improved. For DBS candidates, the most significant issues should stem from typical motor symptoms. The primary symptoms for considering DBS include medically refractory and disabling motor fluctuations, levodopa-induced dyskinesias (LIDs), and tremors [7].

The decision to proceed with DBS surgery is contingent upon the patient experiencing considerable functional impairment due to PD, weighing the potential benefits of the procedure against the inherent risks of surgical intervention. Patients whose primary PD challenges are non-motor symptoms or motor symptoms unresponsive to dopamine replacement therapy (DRT) generally do not qualify as ideal DBS candidates. This exclusion persists even in the presence of significant motor fluctuations and/or LIDs. Motor symptoms that show no improvement with DRT, including impaired gait and balance, freezing, dysarthria, and dysphagia, are considered potential disqualifiers for DBS. Should these symptoms dominate the patient's disability profile, DBS is unlikely to confer marked benefits [8]. In some cases, symptoms that are refractory to DRT may even worsen post-DBS, reducing the likelihood of a positive surgical outcome.

2.1.3. Appropriate timing

Current recommendations on optimal timing outline potential benefits and risks but do not provide practical referral criteria. The EARLYSTIM study shifted practice by showing that earlier STN-DBS improved motor and non-motor outcomes, including QoL, sleep, pain, and anxiety.

[9,10] However, criticisms about patient selection and placebo effects limit its generalizability [11,12]. Recent surveys indicate a split in opinion among healthcare providers regarding the necessary duration of PD symptoms before considering DBS, with some suggesting a minimum of 3–4 years post-diagnosis, while others argue against setting a pre-defined minimum duration [13]. Meanwhile, another group recommended a more conservative waiting period of 5–7 years. This variance in viewpoints underscores the need for a unified effort to develop more concrete guidelines, aiding clinicians in making informed decisions about the timing of DBS for PD patients.

2.1.4. Pharmacological treatment

DBS is considered when optimized pharmacological therapy fails to control symptoms, particularly in the presence of disabling motor fluctuations. Medication regimens should be thoroughly optimized first. If

Table 1

Deep brain stimulation (DBS) standards for Parkinson's disease (PD).

Inclusion criteria

The patient must have a confirmed diagnosis of PD based on established diagnostic criteria.

Patients should demonstrate a significant and sustained response to Levodopa treatment.

The presence of disabling motor symptoms that are not adequately controlled by optimized medical therapy, including motor fluctuations (such as "on-off" phenomena) or dyskinesias.

Disease duration longer than 5 years

Patients must have the capacity to provide informed consent, which includes understanding the potential risks and benefits of DBS surgery, the necessity for regular follow-up, and device adjustments.

A comprehensive evaluation by a multidisciplinary team, including movement disorder specialists, neurosurgeons, neuropsychologists, and psychiatrists

Exclusion criteria

The presence of red flags:

- Prominent postural instability within the first three years following symptom onset
- Early freezing phenomena within the first three years
- Hallucinations not induced by medications within the first three years
- The emergence of dementia before motor symptoms or within the first year
- Supranuclear gaze palsy
- Signs of upper motor neuron involvement
- Significant, symptomatic dysautonomia unrelated to medications
- Evidence of a condition known to cause parkinsonism that could reasonably be linked to the patient's symptoms

Cognitive impairment, particularly dementia

Unstable psychiatric profile (suicide risk etc.)

Poor general health (presence of co-morbidities, short life expectancy, and being unfit for the surgery)

Significant brain atrophy or lesions in critical areas that significantly increase the risk of surgery or reduce the likelihood of DBS effectiveness

fluctuations persist, side effects outweigh benefits, or medication burden becomes intolerable, DBS becomes a compelling option, with patient preference playing a key role.

2.1.5. The extent of dopaminergic responsiveness

Levodopa responsiveness is a key predictor of DBS outcomes. Beyond patient history, objective assessment with the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III is essential, comparing motor function in the 'off' state (after 8–12 h withdrawal) and the 'on' state (after the usual dose). Specifically, a favorable response to levodopa, evidenced by significant improvements in the MDS-UPDRS Part III score, is indicative of a likely positive outcome from DBS. While no universal consensus on cutoff exists, many centers expect at least a 30 % improvement, and the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) recommends ≥ 33 % [14]. However, the test may be less informative in patients unable to tolerate therapeutic levodopa doses due to side effects.

2.1.6. Cognitive status

Cognitive impairment stands as a notable contraindication for DBS in PD, with cognitive changes being a significant concern following STN-DBS [15]. These changes can manifest as impairments in verbal fluency, executive functions, and potentially other cognitive areas. It is essential to know that the extent of these cognitive effects varies among individuals, influenced by factors such as electrode placement precision, stimulation parameters, and the patient's pre-operative cognitive status [16,17]. A comprehensive neuropsychological assessment is thus crucial in evaluating a candidate's suitability for DBS.

The candidacy for DBS in patients with varying degrees of cognitive impairment requires careful, individualized consideration. Comprehensive neurocognitive testing forms an integral part of the pre-DBS neuropsychological evaluation, aiding in the meticulous assessment of cognitive function and potential risks associated with the procedure.

Given the disease progression, many PD patients evaluated for DBS might already exhibit MCI, although this does not automatically exclude them from undergoing DBS. Factors such as caregiver observations, the patient's capability to manage daily activities, clinical behavioral assessments, MRI evidence of brain atrophy, delirium history, and visual hallucinations occurrence are critical in this assessment. Viewing MCI as a spectrum is beneficial, particularly as severe MCI may closely mimic the early stages of dementia. It is noteworthy that individuals with significant educational backgrounds and cognitive reserves may perform within average test ranges while experiencing considerable functional declines, indicating a significant drop from their previous cognitive levels.

