INTEGRATED MASTER'S DEGREE IN MEDICINE

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Directional deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Is directional stimulation redundant?

Sara Filipa Pires Costa

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Directional deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Is directional stimulation redundant?

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Integrated Master's Degree in Medicine

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I, Sara Filipa Pires Costa, number 201704671, of the Integrated Master's Degree in Medicine of the School of Medicine and Biomedical Sciences – Instituto de Ciências Biomédicas Abel Salazar of the University of Porto, declare that all Authors have participated in the present study and have read and approved the final version of this original article. It has not been previously used in any other course or curricular units, from this or any other institution. References to other authors (statements, ideas, thoughts) scrupulously respect the attribution rules and are duly indicated in the text and bibliographical references, per the referencing rules. I am aware that the practice of plagiarism and self-plagiarism constitutes an academic offense.

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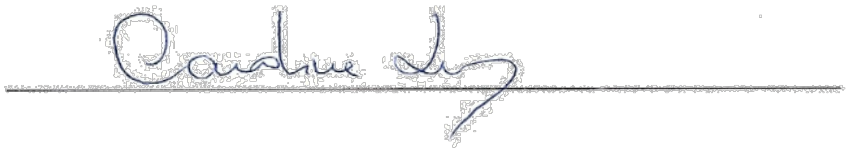
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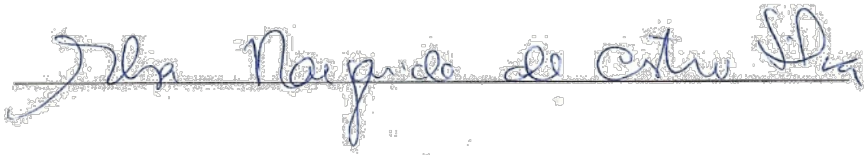
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Submission Section

I. Title

Directional deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Is directional stimulation redundant?

Estimulação cerebral profunda do núcleo subtalâmico na doença de Parkinson. Será a estimulação direcional redundante?

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IV. Resumo e Palavras-Chave

O presente estudo visa determinar o número de pacientes que apresentam estimulação direcional em pelo menos um hemisfério cerebral aos 12 meses de follow-up, e avaliar como a estimulação cerebral profunda (DBS) direcional (dDBS) influencia o benefício dos sintomas motores na Doença de Parkinson (DP). Concluiu-se que a maioria dos doentes submetidos à dDBS tinha estimulação omnidirecional aos 12 meses. Embora as médias dos benefícios da UPDRS-III nos grupos ND e D sejam semelhantes, indicando que a dDBS não provocou melhores resultados do que a DBS omnidirecional (oDBS), nenhuma associação estatisticamente significativa foi encontrada e outros fatores podem ter influenciado os resultados. Pacientes do grupo DMD obtiveram pior média de benefício na UPDRS-III, logo a direcionalidade não se demonstrou benéfica. Não foram encontradas associações estatisticamente significativas entre a direcionalidade e o benefício na LEDD.

Palavras-Chave: Doença de Parkinson; Estimulação Cerebral Profunda; Núcleo Subtalâmico; Estimulação Elétrica; Neurocirurgia.

IV. Capsule and Keywords

The present study aims to determine how many patients have directional stimulation in at least one cerebral hemisphere at the 12-month follow-up and assess how dDBS influences the benefit in the motor symptoms of Parkinson's Disease. It was concluded that most directional deep brain (DBS) stimulation (dDBS) patients had omnidirectional stimulation at the 12-month follow-up. Although the mean benefit in UPDRS-III scores in the ND and D groups was similar, indicating that dDBS did not originate better results than omnidirectional DBS (oDBS), no statistically significant association was found, and other factors could have influenced the results. Patients in the DMD group had a worse mean benefit in UPDRS-III scores, therefore directionality was not beneficial. No association between directionality and the benefit in LEDD results was found.

Keywords: Parkinson's Disease; Deep Brain Stimulation; Subthalamic Nucleus; Electric Stimulation; Neurosurgery.

Resumo Estruturado

Contexto: A estimulação cerebral profunda (DBS) direcional (dDBS) pretende oferecer mais opções de programação e uma janela terapêutica mais ampla do que a DBS omnidirecional (oDBS), aumentando os seus benefícios. Contudo, é mais cara e requer programação mais complexa e acompanhamento mais moroso.

Objetivo: Determinar o número de pacientes com estimulação direcional em pelo menos um hemisfério cerebral aos 12 meses de follow-up, e avaliar como a dDBS influencia o benefício dos sintomas motores na Doença de Parkinson (DP).

