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ADVANCES IN THE TREATMENT OF PARKINSONISM WITH DEEP BRAIN STIMULATION

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ABSTRACT

Deep Brain Stimulation (DBS) has established itself as one of the most effective treatments for Parkinson's Disease (PD), especially in patients with motor symptoms refractory to drug therapy. This review article aims to address recent advances in the application of DBS, highlighting technological improvements, clinical efficacy and challenges associated with the technique. Scientific evidence shows that DBS provides significant improvements in motor symptoms such as tremors, rigidity and dyskinesias, as well as reducing motor fluctuations related to prolonged levodopa use. Technological advances, such as adaptive devices that adjust stimulation in real time and the integration of artificial intelligence and machine learning to personalize treatment, have increased the effectiveness and safety of the technique. In addition, studies have explored

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alternative brain targets and the early application of DBS in the early stages of PD, with promising results that suggest neuroprotective benefits and a positive impact on non-motor symptoms, such as sleep disorders and depression. However, DBS has limitations, including surgical complications, neuropsychiatric adverse effects and the need for rigorous patient selection. Factors such as the high cost of the procedure and unequal access also pose global challenges, especially in low- and middle-income countries. In conclusion, although DBS is a well-established and promising approach to treating PD, further advances in technology, biomarkers and early application strategies are essential to extend its benefits and make the technique more accessible.

Keywords: Parkinson's Disease. Deep Brain Stimulation. Technological Advances. Motor Symptoms. Artificial Intelligence. Brain Targets. Neuromodulatory Treatment.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition that affects around 1% of the population over the age of 60, and is the second most prevalent neurodegenerative disorder in the world (Bloem et al., 2021). Its main characteristic is the degeneration of dopaminergic neurons in the substantia nigra of the brain, leading to reduced levels of dopamine, an essential neurotransmitter for motor control (Poewe et al., 2017). The presence of Lewy bodies, intracellular inclusions composed of alpha-synuclein, is a pathological hallmark of the disease (Brundin & Melki, 2017).

The symptoms of PD are divided into motor and non-motor. Motor symptoms include resting tremor, muscle rigidity, bradykinesia and postural instability, which significantly affect patients' quality of life (Jankovic, 2008). On the other hand, non-motor symptoms, such as cognitive dysfunction, depression, constipation and sleep disorders, have received increasing attention due to their relevance in the overall management of the disease (Chaudhuri et al., 2016). These symptoms often precede motor symptoms by years, highlighting the clinical complexity of PD (Postuma et al., 2015).

Although the exact etiology of PD remains uncertain, it is believed to be multifactorial, involving interactions between genetic predisposition and environmental factors (Kalia & Lang, 2015). Mutations in genes such as SNCA, LRRK2 and PARK2 have been associated with the disease, but most cases are sporadic, with no direct link to genetic factors (Schapira et al., 2017). Environmental factors, such as exposure to pesticides, and protective factors, such as caffeine consumption and physical activity, also play important roles (Ascherio & Schwarzschild, 2016).

Current treatment for PD is symptomatic and focused mainly on restoring dopamine levels in the central nervous system. Levodopa remains the gold standard, but its prolonged use is associated with motor complications such as fluctuations and dyskinesias (Fox et al., 2018). As a result, approaches such as deep brain stimulation and new pharmacological therapies are being explored to offer better therapeutic options (Okun, 2021).

PD is the second most common neurodegenerative condition in the world, affecting around 1% of the population over the age of 60 and up to 3% in people over the age of 80 (Bloem et al., 2021). Recent studies estimate that, in 2019, more than 8.5 million people were living with PD globally, with a significant increase in the disease burden due to population aging and better diagnoses (GBD 2019 Parkinson's Disease

Collaborators, 2021). Men have an approximately 1.5 times higher risk of developing the disease compared to women, possibly due to hormonal and genetic factors (Cerri et al., 2019).

The prevalence of PD varies geographically, reflecting differences in access to diagnosis, exposure to environmental factors and genetic characteristics of populations. In developed countries, prevalence is generally higher due to a more ageing population and better healthcare systems (Kalia & Lang, 2015). Low- an middle- income countries face significant underreporting, which hinders an accurate global understanding of the burden of PD (Dorsey et al., 2018).