Dementia, which becomes increasingly prevalent with the progression of PD and aging, signals a more widespread disease manifestation, potentially diminishing the motor improvement achievable through DBS [18]. Furthermore, dementia complicates achieving optimal DBS outcomes due to challenges in symptom communication and adjustment of DBS settings. Additionally, there is a risk of cognitive decline worsening after DBS surgery in patients with pre-existing dementia, potentially increasing their disability.

2.1.7. Mood and psychiatric symptoms

In PD, patients frequently grapple with neuropsychiatric symptoms alongside their motor challenges. Symptoms such as depression, anxiety, and psychotic features, including hallucinations and delusions, are not only prevalent but also play a critical role across the disease's spectrum, manifesting from its prodromal stages through to the more advanced stages [19–21]. These neuropsychiatric manifestations can arise directly from PD pathology or as a consequence of the medications employed to alleviate motor symptoms. Patients exhibiting pronounced and treatment refractory neuropsychiatric symptoms typically are considered less suitable for DBS. Prior to DBS consideration, it is crucial to identify and

appropriately manage these symptoms.

In many instances, adjusting the PD treatment plan, either by reducing antiparkinsonian medication dosages or integrating an atypical antipsychotic, can mitigate neuropsychiatric symptoms. If otherwise good candidates, patients with disqualifying mood and/or anxiety disorders might be reconsidered as DBS candidates following effective treatment. Also, when a patient exhibits mild symptoms that are clearly induced by medication, proceeding with DBS can be advantageous as DBS often allows for a postoperative reduction in the dosage of medications, thereby decreasing the associated adverse effects.

2.1.8. Appropriate age

Although there is no absolute age limit for DBS surgery, older age is associated with a greater likelihood of comorbidities and cognitive impairments, factors that heighten the risks tied to the DBS procedure. Therefore, the appropriate age for DBS is generally considered to be under 70 years of age, and careful consideration is recommended for candidates over 70 years of age. Age-related anatomical changes in the brain could also reduce the distance between the targeted area for stimulation and adjacent structures, raising the risks of inadvertently affecting nearby areas and eliciting unwanted side effects. In PD patients, advancing age is also often correlated with a diminished response to levodopa, which could result in less pronounced benefits from DBS treatment. Despite these considerations, individuals over 70 years old who still show a clear response to levodopa and are indicated for DBS treatment, provided they are otherwise in good health, may still be considered suitable candidates for the surgery after a very careful evaluation.

2.1.9. Previous ablative surgery

Previous ablative surgery such as pallidotomy and thalamotomy does not exclude patients from DBS. Kleiner-Fisman et al. reported significant motor improvements (42 % MDS-UPDRS-III) in patients who had unilateral pallidotomy followed by bilateral STN-DBS [22]. Similarly, Khabarova et al. found comparable DBS outcomes in patients with or without prior lesioning, with 45 % MDS-UPDRS-III and 75 % MDS-UPDRS-IV improvements, and a 51 % levodopa equivalent daily dose (LEDD) reduction [23]. Notably, there was no significant difference in MDS-UPDRS part III or part IV scores between the two groups 12 months post-DBS. These findings confirm that DBS remains effective and adaptable regardless of prior surgical history, offering meaningful QoL benefits.

2.2. Surgical factors

2.2.1. Target selection

In the realm of DBS for PD, STN, globus pallidus internus (GPi), and ventral intermediate nucleus (VIM) of thalamus stand out as the primary targets for intervention (Fig. 1). The process of selecting the most suitable target for DBS is underpinned by a comprehensive assessment of the patient's specific symptomatology, medication response, potential side effects, and the specific benefits each target can offer (Table 2) [24]. This patient-centric strategy is designed to maximize the therapeutic benefits of DBS, aiming to significantly improve the patient's QoL by mitigating the most severe symptoms associated with PD.

STN-DBS closely mimics the effects of dopaminergic drugs, providing significant relief from PD symptoms. This therapeutic intervention is particularly noted for its ability to substantially reduce, or in some cases, eliminate the necessity for DRT in patients with advanced PD. The smaller size of STN generally necessitates lower levels of stimulation to be effective, which contributes to longer battery life for the implanted device. The established consensus for optimal outcomes for STN-DBS includes a strong response to levodopa, younger age, minimal or no cognitive impairment, and stable psychiatric status. However, certain conditions, including non-responsiveness to levodopa, severe axial symptoms unimproved by levodopa, non-dopaminergic symptoms such

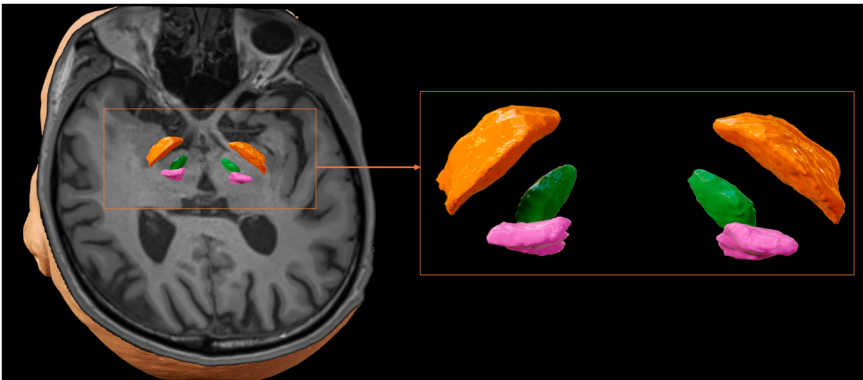


Fig. 1. MR image showing three most common deep brain stimulation targets. The globus pallidus internus is highlighted in orange, the subthalamic nucleus is marked in green, and the ventral intermediate nucleus of the thalamus is depicted in pink.

