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REVISIÓN TEÓRICA DE MÚLTIPLES TEMAS SOBRE ESTIMULACIÓN CEREBRAL PROFUNDA EN LA ENFERMEDAD DE PARKINSON: CONCEPTOS BÁSICOS QUE ENFATIZAN LAS CONTRIBUCIONES NEUROPSICOLÓGICAS

A multiple-topic theoretical review on Parkinson's disease Deep Brain Stimulation: basic concepts emphasizing neuropsychological input

Revisão teórica de múltiplos tópicos sobre a Estimulação Cerebral Profunda na doença de Parkinson: conceitos básicos enfatizando as contribuições neuropsicológicas

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Palavras-chave: Doença de Parkinson; Estimulação Cerebral Profunda; Neuropsicologia; Multidisciplinaridade; Ética.

R E S U M E N

La enfermedad de Parkinson (EP) es una afección crónico-degenerativa asociada con la pérdida de inervación dopaminérgica en el cuerpo estriado. La intervención neuroquirúrgica funcional en la EP tiene como objetivo, principalmente, restaurar las funciones neurológicas y promover la calidad de vida. La terapia de Estimulación Cerebral Profunda (ECP) consiste fundamentalmente en la implantación de electrodos en dianas cerebrales específicas y predeterminadas, especialmente en el Núcleo Subtalámico (STN) y en el Globo Pálido interno (GPi). Usando un dispositivo telemétrico con un programa de software específico es posible seleccionar qué zonas de contacto estarán activas además de la configuración de una variedad de parámetros eléctricos, con el fin de minimizar los síntomas motores y no motores. Además los aspectos neuropsicológicos, una lista de conceptos básicos como criterios de elección para ECP; posibles complicaciones quirúrgicas; configuración del dispositivo; multidisciplinariedad; terapias combinadas; aspectos éticos y desafíos futuros se abordarán de manera sucinta en este breve artículo teórico de revisión.

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A B S T R A C T

Parkinson's disease (PD) is a chronic-degenerative condition associated with the loss of dopaminergic innervation in the striatum. The functional neurosurgical intervention in PD aims, primarily, to restore neurological functions, promoting quality of life. Deep Brain Stimulation (DBS) therapy, in essence, consists of implanting electrodes in specific and predetermined brain targets, mainly in the Subthalamic Nucleus (STN) and the Globus Pallidus interna (GPi). Using a telemetric device with a specific software program, it is possible to select which zones of contact will be active, in addition to the configuration of a variety of electrical parameters, so as to minimize motor and non-motor symptoms. Neuropsychological aspects and a list of basic concepts such as election criteria for DBS; possible surgical complications; device settings; multidisciplinarity; combined therapies; ethical aspects, and future challenges will be succinctly addressed in this theoretical rapid-review article.

R E S U M O

A doença de Parkinson (DP) é uma condição crônico-degenerativa associada à perda da inervação dopaminérgica no corpo estriado. A intervenção neurocirúrgica funcional na DP objetiva, principalmente, restaurar as funções neurológicas e promover qualidade de vida. A terapia de Estimulação Cerebral Profunda (ECP) consiste, fundamentalmente, no implante de eletrodos em alvos cerebrais específicos e pré-determinados, especialmente no Núcleo Subtalâmico (STN) e no Globo Pálido interno (GPi). Utilizando um dispositivo telemétrico com programa de software específico é possível selecionar quais zonas de contato estarão ativas, além da configuração de diversos parâmetros elétricos, de forma a minimizar sintomas motores e não motores. Aspectos neuropsicológicos e uma lista de conceitos básicos como critérios eletivos para ECP; possíveis complicações cirúrgicas; configurações do dispositivo; multidisciplinaridade; terapias combinadas; aspectos éticos e desafios futuros serão abordados de forma sucinta neste breve artigo teórico de revisão.

Introduction

Since Charcot's first attempts at using natural alkaloids derived from the Belladonna plant, the treatment of PD has been primarily pharmacological (Goetz, 2011). Thereafter, several attempts have been tested until settling on the core concept that the cause of PD is due to a dopamine deficiency (principally in the dorsal portion of striatum, the putamen). This finding has initiated controlled researches on precursor agents for this neurotransmitter (L-dopa or Levodopa). Currently, L-dopa therapy remains to be viewed as a first-choice standard treatment for PD (Hauser & Zesiewicz, 2007).

Fluctuations in therapeutic response such as random oscillations, dyskinesias (e.g. peak dose, biphasic, square wave, or "off" period), and end-of-dose deterioration - also known as "wearing-off" - are the most common forms of motor complications associated with L-dopa treatment in PD. Thus, along with the well-known Chronic Dopaminergic Dysregulation Syndrome (CDDS), it is of crucial importance to consider that with the advancing age of patients several collateral symptoms (e.g. cardiovascular, intestinal and urinary), in addition to pharmaco toxic psychosis and cognitive disorders, may represent an additional dilemma associated with L-dopa therapy (Thanvi & Lo, 2004).