Factors such as urbanization and exposure to environmental agents such as pesticides and solvents have also been associated with differences in the prevalence of the disease in different regions (Ascherio & Schwarzschild, 2016). The number of PD cases is expected to more than double in the coming decades, with projections indicating that by 2040 around 17 million people will be diagnosed with the condition, mainly in countries with rapidly ageing populations, such as China and India (Dorsey et al., 2018). The pharmacological treatment of PD is largely based on dopamine replacement,

with levodopa being the gold standard for controlling motor symptoms. However, prolonged use of levodopa is associated with the development of motor complications, such as motor fluctuations and dyskinesias. Motor fluctuations, including periods of "on" (control of symptoms) and "off" (return of symptoms), are attributed to levodopa's short half-life and irregular absorption, especially in advanced stages of the disease (Stocchi et al., 2010). Dyskinesias, characterized by involuntary movements, occur due to changes in dopamine receptors and motor circuits over time (Cenci, 2014).

Although levodopa is effective in the early stages, its effectiveness decreases progressively. In the long term, patients often need higher doses to achieve the same motor control, which increases the risk of complications related to chronic use (Hauser, 2009). Strategies such as combining levodopa with dopa-decarboxylase and catechol-O- methyltransferase (COMT) inhibitors help to prolong its half-life and improve efficacy, but do not completely eliminate fluctuations and dyskinesias (Olanow et al., 2006).

In addition to motor complications, treatment with levodopa does not address the non-motor symptoms of PD, such as depression, sleep disorders and autonomic dysfunction, which significantly impact patients' quality of life (Chaudhuri et al., 2006). Other drugs, such as dopamine agonists and monoamine oxidase B (MAO-B) inhibitors,

are used as alternatives or complements to levodopa, but are associated with side effects, including drowsiness, nausea and impulsivity (Poewe et al., 2017).

The search for therapies that can slow down the progression of PD or offer symptomatic control without the limitations associated with levodopa remains a priority. Non-pharmacological interventions, such as deep brain stimulation, have shown efficacy in reducing motor complications in patients with severe fluctuations, offering a promising alternative in advanced stages of the disease (Fasano et al., 2012).

Deep Brain Stimulation (DBS) is a neuromodulatory intervention that has been used in the treatment of Parkinson's Disease (PD) since the 1990s. This technique was introduced as an alternative to permanent brain lesions, such as thalamotomies and pallidotomies, which were widely used previously (Benabid et al., 1991). DBS is based on the implantation of electrodes in specific brain targets, such as the subthalamic nucleus (STN) or the internal globus pallidus (GPi), allowing the electrical modulation of these motor circuits in a reversible and adjustable way (Lozano et al., 1998). This approach has revolutionized the management of PD, especially in advanced cases with motor complications resulting from prolonged use of levodopa.

Since its introduction, DBS has demonstrated significant efficacy in reducing motor symptoms such as tremors, rigidity and bradykinesia, as well as reducing motor fluctuations and dyskinesias in patients who do not respond adequately to drug treatment (Deuschl et al., 2006).

Technological advances, such as adaptive stimulation systems, have allowed for greater personalization of the treatment, improving its effectiveness and reducing side effects (Little et al., 2016). Despite this, the technique has limitations, such as the need for careful patient selection and the risk of surgical or neuropsychiatric complications (Okun, 2012).

The aim of this article is to review recent advances in the DBS technique, evaluating its effectiveness and the challenges that still need to be overcome. Topics such as the impact of new technologies, the development of more sophisticated devices and studies on alternative targets in the brain will be addressed. Factors that influence clinical outcomes will also be discussed, such as the choice of brain target, patient selection and the impact on non-motor symptoms. This analysis aims to contribute to a better understanding of future prospects and possible improvements in the application of DBS for PD.

OBJECTIVE

Present recent advances in the application of *Deep Brain Stimulation* (DBS) as a treatment for Parkinson's Disease (PD).

METHODOLOGY

This study consists of a systematic literature review aimed at analyzing advances in the treatment of PD with the use of DBS (*Deep Brain Stimulation*). The methodology was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), involving the following steps:

DEFINING THE PURPOSE OF THE REVIEW

The aim of this study was to identify and summarize the technological, clinical and methodological advances related to the use of DBS in the treatment of PD, addressing both the efficacy and the challenges associated with the technique.