Materiais e Métodos: 75 pacientes foram divididos em 2 grupos: submetidos a oDBS (ND) e a dDBS (D). Este último foi subdividido em: doentes com estimulação direcional em pelo menos um hemisfério cerebral aos 12 meses (DMD) e sem ela (DNMD). Dados analisados: sexo; história familiar de DP; idades no início sintomático e à data da cirurgia; resultados da UPDRS-III e LEDD pré-operatórios (medicação-OFF) e aos 12/24 meses (medicação-OFF, estimulação-ON). Calculou-se: tempo entre início sintomático e cirurgia; diferença entre a LEDD aos 12 meses e pré-operatória e benefícios na UPDRS-III e na LEDD. Na análise estatística utilizou-se o IBM SPSS Statistics 29 para iOS, com $p<0.05$ estatisticamente significativo.

Resultados: Dos 12 pacientes dDBS, 66.7% tinham estimulação omnidirecional aos 12 meses e 33.3% direcional em pelo menos um hemisfério cerebral. O grupo ND obteve média mais elevada na UPDRS-III pré-operatória e aos 12/24 meses ($p=0.018$ e 0.038, respetivamente). O grupo DMD obteve a média mais elevada na UPDRS-III aos 12/24 meses (p ajustado=0.029) e o benefício menor na UPDRS-III (p ajustado=0.021).

Conclusão: A maioria dos doentes dDBS tinha estimulação omnidirecional aos 12 meses. Embora as médias dos benefícios da UPDRS-III nos grupos ND e D sejam semelhantes, indicando que a dDBS não provocou melhores resultados do que a oDBS, nenhuma associação estatisticamente significativa foi encontrada. Outros fatores podem ter influenciado os resultados. Pacientes do grupo DMD obtiveram pior média de benefício na UPDRS-III, logo a direcionalidade não se demonstrou benéfica. Não foram encontradas associações estatisticamente significativas entre a direcionalidade e o benefício na LEDD.

Abstract

Background: Directional deep brain (DBS) stimulation (dDBS) intends to offer more programming options and a wider therapeutic window than omnidirectional DBS (oDBS), enhancing its benefits. However, it is more expensive and requires more complex programming and time-consuming follow-up.

Objective: Determine how many patients have directional stimulation in at least one cerebral hemisphere at the 12-month follow-up and assess how dDBS influences the benefit in the motor symptoms of Parkinson's Disease.

Materials and Methods: 75 patients were divided into 2 groups: submitted to oDBS (ND) and dDBS (D). The latter was subdivided into: patients with directional stimulation in at least one cerebral hemisphere at the 12-month follow-up (DMD) and those without (DNMD). Data analyzed: sex; family history of PD; ages at symptom onset and the date of surgery; UPDRS-III scores and LEDD results preoperatively (medication-OFF) and at the 12/24-month follow-up (medication-OFF, stimulation-ON). It was calculated: time between symptom onset and surgery; difference between 12-month follow-up and preoperative LEDD results; and benefits in UPDRS-III scores and LEDD results. Statistical analysis was performed using the IBM SPSS Statistics 29 program for iOS, with a p-value<0.05 considered statistically significant.

Results: Of the 12 dDBS patients, 66.7% had omnidirectional stimulation at the 12-month follow-up and 33.3% directional stimulation in at least one cerebral hemisphere. The ND group had higher mean UPDRS-III scores preoperatively and at the 12/24-month follow-up (p-value=0.018 and 0.038, respectively). The DMD group had the highest mean UPDRS-III scores at the 12/24-month follow-up (adjusted p-value=0.029) and the lowest mean benefit in UPDRS-III scores (adjusted p-value=0.021).

Conclusion: Most dDBS patients had omnidirectional stimulation at the 12-month follow-up. Although the mean benefit in UPDRS-III scores in the ND and D groups was similar, indicating that dDBS did not originate better results than oDBS, no statistically significant association was found. Other factors could have influenced the results. Patients in the DMD group had a worse mean benefit in UPDRS-III scores, therefore directionality was not beneficial. No association between directionality and the benefit in LEDD results was found.

Abbreviations' List

3D - 3-dimensional

D – directional, meaning patients submitted to dDBS

DBS - Deep Brain Stimulation;

dDBS - Directional Deep Brain Stimulation;

DMD - Patients who had at least one of the cerebral hemispheres with directional stimulation at the 12-month follow-up;

DNMD - Patients who did not have directional stimulation at the 12-month follow-up;

LEDD - Levodopa Equivalent Daily Dose;

MDS-UPDRS - Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale;

MRI - Magnetic Resonance Image;

ND – non-directional, meaning patients submitted to oDBS;

oDBS - Omnidirectional Deep Brain Stimulation;

PD - Parkinson's Disease;

STN - Subthalamic Nucleus;

ULSSA - *Unidade Local de Saúde de Santo António;*

UPDRS-III - Unified Parkinson's Disease Rating Scale Part III

VTA - Volume of Tissue Activated.