Table 2
Target selection in Parkinson’s disease (PD).

Supportive criteria		
STN	GPI	VIM
Ideal for younger patients, especially those experiencing severe fluctuations and/or dyskinesias, requiring medication dose reduction, or suffering from nocturnal akinesia.	Preferred in cases of severe dyskinesias, levodopa resistant dystonia, levodopa responsive non-motor symptoms, or dopamine dysregulation syndrome.	The primary choice for patients with severe tremor and those without significant other PD-related symptoms.
Exclusion criteria		
STN	GPI	VIM
Not recommended for older patients, those with depression/apathy, mild cognitive impairment with progressive features, or axial impairments (including balance, speech, or gait problems).	Generally avoided in patients aged over 75–80 years, considering the increased risk of procedural complications and the presence of alternative targets that might offer better outcomes with lower risk profiles.	The risk of side effects from DBS increases with age, and patients with other PD-related bothersome symptoms may not find adequate relief from VIM targeting alone.

STN: Subthalamic nucleus, GPI: Globus pallidus internus, VIM: Ventral intermediate nucleus of thalamus, DBS: Deep brain stimulation.

as balance issues and severe dysarthria, pronounced cognitive decline, and severe depression, are identified as contraindications. STN-DBS requires more rigorous patient selection criteria compared to other DBS targets and demands detailed postoperative care by specialist neurologists. A meta-analysis by Kleiner-Fisman et al. highlighted that STN-DBS resulted in approximately 50 % improvements in MDS-UPDRS part II and III scores, 70 % in part IV scores, and daily “off” time, a 50 % reduction in LEDD, and a 35 % enhancement in QoL [25]. This study identified levodopa responsiveness, higher baseline motor scores, and disease duration as independent predictors of motor score improvements. Longitudinal studies confirm that the benefits of STN-DBS extend over several years, with motor function improvements sustained for up to 10 years [26,27]. These studies also report long-lasting improvements in motor fluctuations and LIDs alongside a continuous effect on reducing DRT intensity. STN-DBS has also been found to improve some non-motor symptoms, such as PD-related pain and sleep quality, with improvements lasting up to eight years after the procedure [28,29]. However, while STN-DBS significantly improves motor and some non-motor symptoms, the advantages tend to wane over extended follow-up periods, suggesting that STN-DBS does not arrest the progression of PD or alter the underlying disease pathology [30].

DBS of the posteroventral **GPI** is less commonly performed than STN-DBS, yet studies suggest that the efficacy of GPI-DBS in mitigating motor symptoms is comparable to that of STN-DBS [31–34]. A distinctive

disadvantage of GPI over STN-DBS is the lack of a significant decrease in LEDD observed with STN-DBS [35]. Instead, GPI-DBS offers a direct antidyskinetic effect, beneficial for managing LIDs, thereby allowing for the continued use of medications to manage PD symptoms more effectively and synergistically [36]. GPI-DBS is particularly advantageous for patients who experience substantial LIDs at low doses of DRT, as these patients may still suffer from dyskinesias with even minimal stimulation from STN-DBS. Another benefit of GPI-DBS is the absence of age restrictions, making it a viable option for a broader patient demographic. Additionally, GPI-DBS presents a lower risk of negatively impacting balance and causing dysarthria, unlike STN-DBS. When considering the risk of side effects, cognitive, mood, and behavioral abnormalities appear to manifest less frequently with GPI-DBS than with STN-DBS [37]. However, some studies report no significant differences in cognitive and psychiatric outcomes between the two targets [38,39]. The larger size of GPI necessitates more energy, leading to more frequent battery changes, but its programming is typically easier. In contrast, patients undergoing STN-DBS need to be managed by highly experienced centers to ensure optimal adjustment of medication dosages and stimulation settings post-surgery.

While dopaminergic medications effectively alleviate akinesia and rigidity, they are less effective against tremors. Therefore, for PD patients who have well-controlled symptoms apart from tremors and who do not experience LIDs, **VIM-DBS** offers a robust and durable solution for tremor control [40]. This procedure has no age restrictions, assuming the patient is generally healthy and MRI scans do not show significant brain atrophy. Despite its efficacy in tremor control, VIM-DBS is utilized less frequently than GPI or STN-DBS. This shift reflects the evolving profile of surgical candidates, who are often at more advanced stages of PD, presenting with a broader array of symptoms beyond tremor. While side effects such as dysarthria and balance issues may emerge, these can often be alleviated through careful adjustments to the stimulation parameters. Over time, a phenomenon of tolerance may develop, requiring incrementally higher levels of stimulation to achieve the same tremor control [41]. In a few instances, patients might experience ataxia, which generally resolves upon temporary cessation of the stimulation [42].

DBS has explored various neural targets beyond the conventional to address PD symptoms, particularly those less responsive to traditional DBS sites and medications. Among these, the pedunculopontine nucleus (PPN), caudal zona incerta (cZI), centromedian/parafascicular (CM/Pf) complex, and the substantia nigra pars reticulata (SNr) have been identified as promising but less traditional targets. The key roles, effects, advantages and disadvantages of these target were summarized in Table 3 [43–53].