SEARCH STRATEGY

The searches were carried out in recognized scientific databases, including PubMed, Scopus, Web of Science and Cochrane Library. The search terms used were combined with Boolean operators for greater comprehensiveness, such as:

- ("Deep Brain Stimulation" OR "DBS") AND "Parkinson's Disease"
- ("neuromodulation" OR "neurostimulation") AND "treatment advancements" AND "Parkinson"
- ("adaptive DBS" OR "intelligent stimulation") AND "motor symptoms" AND "Parkinson's Disease".

The filters applied included: articles published in English, Portuguese and Spanish, and studies with full access.

INCLUSION AND EXCLUSION CRITERIA

- **Inclusion:** Original studies, systematic reviews, meta-analyses and clinical trials related to DBS in PD; articles that addressed technological advances, clinical efficacy and new applications of the technique.
- **Exclusion:** Studies with small samples (<10 patients), opinion articles or without robust methodological description, and studies focusing on other neurological

conditions.

DATA ANALYSIS

The selected articles were analyzed qualitatively, with emphasis on the following aspects:

- Technological advances, such as adaptive systems and artificial intelligence.
- Efficacy in reducing motor and non-motor symptoms.
- Complications associated with the technique and limitations.
- Future perspectives, such as alternative brain targets and early DBS.

LIMITATIONS OF THE REVIEW

This review only considered articles published in selected databases, which may exclude relevant studies outside this scope. Furthermore, the interpretation of the data depends on the methodological quality of the articles included.

This methodology ensured a structured and rigorous process, allowing for a comprehensive and up-to-date analysis of advances in the application of DBS for the treatment of PD.

RESULTS AND DISCUSSION

EFFICACY OF DEEP BRAIN STIMULATION IN THE MOTOR SYMPTOMS OF PARKI NSON'S DISEASE

DBS (FIGURES 1, 2 and 3) has been shown to be effective in treating the motor symptoms of PD, especially in controlling tremors, rigidity and bradykinesia. DBS is a neuromodulatory technique that involves implanting electrodes in specific areas of the brain, such as the subthalamic nucleus (STN) or the internal globus pallidus (GPi), providing relief from motor symptoms by modulating the circuits involved in movement control (Deuschl et al., 2006).

Clinical studies have shown a significant reduction in tremors and rigidity, with improvements also in bradykinesia, providing a substantial improvement in patients' quality of life (Kumar et al., 2000). DBS has been effective in reducing motor fluctuations and dyskinesias associated with chronic levodopa use (Caria et al., 2008).

Figure 1. Electric field distribution for the H4 coil at each location in the two-stage protocol. Source: Hanlon, Colleen A., et al. (2024).

