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Decisions about deep brain stimulation therapy in Parkinson's disease

Decisões a respeito da terapia com estimulação cerebral profunda na doença de Parkinson

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ABSTRACT

Parkinson's disease can be treated surgically in patients who present with motor complications such as fluctuations and dyskinesias, or medically-refractory disabling tremor. In this review, a group of specialists formulated suggestions for a preoperative evaluation protocol after reviewing the literature published up to October 2017. In this protocol, eligibility and ineligibility criteria for surgical treatment were suggested, as well as procedures that should be carried out before the multidisciplinary therapeutic decisions. The review emphasizes the need to establish "DBS teams", with professionals dedicated specifically to this area. Finally, surgical target selection (subthalamic nucleus or globus pallidus internus) is discussed briefly, weighing the pros and cons of each target.

Keywords: Parkinson disease; deep brain stimulation; reference standards; basal ganglia; neurosurgical procedures.

RESUMO

A doença de Parkinson pode ser tratada cirurgicamente em pacientes que desenvolveram complicações motoras, como flutuações e discinesias, ou tremores refratários ao uso de medicação. Nesta revisão, um grupo de especialistas formulou sugestões para um protocolo de avaliação pré-operatória, depois de revisar a literatura publicada até outubro de 2017. Neste protocolo, são sugeridos critérios de elegibilidade e inadmissibilidade para tratamento cirúrgico, bem como procedimentos que devem ser realizados antes das decisões terapêuticas multidisciplinares. A revisão enfatiza a necessidade de estabelecer "equipes de DBS", com profissionais dedicados especialmente a esta área. Ao final, a seleção do alvo cirúrgico (núcleo subtalâmico ou globo pálido interno) é discutida brevemente, ponderando prós e contras de cada escolha.

Palavras-chave: doença de Parkinson; estimulação cerebral profunda; padrões de referência; gânglios da base; procedimentos neurocirúrgicos.

Parkinson's disease (PD), a hypokinetic movement disorder characterized by the classic tetrad of bradykinesia, rest tremor, plastic rigidity, and postural disturbances[1,2], is a neurodegenerative disorder with an increasing impact on the Brazilian social and healthcare system, mirroring known demographic-epidemiological changes such as aging of the population and widening of the apex of the age pyramid[3,4]. Considering a prevalence of 3.3% in those aged 65 or older in the Brazilian population[5], the country has at least 200,000 patients living with the disorder, a definitive challenge to the public health system.

Parkinson's disease has effective symptomatic treatment options that have a positive, but rather limited, effect on minimizing long-term functional motor disability, including levodopa, dopaminergic agonists, catechol-O-methyltransferase inhibitors, anticholinergics, monoamine oxidase B inhibitors, and amantadine[6].

However, most, if not all, PD patients are expected to develop complications related to disease progression and chronic use of the aforementioned therapies, hindering clinical management and limiting therapeutic options. The two

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most frequent of these complications, levodopa-induced dyskinesias and motor fluctuations, may have a significant impact on functionality and quality of life in the mid and late stages of PD.

Functional neurosurgery in Parkinson's disease

Among the limited number of strategies used in the management of some of these long-term motor complications, surgical treatment with stereotactic implanting of electrodes for deep brain stimulation (DBS) has gained considerable importance over the past few decades. Since its pioneer development by Benabid's group in the 1980s[7], the technique has evolved dramatically and revolutionized the treatment of PD and other movement disorders.

Compared to classic lesional procedures such as thalamotomy and pallidotomy, DBS has a few advantages, as it is reversible and adjustable to address problems related to adverse effects and disease progression *per se*. Currently, an estimated 160,000 DBS implant procedures have been performed worldwide[8], consolidating its effectiveness. The procedure, however, has caveats, limitations, and is well recognized as potentially harmful if indicated in the wrong timing and clinical scenario[9]. Therefore, despite the encouraging overall experience, only about 20-30% of patients with PD meet an adequate profile to be considered good candidates for DBS and an even smaller proportion will eventually undergo the surgical procedure[10]. In other words, appropriate patient selection is critical, and surgery must be performed during a relatively restricted window of time during the course of disease, that is, at a time in which it can provide gain (or "regain") of motor functionality while social adaptation is still possible[11].