Multitargeting emerges as a promising strategy for addressing PD symptoms that are not adequately managed by traditional targets like the STN or the GPI. However, the approach of targeting multiple sites with DBS is constrained by higher costs, the extended duration and

Table 3

Emerging deep brain stimulation (DBS) targets in Parkinson's Disease.

Target	Key Role / Connections	Clinical Effects	Advantages	Limitations / Concerns / Potential Side Effects
Pedunculopontine nucleus (PPN) [43,44]	Motor center for gait and posture; trunk control; interacts with GABAergic circuits	Improvements in gait and postural control with low-frequency DBS (uni- or bilateral)	Potentially safe; addresses gait/postural symptoms poorly responsive to STN/GPi DBS	Variable efficacy across studies; inconsistent outcomes; side effects include paresthesia (medial lemniscus/spinothalamic), oscillopsia (uncinate fasciculus/superior cerebellar peduncle), limb myoclonus (cerebellar peduncle)
Caudal zona incerta (cZI) [45–49]	Posterior subthalamic area; adjacent to pallidothalamic fibers	Enhances motor outcomes; reduces dopaminergic medication needs; long-term responsiveness	May provide broader motor benefit than STN alone; reduces medication-related side effects	Risk of dyskinesias, dysarthria; may affect reward/pleasure-seeking behaviors
Centromedian/parafascicular complex (CM/Pf) [50]	Intralaminar thalamus; connects cortex, basal ganglia, brainstem; integrates sensory–limbic–motor processes	Improvement in dyskinesias, tremor, and freezing of gait	Broader network modulation; may outperform VIM for certain symptoms	Less effective than STN-DBS for global motor/extrapyramidal symptoms; side effects as potential cognitive impairments
Substantia nigra pars reticulata (SNr) [51–53]	Midbrain locomotor region; strong basal ganglia and limbic connections	Improvement in axial symptoms (gait initiation, postural stability, freezing of gait)	Targeted benefit for axial symptoms resistant to STN/GPi	Potential psychiatric side effects (mood alterations) due to limbic projections

STN: Subthalamic nucleus, GPi: Globus pallidus internus, VIM: Ventral intermediate nucleus of thalamus.

complexity of surgery, and the increased risk of complications [54]. As technology and scientific knowledge advance, the landscape of DBS therapy, including multitarget approaches, is expected to evolve, promising new insights and improvements in the treatment of PD.

2.2.2. Surgical strategies

The choice of surgical strategy in DBS involves both timing and technique. The feasibility and safety of administering bilateral DBS have positioned it as a favored intervention for PD patients experiencing bilateral symptoms, encompassing both appendicular and axial motor challenges. In scenarios where symptoms are predominantly unilateral, or there is a significant asymmetry in symptom manifestation without major gait disturbances, contralateral DBS can lead to significant symptom alleviation [55]. Nonetheless, research also advocates for considering immediate bilateral STN-DBS for PD patients with markedly asymmetrical motor symptoms, emphasizing its potential to facilitate long-term management [56]. Bilateral DBS, particularly at a moderately advanced disease stage, presents the advantage of potentially reducing medication dosages postoperatively, offering a broader scope of symptom relief compared to unilateral DBS, whose benefits may diminish over time and present more intricate challenges in postoperative management. Bilateral implantation can be performed simultaneously in a single session, reducing hospitalizations and anesthesia exposure, or staged approach with a gap of several months, allowing evaluation of unilateral benefit and potentially lowering risks such as hemorrhage, infection, and cognitive decline [57].

Lead placement may be conducted in awake patients using MER and intraoperative testing, or under general anesthesia with modern imaging guidance (“asleep DBS”). Awake approaches enable direct physiological feedback and macrostimulation to define side-effect thresholds, while asleep techniques improve patient comfort and feasibility, particularly in anxious or severely affected patients. Comparative trials such as GALAXY trial [58] show similar outcomes between approaches, though awake methods may offer greater precision in functional targeting. MER remains most valuable in PD, whereas imaging-based targeting is often sufficient for ET and dystonia.

3. Deep brain stimulation for patients with essential tremor

Traditionally, pharmacological treatment has been the cornerstone for managing ET, with first-line medications achieving an average tremor reduction of 55–60 % as monotherapy [59]. Although combining medications can enhance therapeutic outcomes, approximately 55 % of patients experience tremors that do not respond adequately to medications, leading to consideration of surgical options for those with severe

and treatment-resistant symptoms [60].

3.1. Selection for surgery

3.1.1. Diagnostic certainty

Prior to considering DBS as a treatment option for ET, it is imperative to accurately diagnose the condition, distinguishing it from other tremor disorders such as PD and dystonic tremor. Diagnosing ET relies heavily on clinical history and a thorough physical examination, given the absence of a specific test to definitively confirm the diagnosis. To assist in accurate diagnosis, various clinical criteria have been developed over time. Initially, the Consensus Statement on Tremor by MDS laid down foundational criteria, which were subsequently refined by the Tremor Research Group in 2000 and received further modifications in a revised Consensus Statement in 2018 [61–63]. Moreover, the diagnostic criteria emerging from the Washington Heights-Inwood Genetic Study of ET have become particularly instrumental, especially in the fields of genetic and epidemiological studies [64]. These evolving criteria play a vital role in distinguishing ET from conditions like enhanced physiological tremor, offering clinicians a systematic framework for diagnosing this multifaceted and heterogeneous disorder.

3.1.2. Symptom severity

ET shows wide variability in severity, ranging from subclinical cases to disabling tremor that interferes with self-care, work, and social functioning. Many patients seeking treatment report disability, and severe cases may struggle with eating, writing, or dressing. This highlights that ET is far from a benign condition and can markedly impair QoL.