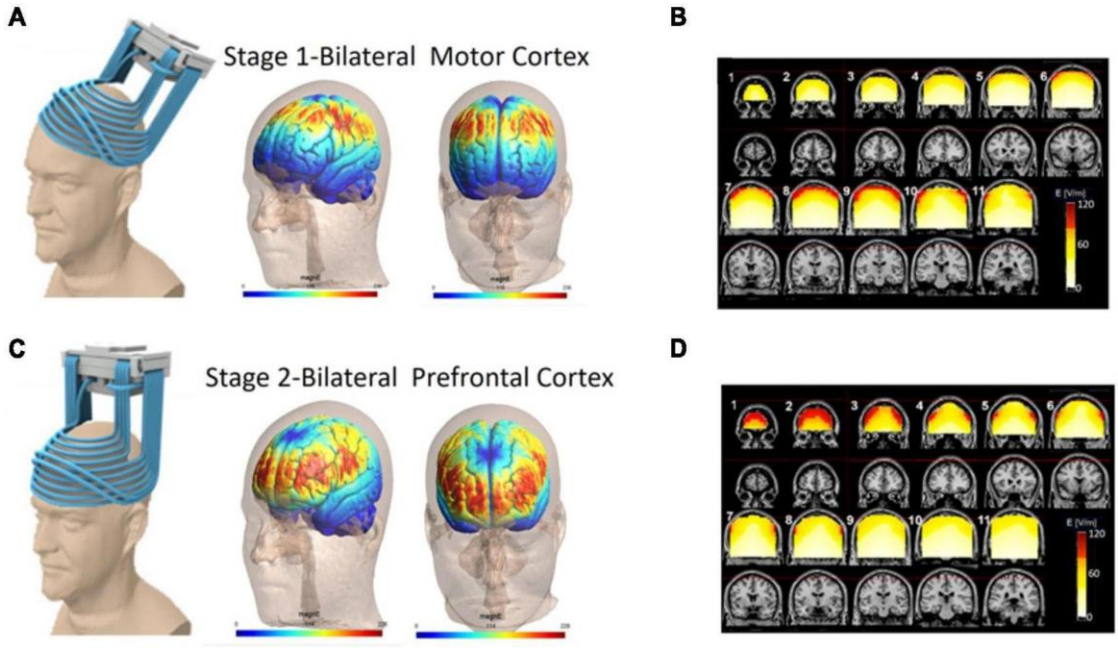


Figure 2: Brain regions that have been safely stimulated using Deep TMS Brainsway. Source: neurocavis.es/en/technology (2025).

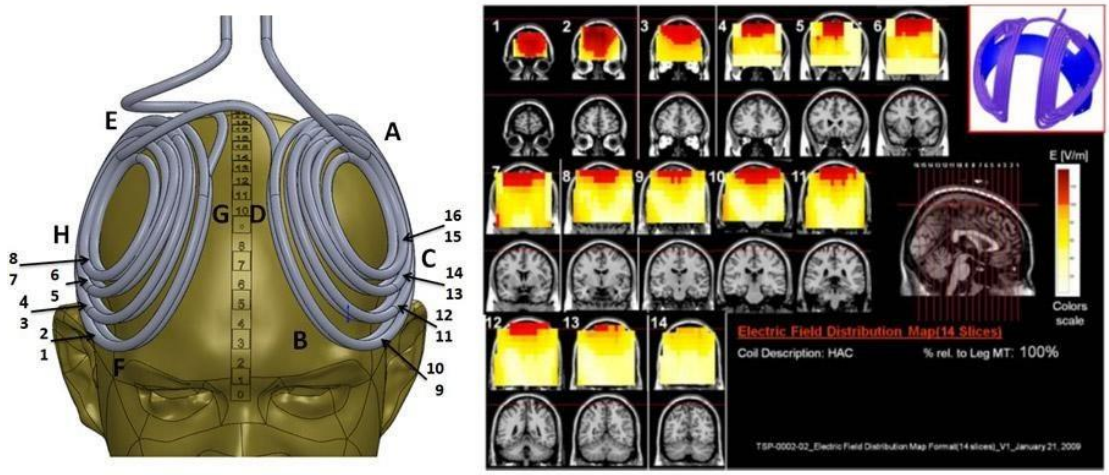
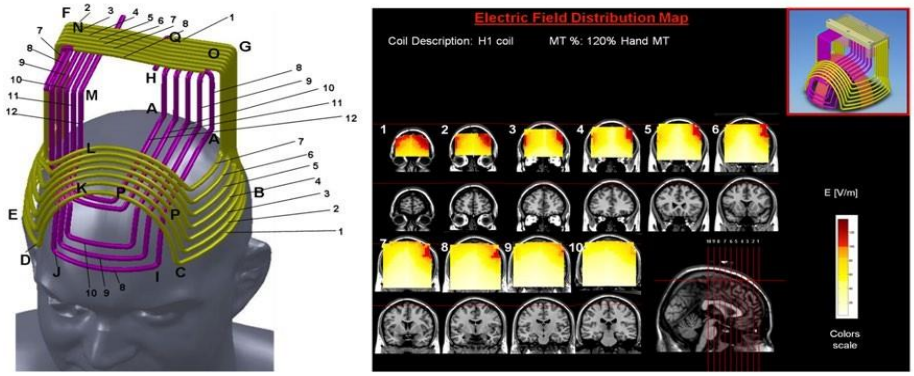


Figure 3: Brain regions that have been safely stimulated using Deep TMS Brainsway. Source: neurocavis.es/en/technology (2025).



Compared to traditional pharmacological treatments, such as levodopa, DBS has significant advantages, especially in advanced stages of the disease, when the effect of the medication diminishes and motor complications arise. Levodopa, although highly effective at the start of treatment, leads to motor fluctuations and dyskinesias as the disease progresses, which limits its long-term use (Hauser, 2009). DBS, on the other hand, not only provides more stable control of motor symptoms, but also reduces the need for high doses of medication, minimizing medication-related adverse effects (Weintraub et al., 2013).