This review aims to provide literature-based clues about indications, contraindications, risks, benefits and their caveats, with the objective of guiding clinicians in the best use of these powerful techniques, especially avoiding inappropriate surgeries and expectations. We also aim to stimulate the creation of a formal reference protocol as a tool for uniform decision-making regarding the indication of these procedures in PD.

METHODS

A literature search was performed using the terms "Parkinson", "Deep Brain Stimulation", "Randomized Trial", "Subthalamic nucleus", "GPi", "STN", and "meta-analysis" in the MEDLINE database, in the period between 1995 and 2014. After an initial reading of 118 abstracts from clinical trials, six randomized and controlled trials with a satisfactory methodological design were selected. Additional references (two clinical trials) were added after an active search in the bibliographical citations of the expert consensuses and meta-analyses.

A working group formed by six neurologists, two neurosurgeons and one neuropsychologist, all experienced in PD and DBS surgery, met formally on two occasions (February and March, 2014), to discuss current scientific evidence, and attempt to adapt these to national and regional realities. The protocol was further addressed in video-conferences, e-mail discussions between the members, and further at the Deep Brain Stimulation International Academy course, hosted by Toronto Western Hospital (in October, 2017), after being updated with current literature.

RESULTS

The results of the literature search that supports the suggestions of our study group are described in Table 1 (randomized and controlled studies), Table 2 (meta-analyses) and Table 3 (consensus of experts). A total of eight randomized controlled trials, seven meta-analyses (or systematic reviews), and six consensuses of specialists were analyzed and included in the protocol.

Table 1 describes year and authorship of the study (to provide information from an historical point of view), number of patients, period of follow-up, the centers' geographic location, duration since PD diagnosis, surgical target [internal globus pallidus (GPi) or subthalamic nucleus (STN)], in addition to a summary of results in terms of efficacy and safety. Table 2 shows data on the meta-analyses and systematic reviews published over the last 22 years, also organized from an historical perspective, compiling the results of motor functional assessments and quality of life after surgery. Table 3 summarizes published recommendations and guidelines from leading national and international neurology and movement disorders specialists' associations concerning indications and contraindications for functional surgery in PD.

From the analysis of these data, suggestions for a clinical eligibility protocol for functional surgery in PD are described.

Suggested criteria for surgical eligibility

1) High level of certainty about the diagnosis of idiopathic PD using the Queen Square Brain Bank diagnostic criteria[33] or the new international Parkinson and Movement Disorders Society (MDS) criteria[2]. An alternative diagnosis of atypical or secondary parkinsonism (Lewy body dementia, vascular parkinsonism, progressive supranuclear palsy, multiple systems atrophy, or other) should be carefully excluded;

2) Clinical progression for a minimum of four years is additionally useful for improving the certainty of a clinical diagnosis of idiopathic PD;

3) Confirmation of levodopa responsiveness using the levodopa challenge test, which is described in detail in a separate section of this manuscript. Improvement of at least 30-40% is required in Part III of the Unified Parkinson Disease Assessment Scale (UPDRS)[34] or MDS-UPDRS[35], the most recent version of the scale;

Table 1. Randomized controlled trials evaluating DBS in Parkinson's disease.