DBS is typically considered in moderate-to-severe cases with functional impairment. Tremor severity and disability are systematically quantified using validated rating scales, most commonly the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) and the Essential Tremor Rating Assessment Scale (TETRAS), which provide structured frameworks for patient selection and treatment planning [65,66]. This meticulous assessment aids in determining the appropriateness of DBS for individuals with ET, ensuring that the intervention is tailored to those who stand to benefit the most from it.

3.1.3. Pharmacological treatment

Prior to considering DBS as a therapeutic option for ET, it is imperative to ensure that pharmacological treatments have been exhaustively optimized. This entails meticulous documentation of the trial history for each medication, encompassing dosages, effectiveness, and any adverse effects experienced, to assess both the efficacy of the treatments and the patient's tolerance to them. In instances where monotherapy is

ineffective, a combination therapy may be pursued. Additionally, botulinum toxin (BoNT) injections have been substantiated through both open-label and double-blind studies as an effective intervention for managing tremors across various body parts, including limbs, head, voice, and palate [67]. Similar to the treatment approach for PD, DBS emerges as a feasible alternative for patients whose tremors remain significantly disabling despite comprehensive trials of medication, providing a potential path to improved QoL for those with treatment-resistant ET.

3.1.4. Previous ablative surgery

The evidence base regarding the efficacy of DBS in patients who have previously undergone surgical interventions for ET, such as pallidotomy or thalamotomy, remains sparse. Despite this lack of extensive data, there are documented instances where patients with a history of unilateral pallidotomy or thalamotomy have undergone successful unilateral or bilateral DBS [68–71]. These cases indicate the potential feasibility of DBS as a subsequent treatment option for ET, even after previous surgical attempts to manage the condition. It is important to highlight, however, that the occurrence of adverse effects has been frequently noted, particularly in scenarios where patients have a pre-existing contralateral lesion resulting from earlier surgical interventions. This suggests that while DBS can offer a viable treatment pathway for individuals with prior surgical histories, careful consideration and thorough preoperative assessment are essential to mitigate risks and manage the likelihood of adverse outcomes effectively.

3.2. Surgical factors

3.2.1. Target selection

The selection of DBS targets for ET is determined by the patient's individual characteristics or phenotype. This personalized approach ensures that the DBS intervention is optimized to address the unique tremor patterns, symptom severity, and overall clinical presentation of the individual.

The most common target is **VIM** for ET. MERs during stereotactic surgeries have identified tremor cells within VIM, establishing VIM as the standard target for DBS in ET. The pivotal role of VIM in the cerebello-thalamo-cortical circuit underpins the efficacy of DBS in this region, attributed to modulating the hyperactivity within this network that is closely linked to tremor amplitude and origin in various tremor disorders [72]. Short-term outcomes after unilateral VIM-DBS have shown significant tremor reduction (up to 62.8 %), particularly affecting action tremor in the upper limbs and related tasks (up to 78.9 % improvement) [73]. Long-term follow-ups up to five years have confirmed sustained action tremor reduction (up to 75 %) and improved daily living activities (up to 51 %) in patients with unilateral VIM-DBS [74,75]. While long-term data are more limited, they generally show a sustained improvement in tremor control, with a minority of patients experiencing a reduction in initial benefits over time. Studies tracking outcomes for as long as 18 years post-surgery reveal a slight decrease in mean tremor improvement (66–48 %) over the years, though improvements remain notably significant [76]. When patients encounter a reduction in DBS benefits, reprogramming the device can offer a potential solution. However, outcomes from such adjustments can be unpredictable, especially if stimulation-induced side effects limit the scope for intensification [77]. This gradual decrease in efficacy observed in some ET patients over time has prompted discussions regarding possible causes, such as the disease's natural progression, surgical factors like electrode placement, or ET evolving into a more generalized cerebellar disorder [78,79]. While the concept of developing tolerance to DBS has been speculated, strategies like switching off the DBS device overnight to mitigate this have not been definitively proven [41]. The hypothesis suggesting that chronic stimulation through DBS may induce reversible ataxia has been introduced as a potential explanation for the worsening of tremor, conceptualized as a reversible cerebellar tremor phenomenon

[80]. However, this theory faces skepticism, primarily because tremor recurrence has been observed even after the alleviation of DBS-induced ataxia symptoms [81]. Adverse events associated with VIM-DBS have been reported at a rate of 32 %, with dysarthria, paresthesia, hemiparesis, and headache being the most common stimulation-induced side effects [82].

The **caudal zona incerta (cZi)** has emerged as a promising alternative to VIM for ET [83]. Studies report 90 % tremor reduction with cZi-DBS compared to 60 % with VIM-DBS [84], with sustained improvements in hand function over several years, particularly with bilateral stimulation. Although some long-term data suggest gradual tremor worsening [48], patient-reported outcomes often favor cZi-DBS over VIM [85].