The main objective of this theoretical-scholarly paper is to promote a rapid and updated review of some of the most discussed concepts related to PD Deep Brain Stimulation (DBS), with a special emphasis on current neuropsychological input.

Deep Brain Stimulation in Parkinson's disease

The treatment or surgical intervention in PD aims, primarily, at restoring a certain neurological function. Also known as stereotactic functional neurosurgery, the measure first appeared in the early 1870s, with animal models introduced by pioneer surgeons in Russia and England. In 1940, via lesion procedures in the basal nuclei, the modern era of neurosurgery in PD was reopened. At the time, the zenith of functional neurosurgery occurred with the advent of stereotactic pallidotomy, performed by USA researchers (Iskandar & Nashold, 1995). Currently, neurosurgical management of movement disorders is divided into ablative, lesional or is carried out by means of Deep Brain Stimulation therapy (DBS).

Neurosurgery in PD is the result of the search for therapeutic alternatives that could compensate for those possible complications stemming from the pharmacological treatment. DBS therapy, in essence, consists of implanting electrodes in specific and predetermined positions (or targets), through a trepanation orifice (cranial opening), once the coordinates of the target are precisely established. Uni- or bilaterally, the implant is allocated simultaneously with neuroimaging techniques (computerized tomography or magnetic resonance), in addition to neuroanatomical atlas overlapping and intraoperative neurophysiological monitoring (Larson, 2014).

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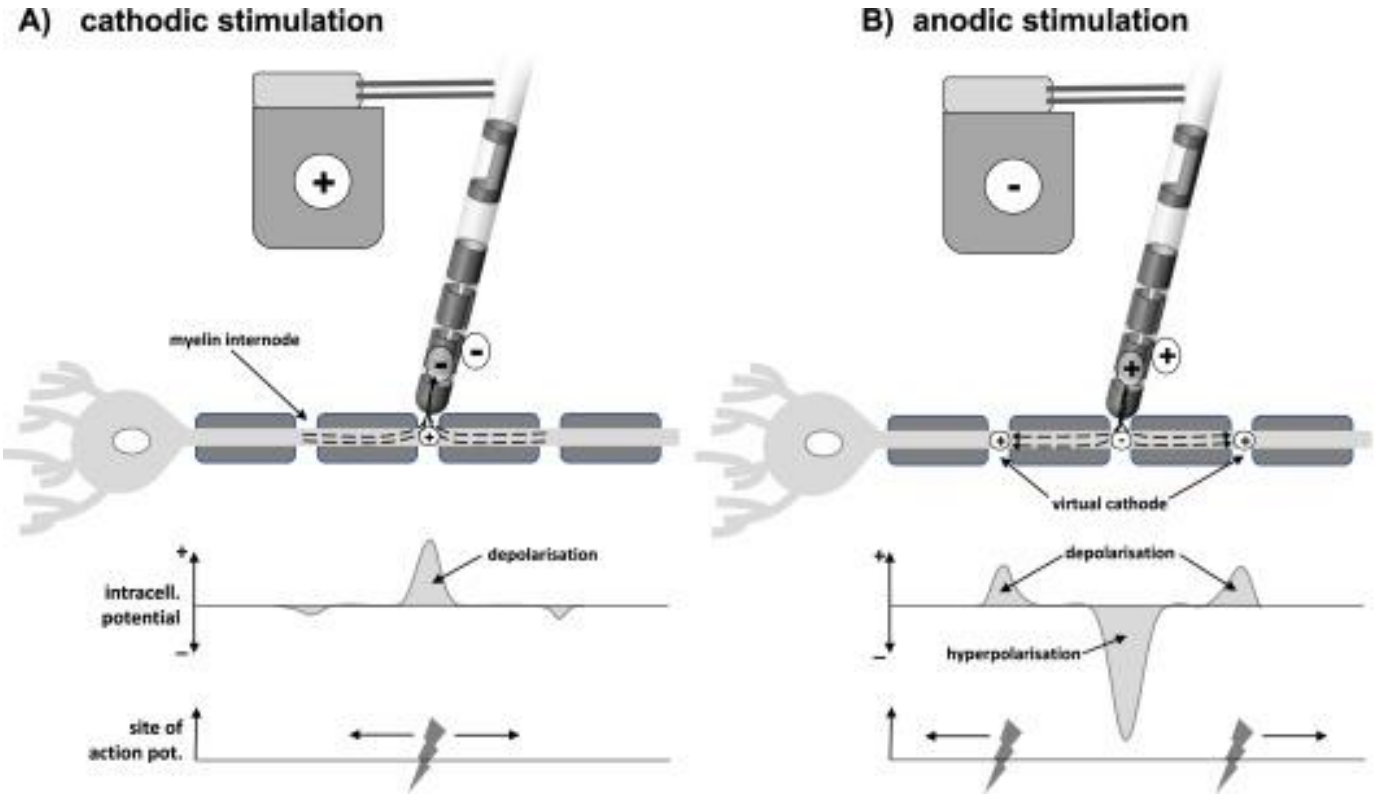
Anaesthesia may vary between conscious sedation utilizing propofol and/or dexmedetomidine, along with a low quantity of remifentanil, to general anaesthesia with endotracheal intubation. At present, the two main conscious sedation techniques are asleep-awake-asleep and monitored anesthesia care, with sedation. As a consensus, awake techniques promise the best conditions for intraoperative neurophysiology and stimulation testing. In a conscious state, the patient is then examined by neurologists to determine the clinical feed-back, and the extension cables connecting the electrodes to the "brain" pacemaker (pulse generator) are subcutaneously placed (Grant et.al., 2015).