Index

Acknowledgments ..... ***i***

Submission Section ..... ***ii***

I. Title ..... **ii**

II. Authors and Affiliations ..... **ii**

III. Corresponding Author ..... **ii**

IV. Resumo e Palavras-Chave ..... **ii**

IV. Capsule and Keywords ..... **iii**

The present study aims to iii

Resumo Estruturado ..... **iv**

Contexto iv

Objetivo iv

Materiais e Métodos iv

Resultados iv

Conclusão iv

Abstract ..... **v**

Background v

Objective v

Materials and Methods v

Results v

Conclusion v

Abbreviations' List ..... ***vi***

Tables' List ..... ***viii***

Figures' List ..... ***ix***

Introduction ***1***

Materials and Methods ***2***

Study Design **2**

Ethical Considerations **2**

Follow-up **3**

Medication **3**

Levodopa Equivalent Daily Dose **3**

Motor Examination **3**

Data Analysis **4**

Results ***4***

Discussion ***5***

Conclusion ***9***

Appendix ***10***

Bibliography ***14***

Data Availability ***17***

Tables' List

- **Table I –** Means of the continuous variables that describe the disease-specific, and medication-specific data of the study population when considering 2 groups.
- **Table II –** Means of the continuous variables that describe the sociodemographic, disease-specific, and medication-specific data of the study population when considering 3 groups.

Figures' List

- **Figure 1 –** Categorical variables that describe the sociodemographic and disease-specific data of the study population when 2 groups are considered.
- **Figure 2 -** Categorical variables that describe the sociodemographic and disease-specific data of the study population.

Introduction

Parkinson's Disease (PD) is a neurodegenerative disorder with rising incidence and prevalence in the past two decades. It progresses slowly throughout several years in a heterogeneous way between individuals.[1] Usually, goes from mild motor unilateral symptoms like bradykinesia, muscular rigidity, resting tremor, and postural instability, that respond well to treatment, to symptoms that do not, requiring more medication, which can cause side effects. Non-motor symptoms start to appear like cognitive decline, depression, or rapid eye movement sleep disorders.[2] This impacts negatively on the person's quality of life and independence.[1]

Symptoms' severity and progression can be evaluated using disease-specific clinical rating scales[3] like the Unified Parkinson's Disease Rating Scale (UPDRS), recognized as the acclaimed scale to measure PD disability.[4] It consists of four parts: part I and part II (non-motor and motor experiences of daily living, respectively); part III and part IV (motor examination and complications, respectively). Based on its clinimetric properties, each part can be considered separately.[5,6] Focusing on UPDRS Part III (UPDRS-III), it assesses parkinsonism using 33 items rated on a 5-point Likert-type scale. The patient can be in an ON (medicated with antiparkinsonians) or OFF (unmedicated) state when evaluated.[3,5,7,8]

Pharmaceutical treatment of advanced PD can be challenging and impose a significant economic burden on the patient and the healthcare system due to the long-duration treatments with antiparkinsonians.[9] Although levodopa is the most effective antiparkinsonian and is well tolerated at all disease stages,[10] balancing symptomatic improvements with drug-related complications becomes difficult.[9] As the disease progresses and patients become refractory to medical management, experiencing motor and non-motor symptoms and more prominent symptom fluctuations, deep brain stimulation (DBS) of the subthalamic nucleus (STN) and *globus pallidus internus* becomes relevant in controlling the motor symptoms.[11,12]

Omnidirectional DBS (oDBS) of STN is a well-established treatment for motor symptoms in movement disorders including PD[13–15] due to its minimally invasive nature and effectiveness[15] in improving levodopa-related motor complications, the patient's quality of life, and the quality-adjusted life expectancy.[16] Nonetheless it has downsides. Since the area stimulated is small, minimal misplacements of electrodes can stimulate areas associated with adverse effects especially if structures like the cortico-spinal tract, the medial lemniscus, or the ventral, limbic part of the STN are stimulated.[17] Since directional DBS (dDBS) allows the direction of the stimulation to the motor part of the STN and away from these areas, it has been studied as an alternative to avoid these undesirable symptoms.[18]

The present study aims to determine how many patients have directional stimulation in at least one of the cerebral hemispheres at the 12-month follow-up and assess its impact on the benefit in PD's motor symptoms. Since dDBS is more expensive and has an increased programming complexity, implying a more time-consuming follow-up than oDBS, this study also aims to evaluate if dDBS's use becomes redundant and does not justify the increased investment of human, time, and financial resources.

Materials and Methods

Study Design

This study is simultaneously descriptive and analytical since it aims to observe how many dDBS patients have directionality at the 12-month follow-up and answer the question "Is the mean benefit in UPDRS-III scores and Levodopa Equivalent Daily Dose (LEDD) results at the 12-month follow-up higher in the dDBS group *vs*. the oDBS group? And the DMD *vs*. the DNMD subgroups?". Thus, it is a comparative, non-interventional, observational, case-control, and retrospective study.