The **posterior subthalamic area (PSA)** has emerged as a noteworthy target in the treatment of ET. An extensive evaluation involving 16 patients, where over 600 stimulation settings were explored, revealed that PSA-DBS provided superior tremor control compared to VIM-DBS, despite a higher occurrence of stimulation-induced side effects [86]. Further supporting this, a double-blind, prospective, cross-over study comparing PSA-DBS to VIM-DBS demonstrated the efficacy of PSA stimulation in controlling tremors at lower stimulation amplitudes without a marked increase in adverse events [87]. Additionally, a review of uncontrolled trials assessing the efficacy of PSA-DBS across various tremor etiologies highlighted a significant tremor reduction with PSA stimulation, achieving a 79 % reduction compared to a 50 % reduction with VIM stimulation [88]. The cZi/PSA-DBS surgeries have demonstrated a range of adverse effects, with reported incidences varying from 20 % to 46 %. Dysarthria emerges as the most frequently encountered stimulation-related side effect. Spasms and postural instability also rank among common adverse effects, along with oculomotor disturbances and paresthesia [85]. Despite these challenges, some research posits that DBS targeting the PSA/cZi might offer a comparatively safer profile than VIM-DBS. This assertion is partly based on the sensitivity of axonal pathways in the PSA/cZi region to electrical stimulation, which may permit the achievement of desired therapeutic effects at lower current intensities [89].

The unique anatomical positioning of the VIM and PSA allows for the possibility of targeting both regions with a single electrode trajectory. Several studies have explored this technique and suggested that the efficacy of dual-target stimulation in reducing tremors is comparable to that achieved with single-target stimulation (either VIM or PSA alone) [90]. However, dual-target DBS presents several potential advantages over single-target DBS. It eliminates the need to choose between targets, reducing the risk of missing the optimal site and the subsequent necessity for additional surgeries. Moreover, having multiple contacts on the electrode permits customized programming for patients, potentially leading to superior tremor control, fewer side effects, and reduced stimulation tolerance [91]. Despite these benefits, dual-target DBS demands greater surgical precision. When evaluating the complications and side effects associated with dual-target versus single-target DBS approaches, studies have generally found little to no significant difference between the two.

3.2.2. Surgical strategies

VIM-DBS can be performed bilaterally, offering broader tremor control, especially for axial, head/neck, and voice tremors [73,92–94]. While bilateral stimulation is more effective than unilateral, disability and QoL outcomes show little difference. Thus, unilateral DBS may suffice when dominant-hand control improves function, whereas bilateral DBS is reserved for patients needing control in both hands, despite higher risks such as dysarthria or imbalance [95,96]. Careful patient selection, strategic lead placement, and intraoperative testing help mitigate these risks, though up to one-third may still develop chronic stimulation-induced dysarthria [97].

4. Deep brain stimulation for patients with dystonia

The management of dystonia poses considerable challenges, particularly as pharmacological treatments often fall short of providing adequate relief or are hindered by side effects that restrict dosage. DBS, especially when targeting the GPi bilaterally, has emerged as an effective intervention for medication-resistant dystonia syndromes. However, DBS surgery for dystonia is generally considered appropriate under specific criteria. First, a clear diagnosis of either primary or secondary dystonia must be established by a neurologist with expertise in movement disorders. Second, the patient should have previously undergone treatment with anticholinergic drugs, benzodiazepines, baclofen, and, in cases of focal or segmental dystonia, botulinum toxin injections, without sufficient success. Finally, despite receiving the best available medical therapy, the patient should continue to experience considerable disability, which may manifest as impaired mobility, pain, social withdrawal, or a combination of these factors. This approach's efficacy is well-documented through a myriad of open-label studies and a handful of blinded, randomized controlled trials, with long-term follow-ups demonstrating sustained improvements [98–103]. Despite these successes, the variability in treatment outcomes at the individual level remains a significant hurdle, including instances of non-responders [104]. Among patients who do respond, the degree of symptom improvement can widely vary, and in some cases, the full therapeutic effects of DBS may unfold only over months or years [105]. Understanding factors influencing treatment outcomes is crucial for optimizing patient care, including selecting candidates for DBS, choosing the treatment approach, and managing aftercare (Table 4).

4.1. Selection for surgery

4.1.1. Diagnostic certainty

Diagnosing dystonia poses significant challenges due to its potential coexistence with other hyperkinetic disorders or its presentation as a blend of hyperkinesia and bradykinesia. Diagnosis relies heavily on clinical judgment, necessitating thorough gathering and observation of movement characteristics such as onset, spread, duration, rhythmicity, affected areas, and predictability. Dystonia is unique among other hyperkinetic movement disorders in having a broader range of conditions that closely mimic its symptoms. Thus, careful clinical evaluation and, when needed, electrophysiology are essential for accurate differentiation.

4.1.2. Symptom severity

A comprehensive clinical evaluation incorporating standardized dystonia rating scales is advisable to accurately establish a patient's baseline symptoms. The Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) is the most frequently utilized scale for assessing the severity and impact of generalized dystonia [106]. While the BFMDRS is extensively utilized, it is primarily validated for adults and not typically used for pediatric cases. For cervical dystonia, the preferred scale is the

Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), a 100-point scale that measures dystonia severity, functional disability, and pain, with higher scores indicating more severe dystonia [107]. These scales, despite offering objective outcome measures, encounter limitations in distinguishing fixed versus mobile dystonia, assessing dystonic tremors, and evaluating complex movements.

The research underscores an inverse relationship between the duration of dystonia and the improvement level post-DBS, indicating that individuals with a shorter history of dystonia often see better outcomes [108]. Furthermore, the presence of orthopedic deformities in dystonia patients also emerges as a negative predictor for DBS outcomes, highlighting the significance of early intervention [104]. This suggests a strong rationale for the prompt application of DBS in dystonia management to avert the progression to orthopedic deformities, ultimately optimizing therapeutic results and improving patient QoL.

Notably, the dynamic or mobile components of dystonia tend to show more immediate and pronounced improvements after DBS, contrasting with the slower progress in tonic or fixed aspects, which may require months to optimize. Discontinuation of DBS typically results in the relapse of the mobile components first. Improvements in the bulbar and laryngeal regions tend to be less significant compared to other parts of the body. This is particularly important for dystonia syndromes like DYT-THAP1 and DYT-KMT2B, where orobulbar and laryngeal involvement are significant [105].