Perioperative complications of DBS may eventually include vasovagal response, hypotension, seizure, intracerebral or intraventricular hemorrhage, ischemic infarction, infections, pulmonary embolism and aspiration pneumonia. Still, rates of complications are extremely low (Goodman et. al., 2006). Thus, DBS is clinically efficient in PD patients and should be considered as a treatment alternative for pharmacological therapy (Umemura et. al., 2003). Technical error during implantation of the DBS pulse generator and failure of lead fixation at the burr hole site followed by lead fracture and lead migration/displacement, may represent the most important findings in postoperative DBS (Morishita et. al., 2017).

Concisely, following the postoperative period of two to four weeks, the neurostimulator is activated. Utilizing a telemetric device with a specific software program, it is possible to select which electrode zones ("contacts") will be active, in addition to the configuration of a variety of electrical parameters such as: Impedance (the resistance over electric current), frequency (volts weighted stimulation level), pulse width (stimulation duration), amplitude (milliampere weighted current intensity), and polarity (mono-, bi-, or tri-polar). Mono- and bipolar stimulation modes are the most common configurations. For both methods, streams flow from the anode to the cathode (A), depolarizing neural components close to cathode and hyperpolarizing the neural elements proximal to the anode (B) (see Figure 1). A cathode is a negative electric potential (sink of current), while an anode is the positive electric potential (source of the electrical discharge), generating action potentials, should threshold potential be reached (Ramasubbu et. al., 2018; Kirsch et. al., 2018).

Figure 1. Conventional cathodic/anodic stimulation configuration.



The exact moment when the DBS device is switched on (device testing plus initial programming) may vary between centers and medical teams. Consensually, an interval of between two and four weeks is deemed the most suitable, considering the neurosurgical extent necessary for natural absorption of micro-bleeds and reduction of edema. Subsequently, dopaminergic agents are gradually reduced from the ongoing pharmacotherapy, to ensure that no overstimulation side effect co-occurs. The initial programming clinical appointment involves determining the amplitude threshold (incrementally increasing in steps

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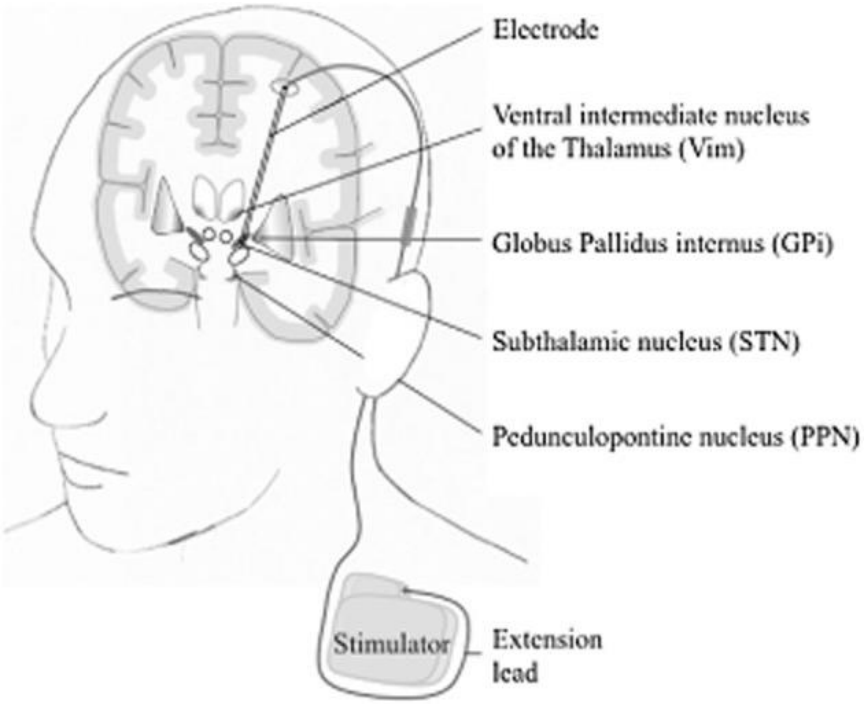
of 0.1–0.2 V) for clinical benefits and side effects for the electrode contacts for each lead, while keeping the pulse width fixed at 60 µs and frequency at 130 Hz, approximately (Malek, 2019). Subsequent programming sessions in a quest for optimum tuning are done periodically and all configurations should be properly recorded, along with the patient's clinical report of positive or negative self-impressions.