Author, year	N	Follow-up	Target	Mean disease duration	Center	Clinical outcomes
Anderson et al.[12]	23	12 m	STN or GPi	15.6 y (STN); 10.2 y (GPi)	USA	STN DBS patients tend to remain on lower levodopa dosage (-38%), but have shown more cognitive and behavioral side effects
Deuschl et al.[13]	156	6 m	Bilateral STN (n = 78) vs. best medical therapy	13.0 y	Germany and Austria	STN DBS: 9.5 pts improvement in PDQ-39 and 19.6 improvement in UPDRS-III. One fatal brain hemorrhage.
Schüpbach et al.[14]	20	18 m	Bilateral STN (n = 10) vs. best medical therapy	6.8 y	France	24% improvement in QoL; -69% severity of motor symptoms in off time; -83% motor complications; -57% reduction in levodopa dosage
Weaver et al.[15]	255	6 m	STN (n = 60); GPi (n = 61); best medical therapy (n = 134)	12.4 y	USA	Longer ON time without dyskinesia (+4.6 hours a day); similar between GPi and STN DBS; worse verbal fluency in STN DBS
Williams et al.[16]	366	12 m	Bilateral STN (n = 183) vs. best medical therapy (n = 183)	11.4 y	United Kingdom	Improved dyskinesia and daily ON time; 5 pts improvement in PDQ-39-SI; 19% serious adverse effects
Follett et al.[17]	299	24 m	STN (n = 147) or GPi (n = 152)	11.1y (STN); 11.4 y (GPi)	USA	GPi and STN DBS similar efficacy. STN DBS: lower dose of dopaminergic agents, higher risk of depression and reduced visuomotor processing speed;
Okun et al.[18]	136	3 m	STN: immediate (n = 131) or delayed (n = 35) stimulation	12.0 y	USA	+2h50 daily ON time; UPDRS-III: improvement (39%);4% surgical site infection; 3% intracranial hemorrhage;
Schüpbach et al.[19]	251	24 m	Bilateral STN (n = 124) vs. medical therapy (n = 127)	7.5 y	Germany and France	Improved motor disability, motor complications, daily life activities and ON time without troublesome dyskinesia.

STN: subthalamic nucleus; GPi: internal globus pallidus; PDQ-39-SI: 39-item Parkinson's disease questionnaire summary index.

Table 2. Systematic reviews and meta-analyses of clinical studies evaluating deep brain stimulation in Parkinson's disease.

Authors, year	Number of studies included	Conclusions
Kleiner-Fisman et al.[20]	22 studies	UPDRS-II: 13.3 pts improvement; UPDRS-III: 27.55 pts improvement; Mean reduction of LED: 55.9% Mean dyskinesia improvement: 69%; Mean OFF time reduction: 68%; PDQ-39: 34.5% improvement; Most severe adverse effect: intracranial hemorrhage 3.9%
Andrade et al.[21]	22 studies (n = 327)	GPi: 19 pts improvement in UPDRS-III; Best programming parameters for 50% improvement in UPDRS-III: amplitude between 2.0-3.5V, pulse width between 70-300 µs and frequency: 100-190Hz.
Sharma et al.[22]	5 studies	Improved motor function and QoL. Higher incidence of side effects. Studies limited due to design and sample size. Surgery is an option after best medical therapy (individual risk/benefit ratio shall be addressed)
Volkmann et al.[23]	6 class I studies; 4 class II studies; comparison with best medical therapy	Consistent evidence of benefit for dyskinesias and motor fluctuations. Evidence was considered insufficient for apomorphine infusion and levodopa duodenal pump. Safe procedure in cognitively intact patients. Dementia must be an exclusion criterion.
Perestelo-Pérez et al.[24]	6 randomized controlled trials (n = 1184)	DBS improved QoL, motor symptoms and disability. Strong effects for OFF motor signs and disability. Reduces levodopa daily dosing and motor complications. Moderate effect for ON motor signs, time without disability in ON.
Liu et al.[25]	6 trials (n = 563), comparing GPi and STN as targets	STN and GPi DBS equally improved UPDRS part II and III. GPi DBS: greater improvement in depression scores.
Mansouri et al.[26]	13 studies (6 original trial cohorts), with follow-up for 6, 12, 24 and 36 months	Motor scores and QoL: long-term benefits are similar between both targets (GPi or STN); STN DBS: lower medication dosage; GPi DBS: better outcomes in Beck Depression Inventory.

UPDRS: Unified Parkinson Disease Assessment Scale; LED: Levodopa equivalent dose; PDQ-39: Parkinson's Disease Questionnaire; STN: subthalamic nucleus; GPi: internal globus pallidus; DBS: deep brain stimulation.