4.1.3. Dystonia etiology

Dystonia is categorized as primary or idiopathic when it manifests without any other neurological signs and is not accompanied by visible brain abnormalities on MRI scans. In contrast, secondary dystonia is associated with a central nervous system lesion resulting from various conditions, including stroke, traumatic brain injury, cerebral palsy, encephalitis, or degenerative brain diseases [109]. Dystonia is further categorized based on the affected body region—focal, segmental, or generalized—and by age at onset, distinguishing between juvenile and adult-onset dystonia.

Idiopathic isolated (primary) generalized and segmental dystonia, notably those linked to the DYT1 gene mutation, have demonstrated considerable improvements following GPi-DBS. BFMDRS scores have shown improvements ranging from 50 % to 90 % post-DBS, with the extent of improvement being gradual, sustained, and heavily reliant on the continuous application of DBS therapy [105,110]. Discontinuing DBS often leads to a rapid resurgence of dystonia symptoms. Furthermore, enhancements in disability and QoL have been reported [100, 111].

Conversely, acquired combined (secondary) dystonia tends to exhibit a more modest response to DBS, with BFMDRS score improvements generally around 20–30 % [112,113]. The relatively lower response rate in patients with acquired combined dystonia is believed to be due to damage within brain networks, which may limit the potential for neuromodulation to be effective. However, a normal brain MRI does not guarantee a favorable DBS outcome, as evidenced by individuals with idiopathic isolated dystonia who exhibit normal MRI scans yet do not respond to DBS. On the other hand, certain dystonia syndromes characterized by abnormal brain MRIs, such as neurodegeneration with brain iron accumulation (NBIA), including DYT-PANK2 and DYT-KTM2B, often show a good initial response to GPi DBS [114]. Recent studies utilizing network analysis on brain MRIs of a broad cohort of dystonia DBS patients have indicated that cortical atrophy and structural integrity loss may predict less optimal DBS outcomes. Moreover, the presence of additional neurological symptoms, like spasticity—which DBS does not ameliorate—may further limit the therapeutic improvements in these cases.

4.1.4. Genetic characterization

Recent literature reviews highlight the variability in DBS efficacy across different monogenic dystonias [115]. The DYT-TOR1A (DYT1)

Table 4
Factors affecting outcome in deep brain stimulation for dystonia.

Better outcome	Worse outcome
Idiopathic isolated (primary)	Acquired combined (secondary)
Normal brain MRI	Structural brain lesions
Limbs, trunk, neck involvement	Bulbar, laryngeal involvement
Shorter disease duration	Longer disease duration
Mobile (more rapid response)	Tonic (slower response)
DYT-TOR1A (DYT1), DYT-SGCE (DYT11), DYT-KMT2B (DYT28), DYT-PANK2	DYT-THAP1 (DYT6), DYT-ATP1A3 (DYT12)
Stimulated contacts within optimal target region	Stimulated contacts outside optimal target region
Sufficient follow-up (≥ 12 months)	Insufficient follow-up
No DBS side effects	DBS side-effects

genotype generally shows high responsiveness to DBS, although a minority of DYT1 patients experience a secondary worsening of symptoms after an initial improvement [116]. Myoclonus dystonia, associated with the DYT-SCGE (DYT11) mutation, stands out for its significant and sustained benefits from DBS, with patients reporting improvements in dystonia, myoclonus, QoL, and social functioning [117]. Other genetic dystonias showing favorable responses to DBS include X-linked dystonia-parkinsonism (DYT/PARK-TAF1/DYT3), DYT-KMT2B/DYT28, NBIA/DYT-PANK2, and chorea associated with DYT-ADCY5 mutations [118]. Despite the generally positive initial responses in patients with DYT-KMT2B/DYT28 and NBIA/DYT-PANK2, disease progression can lead to an increase in disability over time. Conversely, dystonias linked to the DYT-THAP1 (DYT6) mutation exhibit more variable and generally poorer responses to DBS, particularly when compared to the outcomes observed in DYT-TOR1A (DYT1) patients [119]. Similarly, rapid-onset dystonia-parkinsonism (DYT/PARK-ATP1A3/DYT12) typically shows limited improvement with DBS [120]. There is only one case report to document the significant symptom improvement to DBS in *HPCA*-linked DYT2 dystonia [121]. Knowledge of the specific genetic mutation involved can help predict surgical outcomes, offering valuable insights into the potential responsiveness to DBS treatment based on the genetic subtype of the dystonia.

4.1.5. Pharmacological treatment

DBS for dystonia is usually considered when medications provide insufficient benefit. First-line options include anticholinergics, baclofen, benzodiazepines, and, in specific cases, levodopa, though efficacy is often limited by side effects. For focal and segmental dystonia, BoNT A/B is the most effective treatment, though partial responses and resistance can occur. Physical therapy supports muscle control and prevents contractures, while psychiatric care (psychotherapy and behavioral therapy) is essential to address common comorbid depression and anxiety, improving overall QoL.

4.2. Surgical factors

In the realm of DBS for dystonia, the GPi has traditionally been the preferred target. This preference is based on the robust effectiveness of GPi-DBS in symptom management across various forms of dystonia. However, the potential of STN-DBS has increasingly come into focus for certain dystonia types, positioning it as a viable alternative to GPi targeting. The choice between GPi and STN remains a subject of ongoing clinical discussion and research. The debate centers around which target provides the most benefit in terms of symptom relief, QoL improvements, and reduction of adverse effects.