Even with appropriate guidelines suggesting clear-cut criteria for DBS patient selection, one of the most arguable questions raised by medical teams promoting DBS therapy relates to who actually has clinical indication to the detriment of the well-known contraindications. In turn, its importance beyond doubt justifies the success that can be ultimately achieved. Suggestions for clinical eligibility, therefore, may include some of the following aspects: confirmatory diagnosis of idiopathic PD (and exclusion of secondary or atypical parkinsonism); a minimum of four years of PD; motor fluctuation with off periods and disabling dyskinesias (even with optimized treatment); significant resting tremor resistant to dopaminergic therapy, and responsiveness to L-dopa therapy (with a minimum improvement of 30-40% in the levodopa challenge) (Brandão et. al., 2018).

Contraindications may include: severe 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); major psychiatric disorders (e.g. anxiety, depression, bipolar disorder, and psychotic symptoms unrelated to PD treatment); marked cognitive decline accompanied by well-established criteria for dementia; marked ventricular enlargement and/or cerebral atrophy; severe axial symptoms resistant to treatment with L-dopa (e.g. dysarthria, dysphagia, postural instability or disturbances in gait), absence of family/social support, and low adherence to prospective clinical follow-up (Lang et. al., 2006). Mild Cognitive Impairment (MCI) in PD (PD-MCI), where there are cognitive changes, yet functionality remains preserved and criteria for dementia are insufficient, does not, as of yet, have well-established indication-contraindication rules for DBS therapy (Cernera et. al., 2019).

Although other targets are able to be stimulated via extension lead, the subthalamic nucleus (STN) and the globus pallidus interna (GPi) have come to be considered the two main targets in DBS therapy for PD (see Figure 2). An aggregated body of evidence indicates that the two targets are identical in terms of their motor benefits, yet STN may be higher than GPi in terms of economic profile (less battery replacements) and reduction of medication. GPi, on the other hand, is higher than STN in terms of dyskinesia regulation and flexibility on pharmacological treatment. So far, few studies have been objectively carried out to differentiate each of these targets' peculiarities. Apparently, STN treatment remains the preferred choice for PD patients in need of significant tremor control, while at the same time, a target to avoid in patients with significant comorbid psychiatric illness and multiple cognitive impairments (Poortvliet et. al., 2015).

Figure 2. Subthalamic nucleus (STN) and the globus pallidus interna (GPi).



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Neuropsychological Input

Patients with PD, as well as those with other progressive and degenerative neurological conditions, can and tend to present neuropsychological changes over time. As a result of the dopamine deficiency in the nigrostriatal pathways and its correlation with neuropsychological models, cognitive deficits are mistakenly considered solely as an executive dysfunction. Nonetheless, unanswered questions as to the origin, dissociation, and progression of PD attentional impairment, visuo-spatial processing, memory loss, language and semantic deterioration (particularly syntactic, action-verb, and semantic action skills), require further studies.

The definition of MCI was introduced in PD clinic to enhance early detection of dementia and is currently applied to identify the heterogeneous deficits found in the continuum between PD normal cognition and Parkinson's Disease Dementia (PDD). PD-MCI patients have an annual rate of dementia between 9 and 15%, yet, the poor reliability of the PD-MCI definition has led to significant variation, primarily due to technical instabilities within classification criteria (such as deviant threshold ranges from −1 to −2 standard-deviations in the neuropsychological scoring system). In fact, there is no consensus as to which cognitive domains should be privileged in neuropsychological assessment, which instruments should be used as a gold-standard measure, nor an international testing consortium that has been validated at different centers worldwide, so far (Biundo et. al., 2016).

In response to the above-mentioned cognitive variability, the Movement Disorder Society (MDS) commissioned a task force to establish standardized diagnostic criteria for PD-MCI, released in 2012, and included a two-level operational step-by-step composition regarding the neuropsychological assessment (Litvan et. al., 2012). In brief, level I is based on an abbreviated evaluation including a global cognitive scale and/or a normalized screening test, such as The Mattis Dementia Rating Scale and The Mini Mental State Examination (Holtzer et. al., 2002; Folstein et. al., 1975), while level II is focused on rigorous neuropsychological testing along each of the five cognitive domains, such as: attention and working memory, executive function, language, memory, and visuospatial function (see Figure 1). As mentioned, decay is demonstrated through scores approximately 1 to 2 standard deviations below age, education, gender, and culturally appropriate norms (Geurtsen et. al., 2014).

Figure 3. Movement Disorder Society task force protocol for levels I and II of cognitive impairment.