Table 3. Expert consensuses on functional neurosurgery in Parkinson's disease.

Authors, year	Institution	Country	Surgical eligibility	Ineligibility	Recommendations
Pahwa et al.[27]	American Academy of Neurology (AAN).	USA	Response in levodopa challenge test is an outcome predictor for STN DBS (Evidence level B).	Not addressed	STN DBS could be offered as a therapeutic option to improve motor function and reduce dyskinesia, motor fluctuations and medication dosage (level C).
Lang et al.[28]	International Parkinson and Movement Disorder Society (MDS); Congress of Neurological Surgeons	Diverse	Defined PD diagnosis; levodopa responsive; significant functional impairment;	Age does not predict outcome.	Mandatory preoperative MRI.
			UPDRS-III > 30 in OFF time and UPDRS-III < 30 in ON time;	Trials have excluded patients with comorbidities.	STB DBS could impair verbal fluency, induce psychiatric side effects (depression, hypomania, dopaminergic dysregulation syndrome, suicide risk)
			Individualized decision; evaluate interpersonal relations, work situation, expectations;	Active depression, suicidal ideation history, psychosis, bipolar disorder, medication abuse history, unable to give informed consent.	Psychiatric and neuropsychological evaluation is mandatory before surgery.
			Disease progression for, at least, 5 years.		Vim thalamic DBS could be considered if tremor is more important than rigidity or bradykinesia.
Bronstein et al.[29]	Multi-institutional	Diverse	PD diagnosis for, at least, 5 years; dyskinesia, tremor or fluctuations refractory to best medical therapy. > 30% improvement in UPDRS-III in the levodopa test;	Dementia; Active psychiatric disorder	-
Fox et al.[30]	International Parkinson and Movement Disorders Society (MDS)	Diverse	Not addressed	Not addressed	STN DBS is effective for dyskinesia and motor fluctuation; GPi DBS is effective for motor symptoms, as an adjunct to levodopa, and to treat dyskinesia and motor fluctuations.
Rieder et al.[31]	Academia Brasileira de Neurologia (ABN)	Brazil	Defined PD diagnosis, lasting at least 5 years; Levodopa-responsive (> 25-50% improvement in UPDRS-III) (with the exception of tremor); Unsatisfactory symptom improvement with best medical therapy (dyskinesia, tremor or fluctuations) Easy access to the medical centre; Intolerance to dopaminergic therapy;	Dementia; Active psychiatric disorder (depression and psychosis); Significant brain atrophy, Significant ventricle enlargement.	Class B recommendation
Ferreira et al.[32]	European Federation of Neurological Societies (EFNS)	Europe	Defined PD; severe motor fluctuations, unpredictable ON-OFF, dyskinesia*; * There was no reference to disease duration, levodopa response.	Exclude patients with advanced age (>70 y); Major cognitive or psychiatric disorder.	STN DBS: level A for reducing dopaminergic drug dosage; GPi DBS: level A for reducing severe dyskinesias; STN or GPi DBS: level A for treating severe dyskinesia or motor fluctuations; Slight decline in executive functions may occur (Stroop test and verbal fluency).

STN: subthalamic nucleus; DBS: deep brain stimulation; MRI: magnetic resonance imaging; GPi: internal globus pallidus; UPDRS-III: Unified Parkinson's Disease Rating Scale Part III.

4) Exceptions to the need for levodopa responsiveness include patients with severe disabling resting tremor, resistant to dopaminergic therapy. In these patients, the symptomatic benefit is likely, regardless of the levodopa challenge test response;

5) Disabling motor complications of levodopa therapy (dyskinesias or motor fluctuations), not responsive to the optimization of drug treatment, according to guideline recommendations[31].

This definition applies, for example, to patients with severe dyskinesias, OFF time that lasts more than 25% of the awake time, OFF periods with disabling symptoms (e.g., pain, dystonia, panic attacks, autonomic reactions), or unpredictable OFFs. Young patients who are intolerant to dopaminergic agents (due to nausea or emesis despite adequate symptomatic therapy), an infrequent situation, are also cited as a group who could benefit from surgery[36].