DBS has the advantage of being a reversible and adjustable approach, which makes it an attractive option compared to more invasive surgical options such as brain lesions. The ability to adjust stimulation parameters allows for precise symptom control and adaptation to disease progression, which is a significant advantage compared to pharmacological treatments (Okun et al., 2012). However, DBS is not a cure for PD and has limitations, such as the need for rigorous assessment of candidates and the risk of complications, such as infections and neuropsychiatric side effects (Fasano et al., 2012).

TECHNOLOGICAL ADVANCES IN DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

Technological developments have played a crucial role in improving DBS as a treatment for PD. New DBS devices, equipped with automated adjustments and real-time customization features, have revolutionized the control of motor symptoms. These systems use sensors to monitor neural activity and adjust stimulation parameters dynamically, improving treatment efficacy and reducing side effects (Little et al., 2013). An example of this is the introduction of *adaptive* stimulation systems (*adaptive DBS*), which adjust electrical pulses based on signals recorded in real time, such as beta oscillation in the subthalamic nucleus, allowing for more precise control of symptoms (Meidahl et al., 2017).

The integration of artificial intelligence (AI) and *machine learning* has shown promise in optimizing DBS parameters. These technologies allow for the analysis of large volumes of data on patients' brain activity and motor behavior, identifying patterns that can guide personalized treatment adjustments (Herron et al., 2020). *Machine learning-based* models have also been used to predict individual response to DBS, aiding in the

selection of ideal candidates for the procedure and the choice of the most effective brain targets (Zhang et al., 2021). These advances reduce the need for frequent visits for manual adjustments, improve clinical outcomes and make treatment more efficient and affordable.

Technological advances in DBS also include rechargeable devices and systems with multiple electrode contacts, which allow for targeted stimulation. This approach reduces stimulation in unwanted areas, minimizing adverse effects such as dysarthria and muscle twitching (Pollo et al., 2014). In the future, these technologies, combined with the seamless integration of AI, are expected to offer more effective and less invasive therapies for PD patients, with the promise of further extending the positive impact of DBS on the quality of life of these individuals.

IMPACT OF DEEP BRAIN STIMULATION ON NON-MOTOR SYMPTOMS OF PARKI NSON'S DISEASE

DBS has shown benefits not only in motor symptoms, but also in some non-motor symptoms of PD, such as sleep disorders, depression and other neuropsychiatric comorbidities. Studies indicate that DBS, especially when targeting the subthalamic nucleus (STN), can significantly improve sleep quality, reducing fragmentation and insomnia, and restoring more regular sleep patterns (Lopes et al., 2016). DBS has shown positive effects in reducing depressive symptoms in PD patients, possibly due to the modulation of limbic circuits involved in emotional regulation (Castrioto et al., 2014). Other benefits include the improvement of chronic pain and autonomic dysfunctions, such as constipation and urinary urgency, which often accompany the progression of the disease (Kistner et al., 2017).

Despite these advances, DBS has limitations when it comes to managing the cognitive symptoms of PD. Studies suggest that although the technique is effective for motor symptoms, it may not be enough to prevent or improve cognitive deficits that often arise in advanced stages of the disease (Witt et al., 2008). In some cases, DBS can even exacerbate cognitive problems such as attention difficulties and executive function, especially in patients with pre-existing cognitive deficits or mild impairment (Okun, 2012). The choice of brain target also plays an important role, with evidence indicating that DBS in the STN may be associated with a higher risk of cognitive adverse effects compared to the globus pallidus internus (GPi) (Smeding et al., 2006).

Although DBS has a positive impact on a number of non-motor symptoms, cognitive deficits remain a therapeutic challenge. This highlights the need for rigorous evaluation to select suitable patients for therapy and monitor potential adverse impacts on cognitive functions. Future studies should explore strategies to improve the cognitive benefits of DBS, such as targeted and personalized modulation of different brain circuits.

CHALLENGES AND LIMITATIONS OF DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

Selecting patients for DBS in PD remains one of the main clinical challenges. Although the technique is most effective in patients with motor symptoms refractory to drug treatment and severe motor fluctuations, strict clinical criteria are needed to identify those who will gain the greatest benefits. Patients with dementia, severe psychiatric disorders or unrealistic expectations are generally not considered good candidates for the procedure (Okun, 2012).