Cognitive Domain	Neuropsychological Tests	Estimated Application Time (in minutes)
Attention and Working Memory	Letter Number Sequencing - WAIS (Wechsler, 2008)	5
	Coding – WAIS	5
	Forward and Backward Digit Span Task - WAIS	5
	Trail Making Test - and B (Llinàs-Reglà et. al., 2017)	5 to 10
	Stroop Color-Word Test (Erdodi et. al., 2018)	5 to 10
Executive Function	Wisconsin Card Sorting Test (Kopp et. al., 2021)	15
	Tower of London Test - Drexel Version (García-Alba et. al., 2017)	10 to 15
	Stockings of Cambridge - CANTAB (Cacciamani et. al., 2018)	10 to 15
	Verbal Fluency Tasks – letter/category (Wajman, 2020)	5
	10-points Clock Drawing Test (Yoo & Lee, 2016)	5
Language	Similarities – WAIS	10 to 15
	Boston Naming Test (Miotto et. al., 2010)	5 to 15
	Graded Naming Test (Murphy et. al., 2020)	5 to 15
Memory	Rey Auditory Verbal Learning Test (Weitzner et. al., 2020)	10 to 20
	California Verbal Learning Test (Alioto et. al., 2017)	10 to 20
	Hopkins Verbal Learning Test (Ryan et. al., 2020)	10 to 20
	Selective Reminding Test (Castilhos & Chaves, 2017)	10 to 20
	Prose Recall Test (Chapman et. al., 1997)	10 to 15
	Logical Memory - WAIS	10 to 20
	Brief Visuospatial Memory Test (Havlík et. al., 2020)	10 to 15
Visuospatial Function	Benton Judgment of Line Orientation Test (Gasser et. al., 2020)	5 to 10
	Hooper Visual Organization Test (Lopez et. al., 2003)	10

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Several cognitive tools are utilized in clinical neuropsychology, for different purposes. Considering the neuropsychological PD profile and the most sensitive and specific tools available for its rationale assessment (applicability parameters), calibrated protocols include tests of general cognitive functioning, memory, language, visuoperceptual ability, attention, executive functions, and speed of processing. As many cognitive instruments are not directly replicable in different languages and cultures, it is expected that each of these domains will be properly accessed by tests that have local normative data. Comprehensively, these tests may include a global scale, screening tests, sustained attention assessment, verbal and non-verbal episodic memory, verbal fluency, naming, processing of speed, cognitive flexibility: inhibitory control and alternation, and visual perception. Premorbid intelligence tests may be included for research purposes, since PD cognitive changes usually affect fluid and non-crystallized competencies.

A reasonable motive for listing major criteria against the DBS fulfilment in PD patients is that the therapy *per se*, although safe, could - among other reports - accelerate possible pre-existing cognitive impairments, aggravate symptoms of anxiety or depression, and may even cause a psychotic condition (Giannini et. al., 2019). A comprehensive meta-analysis study has applied fashionable models along with a novel p-curve analytic procedure to compare potential cognitive impairments associated with STN-DBS to those associated with GPi-DBS. Forty-one articles were reviewed with an aggregated sample size of >1600 patients. GPi-DBS resulted in fewer neurocognitive declines than STN-DBS (mild decline in attention and mild-to-moderate decline in verbal fluency), both being non-progressive modalities, as long as patient selection criteria are fully adopted and strictly followed (Combs et. al., 2015).

Non-motor behavioral disturbances in PD are frequent, and have an important impact on a patient's quality of life (QoL). Main psychiatric conditions observed in patients with PD include psychotic disorders, mood disorders, apathy, anxiety disorders, and impulse control disorders. Effective assessment of cognitive profile pre-surgery and the identification of any psychiatric disorder, the correct positioning of the electrode, assertive programming parameters enforcement and tailored pharmacological therapies may help in minimizing clinical aggravating factors post-DBS and to improve the QoL for these patients (Buoli et. al., 2016). Simultaneously, the DBS technique usually has a positive effect on the aggregate measures of these syndromes, regardless of the target chosen (Okun et. al., 2009). No specific benefit has been consistently found in either goal (STN vs. GPi), both successful and with a favorable long-term progression. Withall, clinical characteristics and anatomical conditions of each patient will further be the main indicators guiding neurologists and the neurosurgeon in the search of the most assured decision (Accolla & Pollo, 2019).

As part of the psychological findings that may influence cognition, body discomfort and pain are some of the conditions recognized as disabling in PD. Associated or not with other symptoms, functional capacity after DBS has not been extensively studied in PD. A multiple-treatment meta-analysis of randomized controlled trials reported that GPi-DBS may be more effective in improving the score on an Activity of Daily Living questionnaire for Parkinson's disease (PDQ-39 ADL) (Peto et. al., 1995), compared with STN-DBS (Xie et. al., 2016). However, most of these studies focused on the short-term (≤1 year) efficacy. Another meta-analysis, assessing the long-term efficacy of STN and GPi DBS for PD, has also shown GPi-DBS to be associated with a greater improvement of PDQ-39 ADL (Peng et. al., 2018). Still, an 11-year long-term follow-up on 26 PD-DBS patients bilaterally implanted in two different centres reported that the functional capacity worsened over time, mainly for the onset and progression of levodopa-resistant and non-motor symptoms, despite the improvement of dyskinesias and motor fluctuation (Rizzone et. al., 2014).