6) The clinical evaluation should be performed in a specialized multidisciplinary Movement Disorders service[37];

7) Functional disability must be defined by scales [e.g., Schwab & England Functional Scale[38], PDQ-39[39]];

8) The following attributes give support to the surgical eligibility: young age onset, severe tremor, need to reduce medications, nocturnal akinesia.

Suggested absolute criteria for ineligibility

1) Unstable clinical comorbidities (e.g., coronary artery disease, active infection, significant subcortical arteriosclerotic encephalopathy, other disabling cerebrovascular diseases, malignancy or organ failure associated with reduced life expectancy)[28];

2) Major psychiatric or neurobehavioral disorders (e.g., primary psychotic disorder, uncontrolled bipolar disorder, major or drug-resistant depressive disorder, psychoactive substance abuse, severe personality disorder with chances of interfering with tolerance, understanding or adherence to treatment);

3) Definitive dementia[29];

4) Doubtful diagnosis of PD[29];

5) Significant ventricular enlargement or cerebral atrophy in magnetic resonance imaging (MRI)[28];

6) Severe axial symptoms resistant to treatment with levodopa (dysarthria, dysphagia, postural instability or gait disturbances)[40];

7) Inability to provide informed consent;

8) Social or geographic difficulties in gaining access to the center, for follow-up visits and programming of the stimulator;

9) Absence of functional disability;

10) Inadequate or fragile social support (family or caregivers).

Suggested relative criteria for ineligibility

1) Any cognitive disorder that may interfere with adequate understanding about the treatment procedures (surgery and follow-up), or potential for worsening or interference with daily activities after surgery; significant impairment of semantic or phonemic verbal fluency in the preoperative evaluation;

2) Untreated, unstable or recurrent major depression;

3) In general, there is a reluctance to recommend surgery in patients of advanced age (defined as over 70), as the risk/benefit ratio is less favorable due to cumulative comorbidities and cognitive burden[37];

4) UPDRS Part III with a score lower than 30/108 in "defined OFF", representing a low functional disability in the absence of significant therapeutic effect of levodopa[28];

5) UPDRS Part III with a score greater than 30/108 on "definite ON", representing an unsatisfactory response to levodopa in the period with strongest effect (except when high scores are driven for the most part by treatment resistant tremor)[28];

6) DBS is not usually recommended if the disability is related to symptoms that are levodopa-unresponsive, such as gait, postural instability, and dysarthria, (except for tremor)[28].

Controversial issues about ineligibility criteria

Impulse control disorders, manifested in the extreme form as the "dopaminergic dysregulation syndrome", are controversial relative ineligibility criteria. The outcomes for impulse control disorders and dopaminergic dysregulation syndrome after DBS are unpredictable: there are reports of ameliorated or worsened symptoms, and even the onset of novel impulse control disorders[41,42,43,44,45]. These so-called hyperdopaminergic behavioral manifestations could denote a background of susceptibility for psychiatric disorders and, even though some have reported good outcomes[44,45], these effects may not materialize in the long-term[41,42,43]. In our experience, their presence should be viewed as a warning sign, and a case-by-case analysis is advised, taking into consideration other cognitive and behavioral comorbidities.

Suggested mandatory procedures before the evaluation of the multidisciplinary team, regarding candidacy for surgery

Levodopa challenge test

General guidelines for test performance

1) Patient should start the test in a "definite OFF" condition, i.e., after withdrawal of antiparkinsonian medication for at least 12 hours; this interval should be adapted as some patients may require longer withdrawal periods to achieve the definite OFF state.

2) The "definite ON" condition must be achieved during the test, i.e., the patient and the physician must agree that, after the administration of levodopa, the best possible functional state has been achieved;

3) Levodopa dosing at the test: either the patient's regular dose (according to the CAPSIT-PD protocol)[46] or supra-threshold dosage (1.5 times the usual effective dose or usual effective dose + 50 mg, or usual effective dose + 100 mg if the patient is on a dopaminergic agonist) can be used, according to the service's preference;

4) Assessment: scales used for the grading the motor signs of parkinsonism and staging of PD, such as the Part III of the UPDRS[34] or MDS-UPDRS[35], Hoehn & Yahr scale and, if possible, a dyskinesia scale;

5) It is desirable to record the test on video for discussion at a consensual multidisciplinary experts meeting.