Specific biomarkers, such as beta oscillation patterns recorded during the procedure, have been explored to help select and personalize treatment, but are not yet widely applied in clinical practice (Little et al., 2016).

Despite its effectiveness, DBS has risks associated with the surgical procedure and prolonged use of the device. Complications such as infections, electrode displacement and intracranial hemorrhages are frequent concerns, although their incidence is relatively low when the surgery is performed by experienced teams (Fenoy & Simpson, 2014).

Neuropsychiatric adverse effects, such as depression and impulsivity, can occur in some patients, requiring continuous monitoring and adjustments to stimulation parameters (Moro et al., 2010). The need for technical follow-up for device maintenance and regular adjustments also represents a challenge for patients living in areas with limited access to specialized services.

The cost of DBS is another limiting factor affecting its accessibility, particularly in low- and middle-income countries. The procedure requires advanced technology and specialized infrastructure, resulting in high initial costs and ongoing expenses related to device maintenance (Dewan et al., 2019). Studies suggest that DBS can be cost-effective in the long term due to reduced medication use and improved quality of life, unequal access to this technology in different health systems creates significant

disparities (Castillo et al., 2020). These challenges reinforce the need for global strategies to expand access to DBS, such as reducing device costs and developing training programs for medical staff in underserved regions.

ONGOING STUDIES ON DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

Recent research has investigated alternative targets in the brain to improve the results of DBS in PD. Although the subthalamic nucleus and the internal globus pallidus are the traditional targets, other nuclei, such as the pontine peduncle and the ventral intermediate nucleus of the thalamus, have been explored to treat specific symptoms, such as refractory tremors and gait disturbances (Collomb-Clerc & Welter, 2015).

Studies also suggest that DBS targeting the caudate nucleus can have an impact on non-motor symptoms, such as emotional and cognitive changes, broadening the therapeutic scope of the technique (Frizon et al., 2020). Although promising, these alternative targets are still in the early stages of research and require additional studies to prove their efficacy and safety.

Another important field of research is the application of DBS in the early stages of PD, before the development of severe motor complications. Clinical trials, such as the EARLYSTIM study, suggest that early DBS can improve patients' quality of life and autonomy, reducing the progression of complications related to prolonged drug therapy (Schuepbach et al., 2013). The hypothesis is that early neuromodulatory stimulation can act in a neuroprotective way, slowing down neural degeneration, although this possibility still needs confirmation (Charles et al., 2020). However, the early use of DBS raises ethical and clinical questions, such as the need for strict selection criteria and the balance between the benefits and risks of intervention in patients with less severe symptoms.

These studies reflect the ongoing efforts of the scientific community to expand the potential of DBS in the treatment of PD. The investigation of new targets and strategies for early intervention may not only improve clinical outcomes, but also change paradigms about the timing and therapeutic approach of DBS. However, significant advances will depend on longitudinal, randomized studies that can provide robust evidence on the benefits and limitations of these emerging approaches.

CONCLUSION

Deep brain stimulation represents a significant advance in the treatment of Parkinson's Disease, especially for patients with motor symptoms refractory to drug treatment. A review of the literature shows that DBS offers significant benefits, such as improving tremors, rigidity and dyskinesias, as well as helping to reduce dependence on medication and improving patients' quality of life. However, recent advances, such as the introduction of adaptive stimulation systems, real-time personalization and the integration of technologies such as artificial intelligence, highlight the potential of DBS to become even more effective and safe.

Despite the progress, important challenges remain, including the need for more robust clinical criteria and biomarkers for patient selection, the mitigation of complications associated with the procedure and expanding access to DBS in regions with limited resources.

Research into alternative targets in the brain and the early application of DBS in the early stages of PD open up new therapeutic possibilities, but require additional studies to validate its efficacy and safety.

Therefore, although DBS is currently an indispensable tool in the management of advanced PD, its full potential has not yet been reached. Continued research, combined with the development of new technologies and therapeutic strategies, is essential to overcome existing limitations and expand the benefits of DBS to a greater number of patients. With this, it is hoped that DBS will continue to evolve as an essential component in the personalized treatment of PD, significantly improving clinical outcomes and the quality of life of individuals affected by the disease.

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