The aim of the neuropsychological assessment applied to PD-DBS is not to solely determine test results, but rather to provide information to the treatment team, the patients themselves and their relatives, to better evaluate the risk-benefit ratio of the procedure within the context of the patient's desired outcomes. With this in mind, the main purpose of pre-operative neuropsychological assessment is to identify potential, relative cognitive and emotional contraindications to the DBS procedure (Tröster, 2017). Indeed, an analysis of exclusion cases has shown that almost 1 in 2 candidates for surgery (48%) was considered ineligible due to cognitive and/or psychiatric findings (Lopiano et. al., 2002). In close association, this well-balanced baseline assessment will serve, later on, as a measure for future comparisons, for the immediate identification of other neurological conditions (such as a dementia already installed), for the patient's recognition of their own abilities, and finally for the continuing education of non-neuropsychologist colleagues.

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New Outcomes and Future Challenges in PD-DBS

Progress on DBS Therapy

Among all the neurological conditions leading to progressive and inexorable cell death, PD is probably the one that benefits most from the technological advances applied to its therapy for refractory and/or difficult pharmacological management situations. In addition, not only was this technological benefit added to other existing techniques (high-resolution neuroimaging), but also a significant scope of the surgical and medical approach was changed. Artificial cables and wires became part of the neural circuitry, and brain function also started to operate through remote adjustment devices. Despite unquestionable advances, DBS therapy has not undergone major updates of late, mostly due to the lack of internal pressure (a healthy competition among start-ups sponsors, pharmacological industry and researchers).

Some of these long awaited initiatives for advancement in DBS technology starts from self-rechargeable batteries (with a prolonged useful life), optimized electrodes with multiple contacts (increasing the options of therapeutic within "polizones"), stimulation on demand (also called "closed-loop": electrical activation by some patients' movement) or the continuous modulation of DBS by endogenous neurochemical feedback (the "adaptive closed-loop"), coordinated reset (disruption of local oscillations and changing synaptic strengths by means of activity suppression) to miniaturized pulse generators (for eventual implant directly into the skull) (Lozano et. al., 2019). For the sake of facilitating information, the current and conventional model used is called "open-loop" DBS, in which a neurologist manually adjusts the stimulation parameters every 3–12 months after DBS implantation. In other words, "closed-loop" disables when the brain reaches normal condition, while "open-loop" model continues to stimulate irrespective of the state of the brain (Parastarfeizabadi & Kouzani, 2017).

A final yet utterly important issue rarely mentioned regarding DBS therapy is the reversibility of the procedure. Unlike other neurosurgical procedures (such as pallidotomy and thalamotomy), DBS therapy may be deactivated. In most cases, system components are able to be removed, preserving options for future therapies and treatments.

Combined Therapies

In addition to the countless patients with PD undergoing the well-established dopaminergic therapy, DBS has been repeatedly proven to be a safe and efficient treatment. Combination therapy is characterized as treating disease with two or more drugs, so that an additional compound may show higher efficacy, obtain additive or synergistic effects, or combat expected resistance, or reduce the risk of drug resistance developing (Bharadwaj, 2019). The optimal combination of dopaminergic therapies and stimulation setting relies on the prior knowledge of both alternatives. Reduction in Levodopa equivalent daily dose (LEDD) and other dopaminergic medications is widely endorsed after DBS, especially STN-DBS. At the same time, an indiscriminate change in the ongoing dopaminergic therapy can elicit other (mainly non-motor) problems.

A 2019 meta-analysis (Vizcarra et. al., 2019) of all studies reporting motor, dyskinesia, and Activities of Daily Living (ADL) outcomes following bilateral STN-DBS in PD, with pre- and postsurgical Unified Parkinson's Disease Rating Scale (UPDRS-III) (Movement Disorder Society, 2002) in medication-OFF and medication-ON states, has shown that DBS stimulation and Levodopa therapy independently lessened motor severity in PD to similar rates while their synergistic effect was superior than either treatment alone, after a 5-year follow-up. To date, there have been no similar or improved studies on this therapeutic association involving GPi-DBS. Another recent meta-analytic review, comparing DBS to the best medical option (BMT) in PD was performed. Main outcome measures were the UPDRS, PDQ-39, LEDD, and rates of serious adverse events (SAE). Findings suggest DBS to be superior to BMT in improving impairment/disability, quality of life and reducing medication doses (Bratsos et. al., 2019).