Important observation: the ideal candidate is a patient who is severely disabled in the OFF condition and independent in the ON condition, with a difference of at least 30% in the UPDRS Part-III scores; this is calculated by dividing the difference between the OFF and ON scores by the OFF score. The result is then multiplied by 100.

Brain magnetic resonance imaging

Suggested minimum protocol of imaging sequences

1) Volumetric (three-dimensional thin slice acquisition) MRI slices with emphasis on the basal ganglia: T1- and T2-weighted images;

2) A specific search should be done to rule out findings that suggest an alternative diagnosis (atypical parkinsonism) or co-morbidities. These findings include: a marked small vessel disorder of the subcortical white matter or brainstem, hot cross bun sign, putaminal rim sign, morning glory sign, significant atrophy of the midbrain tectum, diffuse cortical atrophy, hydrocephalus, caudate atrophy. Specific sequences that emphasize the basal ganglia, substantia nigra, subcortical white matter and midbrain should be used;

3) Patients who present with significant cerebral atrophy, significantly enlarged ventricles, structural lesions, or other findings that, in keeping with atypical clinical findings, suggest the diagnosis of a secondary or atypical parkinsonism, should not be submitted for DBS.

Some DBS centers (e.g. University of Florida) have advocated the use of a novel 3T volumetric (thin-slice, 1 mm thick) MRI sequence, named FGATIR (fast gray matter acquisition T1 inversion recovery), which could provide a sharper delineation of the contour of the basal ganglia nuclei[47].

Neuropsychological and psychiatric preoperative assessment

The purpose of the cognitive assessment in the preoperative evaluation is to provide a cognitive diagnosis (PD with intact cognition, PD with mild cognitive impairment [PD-MCI] or PD with dementia [PDD]), allowing a rough prediction of the risk of future cognitive decline and guidance in planning surgical target selection. A comprehensive cognitive evaluation is advised, ideally including two tests for each of five cognitive domains (attention and working memory, executive functions, memory, language and visuospatial function), as proposed by level II MDS criteria for PD-MCI and PDD[48,49]. The tests must have local (preferably national) psychometric validation. Relying only on screening instruments is not recommended, because they are not accurate enough to identify high- and low-risk groups. The screening tests also do not permit accurate identification of the subtypes of cognitive impairment and information of peculiar prognostic implications, as shown in previous cohort studies[50,51,52].

A psychiatrist experienced in PD is an important member of the multidisciplinary group. Psychiatric presurgical assessment and post-DBS follow-up is essential for the identification and management of anxiety disorders, depression, apathy, and behavioral issues such as dopamine dysregulation syndrome and impulse control disorders. Another psychiatric facet of this population is described well by paraphrasing Dr. Mateusz Zurowski, the neuropsychiatrist affiliated with the Neuromodulation Service of the Toronto Western Hospital: good outcomes in DBS cases might be viewed as a "sudden transition for individuals in the midst of coping with a degenerative disorder with progressively diminishing resources". That sentence more than suffices to ascertain the importance of this kind of mental care in DBS candidates, reminding us that even good outcomes can be a source of uneasiness when adapting to a sudden change in self-image and the individuals' role in their families and society.

What are the purposes and benefits of the multidisciplinary approach for surgical indication?

A multidisciplinary DBS team is a group of professionals with technical expertise, dedicated to the preoperative, intraoperative and postoperative phases of this therapeutic technique. In most centers, it comprises neurologists (specialized in movement disorders and experienced in DBS programming), neurosurgeons, neuropsychologists, neuropsychiatrists, nurses, and administrative assistants. Their roles vary from center to center and are not formally established in guidelines, but should cover essential aspects including the adequate selection of candidates for surgery, arrangement and performance of all preoperative assessments and the surgery *per se*, immediate postoperative (including initial programming) and long-term care and device management[53,54]. We argue that the special dedication to these functions minimizes treatment failures and optimizes care for long-term troubleshooting[55]. Also, the existence of this group of professionals and their interaction is only possible in a center with a special interest, commitment and expertise in these surgical techniques.