GPi-DBS is the preferred surgical option for children and adults with disabling isolated generalized or cervical dystonia unresponsive to medication or BoNT [122,123]. A randomized trial of 40 patients with segmental or generalized dystonia [124] showed significant motor improvement with GPi stimulation versus sham, with benefits sustained long term and corroborated across various dystonia types, including DYT-TOR1A, blepharospasm, and Meige syndrome, with effects lasting up to 10 years [125–127]. Beyond motor relief, GPi-DBS consistently reduces pain across dystonia subtypes, with stronger evidence for generalized and cervical forms [128].

Adverse effects include stimulation-induced parkinsonism (bradykinesia, gait disturbance, micrographia), largely reversible by adjusting settings [129], and speech impairment in 10–30 % of patients, often linked to medial/posterior electrode placement [130,131]. This may be due to the electrical current spread to capsular fibers or its interference with pallidal output. Capsular effects, reflecting the proximity of the internal capsule to the medial border of the GPi, can lead to tonic contractions in the contralateral face, arm, or leg. These effects are particularly noted with medially placed electrodes or higher stimulation settings. Adjusting the stimulation intensity or opting for bipolar stimulation can help mitigate these symptoms by concentrating the

stimulation field, thereby reducing the spread of electrical current [129]. Optic tract involvement can induce phosphenes [124]. Rarely, neuropsychiatric or cognitive side effects occur, typically with stimulation of ventral pallidal region, associated with more limbic functions [132]. However, they are infrequently thought directly attributable to the stimulation itself.

The exploration of **STN-DBS** initially yielded disappointing results in a mixed cohort of patients, leading to a period during which the STN was largely overlooked as a potential target for dystonia treatment [133]. STN-DBS, initially dismissed after poor early results [133], has since shown comparable benefits to GPi-DBS [134–137], particularly in cervical and generalized dystonia, with improvements sustained up to 10 years [138,139]. Comparative studies suggest GPi may be preferable for axial symptoms, while STN offers faster onset of benefit, lower battery use, and potential advantages in ocular dystonia [140,141]. Both targets are effective and safe, though STN-DBS may cause dyskinesia, typically manageable with programming adjustments [142].

While the GPi remains the primary DBS target for dystonia, the **globus pallidus externa (GPe)** has also been explored, with modest improvements compared to GPi stimulation and occasional symptom worsening with dorsal contacts [143]. Beyond pallidal targets, the **ventral oralis (VO)** complex of the thalamus has shown promise, particularly in focal hand dystonia and writer's cramp [144], as well as in small series of post-anoxic dystonia [145], with good efficacy and minimal long-term adverse effects.

5. Recent developments and future perspectives

DBS has evolved significantly with advances in targeting, hardware, and programming. Directional steering using segmented leads allows clinicians to direct current toward therapeutic zones while minimizing off-target effects, expanding the therapeutic window and reducing battery use [146]. Image guidance integrating postoperative CT with preoperative MRI improves accuracy and programming efficiency [147].

New capabilities include sensing of local field potentials (LFPs), particularly beta band activity, to guide individualized programming [148]. This has led to adaptive or closed-loop DBS, where stimulation adjusts dynamically to patient symptoms, showing promise in reducing side effects and conserving battery life [149].

Remote programming via secure telemedicine platforms now expands access for patients in remote areas, though initial programming still requires in-person visits [150].

Research into new targets beyond traditional sites (STN, GPi, VIM) is ongoing, aiming to better address symptoms like freezing of gait and postural instability. Early investigations include the rostral zona incerta, pedunculopontine nucleus, centromedian/parafascicular complex, and cerebellar dentate nucleus.

Finally, new indications for DBS are broadening. In addition to PD, ET, and dystonia, DBS is FDA-approved for OCD and epilepsy, with exploratory use in tremor syndromes, Huntington disease, and tardive dyskinesia [151].

Overall, these innovations underscore DBS as a rapidly advancing therapy that is becoming increasingly tailored, effective, and accessible for a growing spectrum of movement disorders.

6. Conclusion

DBS is an established, evidence-based treatment for PD, ET, and dystonia. When appropriate patient selection, accurate targeting, and careful programming are combined, DBS provides long-term improvements in motor symptoms, functional capacity, and QoL. However, its benefit is limited in certain situations, such as levodopa-unresponsive axial and speech problems in PD, or fixed and bulbar involvement in dystonia, underscoring the importance of proper indication.

In PD, the STN and GPi remain the main targets, chosen according to patient profile and treatment goals. VIM-DBS is most effective for

tremor-predominant cases, while GPi remains the primary target for dystonia, with STN as a reasonable alternative in selected cases. Bilateral implantation can enhance outcomes but increases the risk of stimulation-related side effects, particularly dysarthria, highlighting the need for careful surgical and programming strategies.

Overall, DBS is safe, with most complications being device- or stimulation-related and manageable. Multidisciplinary care before and after surgery is essential to optimize outcomes, manage medication adjustments, and support patients.

Technological advances, including directional leads, imaging-guided planning, tele-programming, and adaptive (closed-loop) stimulation, are further improving precision, safety, and accessibility. Exploration of novel targets and new indications continues to expand the role of DBS.

In summary, DBS is a powerful therapy when applied to the right patient with the right target and strategy. Future developments are expected to bring more personalized, biomarker- and connectome-guided approaches, expanding indications and improving access for patients who may benefit from this therapy.

Declaration of Competing Interest

There is no known competing financial interests or personal relationship that could have appeared to influence this study.

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