Future studies comparing these two combined therapies (Levodopa *plus* STN/GPi-DBS) with early and late PD onset; specific motor and non-motor manifestations; association between LEDD and cognitive performance, through prospective neuropsychological comparisons, unsuccessful attempts configuration analysis of the clinician programmer, among several unanswered assumptions are to be expected.

Clinical Trials

Studies based on scientific principles, such as the Clinical trials (CT's) are essential to measure the efficacy of new therapies. Every recognized medication and methodological care starts off with volunteers participating in CT's. Despite the research not showing the expected results, the outcomes of the trial will further help to guide scientists in the right direction. At the same time procedures must be standardized by the clinical team, patients are encouraged to inquire about objectives, methods and procedures, as far as possible, and feel confident requesting updated information from the involved specialists.

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Considering the main clinical characteristics of PD and the usual procedures of DBS therapy, most studies have only focused on the motor function comparing GPi with STN techniques. With this in mind, 2016 meta-analytic research on controlled CT's comparing the efficacies of GPi and STN DBS was performed. Motor function, non-motor function, and QoL data were equally collected (Tan et. al., 2016). From ten eligible trials involving more than one thousand patients, researchers found that GPi and STN DBS significantly improve advanced Parkinson's patients' symptoms, functionality, and QoL. Additionally, GPi-DBS provided better verbal fluency scores, also reducing symptoms of depression. Simultaneously, GPi-DBS was also associated with increased dosage of LEDD.

In addition to the aforementioned study, extensively covering the CT's present in the specialized literature, it is also possible to find other randomized and non-randomized controlled CT's at the clinicaltrials.gov electronical site: a database of privately and publicly funded CT's conducted around the globe. One of which, under responsibility of the North Bristol National Health Service (NHS) Trust, and expected to end in 2023 and called Simpler and Safer Deep Brain Stimulation for Parkinson's Disease (SPARKS), has, as a main objective: "*to improve availability and acceptability of deep brain stimulation (DBS) for the treatment of Parkinson by shortening and simplifying the implantation procedure, thereby reducing time in surgery, complexity, post-surgery complications and cost, and increasing patient satisfaction*". This initiative is also aimed at other clinical outcomes, such as mood and behavior, cognitive functions, QoL, and functional capacity (Retrieved from https://clinicaltrials.gov/ct2/show/NCT03837314).

Finally, other CT's have been conducted by private medical equipment companies. These global public-private partnership studies (completed or in progress) have been truly essential, considering the significant investment made by the sponsor and the access of the under-privileged communities to this therapy. Concurrently, specialists are compelled and committed to the advance of PD-DBS, and also to current and recommended standardized clinical practices.

From Invasive to Less-invasive DBS

As widely reported and previously mentioned in this text, DBS therapy is considered a safe and efficient procedure. Despite the need for surgical preparation, mobilization of medical staff, hospitalization (a factor generally increasing the risk of infections), the surgery itself, and post-surgical care, solid results justify the procedure. All these mishaps have led the scientific community to envision a future technique where brain stimulation therapy could be non-invasive.

Perhaps, this new direction might be an experimental strategy performed on mice aiming at targeting deeply situated neural cells without interfering with the overlying cortex activity by applying high-frequency oscillating fields at various locations from outside the brain (Grossman et. al., 2017). Although elegant and non-invasive, the principle is not completely valid as dimensions of the human brain are much larger compared to the brain of rats. A factor that would hinder the precise establishment and reaching of deeper neural connections (subthalamic nucleus and the globus pallidus zones).

A different noninvasive-invasive technique (or a mixed type) is the optogenetic stimulation, developed over the last decade. Throughout the use of light to regulate neuronal ion channels in vivo, Optogenetics can selectively stimulate neurons deep inside the rodent brain. Neural circuits can thus be controlled by accurate excitation and inhibition of particular circuit components, switching from invasive to non-invasive DBS (Hell et. al., 2019). The "mixed type" term persists due to the fact that Optogenetics yet too requires a continuously implanted optical fiber, and, to date, is not considered a fully non-invasive technique (Bernstein et. al., 2012).

Be as it may, any of these suggested techniques are still to pass the scrutiny of medical engineering, where machine learning algorithms would be designed and tested, until reaching optimal means of experimental and controlled application in subsequent stages of human research.

Cost Effectiveness Analysis and Patient Expectations

The financial cost associated with DBS still exceeds other therapies in terms of initial investment. The value of all the equipment itself, the occupation of surgical centers and the remuneration of the professionals involved represent the bulk of this investment. Still, in addition to its justification in terms of therapeutic gain, DBS therapy may prove to be more economical than high-end novel pharmacological treatments, in the medium to long term. A European study found that, relative to continuous subcutaneous Apomorphine infusion or continuous duodenal Levodopa + Carbidopa infusion, the mean average 5-year cost per patient was substantially lower with DBS (€141,393, €233,986 and €88,014, respectively) (Valldeoriola et. al., 2013). This substantial difference between figures, especially in countries where access to health and technology is still marked by socioeconomic restraint, demonstrates the therapeutic importance of DBS.