Selection of the surgical target

The topic of target selection has created numerous controversies over the years. It is generally accepted that GPi DBS has a direct effect on dyskinesia reduction, while STN DBS may have a similar but indirect effect, dependent on the reduction of the total dopaminergic medication daily dosing (Figure). Also, in general, GPi DBS is not rewarded by significant medication reduction but allows flexibility in the medication regimen[55].

Most of the motor improvement is expected for non-axial signs and symptoms, with attenuation of motor fluctuations. The effect on speech can be negative, especially due to hypophonia after STN DBS. Cognition, if unimpaired, should not suffer a negative or positive influence, but might decline in those with baseline impairments[56]. Carefully selected patients with MCI may be candidates for DBS surgery; in these cases, the preferred target should be the GPi, which seems to be safer, with the caveat that conclusive studies confirming this impression

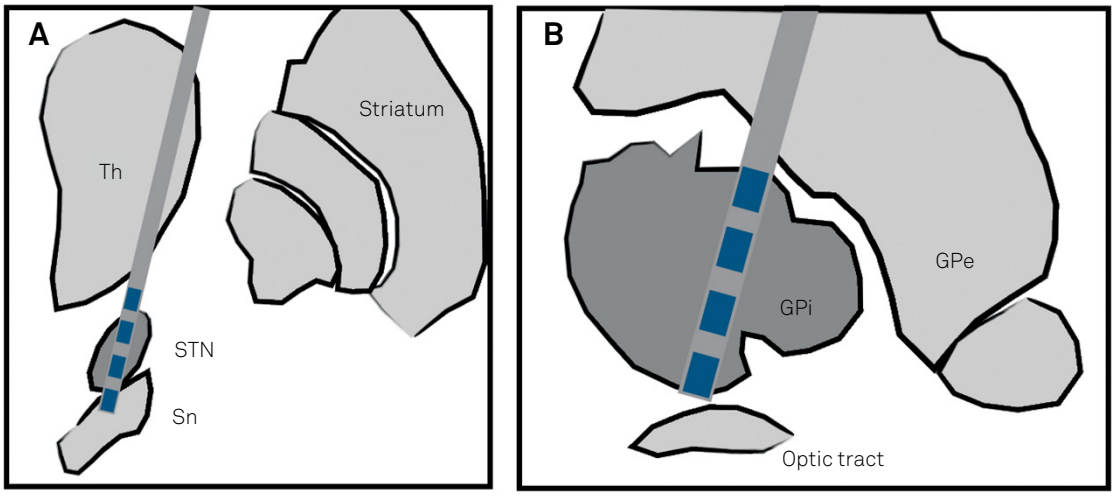

Figure. Anatomic relationships between the DBS leads and the most common targets, STN and GPi. (A) The subthalamic nucleus (STN) is closely related to the substantia nigra (Sn), red nucleus and third nerve (ventromedial); zona incerta (dorsal), and internal capsule (lateral). (B) The internal globus pallidus [GPi] is closely related to the optic tract (ventral), internal capsule (medial and posterior), and the external globus pallidus [GPe] (dorsal).

are still lacking. Yet, even in these situations, case-by-case discussions are essential. If MCI is characterized by a profile considered atypical for PD or is felt to be progressive, the decision for surgery should be strongly questioned, regardless of target.

In terms of motor effectiveness, a few variables were compared in a recent meta-analysis of the outcomes between the two targets after 36 months follow-up[26]. Improvements in motor symptoms during the "on-medication" period, was not different between STN and GPi DBS, however, reduction of the impact of motor symptoms during the "off-period" and the total daily medication dosage were more significant for STN DBS. The GPi DBS procedure showed a trend towards stronger dyskinesia reduction. Off-period motor symptoms and daily functioning were better for STN DBS, when compared with GPi, in a randomized, controlled trial with three years follow-up[57].