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More recently, a systematic-review of the literature on the economic analysis of PD-DBS has shown DBS to be a cost-effective intervention for patients with PD, yet it has a high initial cost compared with BMT. Furthermore, DBS decreases the costs of pharmacological care and would also minimize the direct, indirect, and long-term social costs of PD. Presented in US dollars, this study has established that the average cost of DBS for a patient with PD over a period of 5 years came to US$186,244. Following a minimum of 2 years of care, the quality-adjusted life year in DBS was higher compared to BMT, with an average marginal cost benefit ratio of US$ 41,932 per additional quality-adjusted life-year acquired. All nine studies included in this analysis have shown better results with a longer time horizon (up to 5 years) (Becerra et. al., 2016).

Value of Multi- and Interdisciplinary Teams

All steps of the DBS must be strictly followed so as to minimize any deleterious occurrences throughout the process. From the initial application of inclusion criteria to post-operative care, different specialists are requested. Monitoring with a movement disorder neurologist, neuropsychological testing and consecutive re-testing, the application of motor and non-motor scales by a nursing staff, clinical assessment of mood and behavior weighted by a psychiatrist, in addition to the neurosurgical preparation and procedure are some of the expertise justifying the need for the multiprofessional team in DBS.
Yet still, despite its recognized importance, there are practically no specific manuals or guidelines emanating from professional Councils regarding the competencies specifically related to the activity performed by multidisciplinary teams. The tasks assigned to each of these professionals, therefore, are usually put forward by a board of specialists, such as the task force headed by the Movement Disorders Society study group. In this way, the obligations of each specialist are described in terms of the appropriate approach of patients and not specifically related to the formal certification of each professional. However, given the complexity of the therapy, it is expected that these professionals have sufficient experience with PD, along with their work tools.

Ethical Implications

In the context of treating a movement disorder patient with DBS therapy, numerous ethically nuanced and thorny issues may arise. Patients undergo elective DBS to enhance quality of life and this goal underscores the particular importance of all professionals involved. An eminent seminal book on bioethics suggests four principles: beneficence; non-maleficence; respect for persons (autonomy); and justice (Beauchamp & Childress, 1994). These precepts have been highly influential and are reflected in the American Psychological Association's (APA) Code of Ethics (2016). In short, the observation of these guidelines in daily practice gives the patient and his/her relatives security and confidence in relation to the procedure, and also regarding the medical team.
Some examples of potential values in conflict in the context of clinical decision-making for DBS are: respect for patient's decision (autonomy) vs. respect for team's (autonomy) obligation to do what is believed to be safe; respect for patient's choices based on personal values (autonomy) vs. respect for the broader needs of the community (e.g. potential increased costs associated with extra care); providing gold standard therapy for which the patient will likely be non-adherent vs. providing a less effective therapy not requiring adherence (e.g. DBS vs. ablation); fiduciary responsibility to the patient vs. fiduciary responsibility safeguarding the field by minimizing likelihood of significant negative outcomes; do no harm vs. professional integrity in light of limits of knowledge and literature; and responsibility to communicate and contribute to the larger clinical research community, among others (Kubu & Ford, 2017).
Adopting the recommendations outlined will further assist in protecting the health and rights of patients and professionals participating in DBS procedure, and also have the potential to support other stakeholders in the testing process including CT's and product manufacturers. With this in mind, an intense and significant commitment from many of these same stakeholders to adhere to the guidelines will ensure the progress of the therapy itself and science as well.

Conclusions

PD is one of a series of progressive neurodegenerative diseases, for which pharmacological treatment is primarily symptomatic, that is, it does not offer reversible therapy yet alone a cure. Controlled studies have been unanimous in pointing out, through CT's, systematic reviews and meta-analysis papers, the safety and efficacy of DBS therapy for those patients. DBS can be a supporting strategy to pharmacotherapy, decreasing the LEDD and promoting QoL. Both of the most used targets (STN and GPi) have shown positive outcomes in the treatment of PD, despite maintaining their own particularities. Although its high initial investment, DBS outperforms other therapies in PD as its cost in the medium to long

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term is lower, yet still effective. It is important to highlight the need for a multidisciplinary coalition, in view of current PD-DBS multifaceted criteria. Ethical considerations must drive practice undertaken by researchers and keep abreast with the technological progress of the DBS therapy and finally, just as is observed in associated areas of the neurological clinic, the role of the neuropsychologist represents an important ally prior to, during and following the surgical procedure, bringing with it well-established parameters and duly substantiated techniques. Taken together, the findings of this academic paper starkly demonstrate the usefulness of the neuropsychology approach in the clinic of PD, offering different insertion possibilities to students and contributing with knowledge to readers in general, as well as colleagues inserted in the sphere of applied neurosciences.

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