The trials that evaluated depression scores (with the Beck Depression Inventory) have shown better outcomes for GPi DBS[17,25,58,59]. As the STN is a smaller target, it is more susceptible to slight electrode misplacements, which could produce stimulation in structures that have a strong connection to the limbic system. The anatomic configuration of the nucleus and its connections could, thus, explain these adverse effects over mood and behavior[26,60].

The effects of DBS over impulse control disorders are less predictable, with previous descriptions of resolution (partial or complete) and also emergence of new impulse control disorders[41,42,43,44,45]. The existence of impulse control disorders should be addressed in the presurgical assessments and attempts to treat these symptoms should be done before surgery[61]. Binge eating has been related to STN DBS and could explain, at least partially, the weight gain observed following surgery[62]. In general, the presence of impulse control disorders and dopaminergic dysregulation syndrome should be seen as clues to the existence of potential susceptibility to psychopathology.

Regarding axial symptoms, there is no certainty about differences between the two targets in short- or long-term follow-ups. In theory, impairments in speech and swallowing could be induced more frequently by STN DBS, due to its proximity to corticobulbar fibers, but the cited meta-analysis and an additional systematic review did not confirm this association[26,63]. Some features of gait, such as anticipatory postural adjustments and freezing of gait, could improve with surgery, but postural instability and falls are less likely to improve, and might, in fact, worsen after DBS[40].

As a general principle, the STN is a target that seems to be superior in controlling bradykinesia and rigidity, off-period dystonia, and has a better economic profile (lower charge density is needed, with could spare equipment batteries, and allow lower medication dosage)[17,64,65]. On the other side, STN DBS may have a less favorable profile when it comes to cognitive and behavioral adverse effects. It correlates with worsened attention, working memory and processing speed, verbal fluency and cognitive flexibility, and possibly with faster decline in memory tests[56,58,59,66]. The GPi DBS seems to be superior in controlling dyskinesias and on-period dystonia, and could also be useful in a unilateral-only approach in patients with highly asymmetric PD features. Mood and apathy scores seem to be less affected when the target is the GPi, probably due to a less significant dopaminergic medication dosage reduction[11].

The target selection should take the patient profile into account (Table 4) and ideally be decided in a multidisciplinary meeting, after weighing the pros and cons. A patient with PD-MCI or with prominent levodopa responsive non-motor symptoms, for example, would probably get more benefit from the GPi as a target. In contrast, a patient with prominent medication-induced dyskinesias would be better treated with STN-DBS[61,64].

Table 4. Patient profile features that help guide the target selection (GPi or STN).

GPi	STN
May be indicated in cases with mild cognitive impairment	Intact cognition
Severe dyskinesias induced by relatively low doses of levodopa	Severe motor fluctuations on high doses of levodopa
On-period dystonia	Off-period dystonia
Levodopa responsive non-motor signs, including mood and behavior (levodopa reduction is not desirable)	Side effects with dopaminergic medications requiring reduction of levodopa dose
Usually less laborious postoperative programming	Usually requires less energy usage, delaying implantable pulse generator replacement

GPi: internal globus pallidus; STN: subthalamic nucleus.

CONCLUSION

In this article, we sought to address the complexity of therapeutic decisions regarding the treatment of PD with DBS, calling attention to the need to form dedicated multidisciplinary groups in order to optimize surgical outcomes. It is important to highlight that a group of features should be assessed before indicating DBS surgery, including not only the motor performance or response to levodopa. The criteria involve several domains, passing through psychiatric and neuropsychological evaluation, associated with speech therapy, social and educational aspects. All of the domains are highly relevant to the final therapeutic decision, and it is not advised to conduct this therapy without a comprehensive assessment. A multidisciplinary team is essential to approach the parkinsonian patient in the DBS context, not only during the preoperative evaluation but also during the follow-up.

This article is not intended to exhaust the discussion on this topic, but rather to stimulate rational, and therefore possibly more effective, surgical procedures.

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