Ethical Considerations

The necessary documents were completed, including the *Departamento de Ensino, Formação e Investigação* (DEFI)'s form, the request for waiver of informed consent for the *Comissão de Ética para a Saúde da Unidade Local de Saúde de Santo António (ULSSA)*, the *Responsável pelo Acesso da Informação* (RAI), and the Data Protection Officer (DPO). All documents were approved [reference: 273-23 (234-DEFI/225-CE)], and patient data were used solely for statistical purposes and did not have a sensitive nature. No additional data was needed beyond those registered during the Neurology appointments, nor reuse/use of biological products or new diagnostic tests.

DBS Surgery

At ULSSA, PD patients are required to meet several criteria to be eligible for DBS: (a) motor symptoms no longer well managed with medication; (b) disease duration of 5 years or more to exclude atypical parkinsonian syndromes; (c) good preoperative levodopa response; (e) no significant cognitive or psychiatric disorders, like dementia, depression (especially if suicidal ideations are present), and/or psychosis; (f) no unstable severe comorbidities; (g) a normal or near-normal preoperative Magnetic Resonance Image (MRI); (h) understanding of the benefits and possible complications of the procedure, and (i) a solid support system, as DBS rquires cooperation and motivation from both patients and caregivers.[19,20]

At ULSSA, electrodes and neurostimulator implantations are done in one surgery under local anesthesia to allow for motor tests so that the placement of the electrodes has the most accuracy possible. Since December 2021, the Leksell Vantage® head frame has been used, replacing the Leksell G® frame. 3 trajectories (central, anterior, and lateral) are calculated, unless vascular conflict prohibits it, using a fusion between preoperative contrasted MRI and CT scans and an intraoperative 3-dimensional (3D) image obtained with the O-arm® system. Electrode placement is confirmed with microelectrode recording and macrostimulation testing up to 4.0 mA at 2 levels. If necessary, a new 3D image is obtained to confirm or correct the electrode's position. No electrodes have been implanted with adverse effects below 3.5 mA.

Follow-up

At ULSSA, every patient undergoes electrode revision 6-7 days after surgery and again after 3 months to assess side effects without the microlesion effect and medication influence. During these revisions, the pulse width and frequency remain the same (60 μs and 130 Hz, respectively).[21,22] Adjustments are made in amplitude values to test clinical improvements, particularly in rigidity and side effects. Directional stimulation is tested when side effects emerge with amplitudes currently used in chronic stimulation (2.5-3.5 mA), as it can avoid stimulating the structures responsible for them.

The follow-up method changes if patients exhibit axial symptoms like gait disturbances or dysarthrophonia, where the neurologist tests a lower frequency (80 Hz). If dysarthria or pyramidal symptoms occur, making efficient stimulation difficult, a lower pulse (30 μs) is tested to improve the therapeutic window.

Medication

In the weeks before surgery, antiparkinsonian medication with long half-lives or medication with potential mental side effects is removed. Only levodopa, due to its short half-life[23], is maintained until the night before surgery to induce a parkinsonian state for symptom testing during surgery. After surgery, levodopa is reintroduced, and the addition of more medication will depend on the patient's response to DBS and levodopa. Finding a balance between stimulation and medication is crucial to avoid motor or neuropsychiatric complications.

Levodopa Equivalent Daily Dose

LEDD is calculated by adding the levodopa equivalent doses of all antiparkinsonian drugs to determine the total daily dosage of levodopa patients receive.[24]

Motor Examination

Part III of the UPDRS was used to assess parkinsonism preoperatively (medication-OFF) and at the 12-month follow-up or 24-month follow-up in the DMD group if the 12-month follow-up scores had not been calculated (medication-OFF/stimulation-ON). Higher scores indicate worse motor symptoms.[5]

Patient Selection

The inclusion criteria were: (a) patients bilaterally implanted with Boston Scientific® or Medtronic Sensight® directional electrodes[18] in the STN for PD's treatment between 2018-2022; (b) patients bilaterally implanted with omnidirectional electrodes in the STN PD's treatment between 2009-2022 and (c) completion of a 12-month follow-up. The exclusion criterion was: the absence of UPDRS-III scores at the 12-month follow-up in the oDBS group.

2 groups were defined: patients submitted to oDBS (ND), and to dDBS (D) to compare both DBS types. The latter was further subdivided into 2 subgroups: patients who had at least one of the cerebral hemispheres with directional stimulation at the 12-month follow-up (DMD) and patients who had omnidirectional stimulation at the 12-month follow-up (DNMD). This division aimed to assess how many patients had directionality at the 12-month follow-up and to compare whether, even with omnidirectional stimulation, is superior to oDBS.

The following data were collected: sex; family history of PD; age at symptom onset; age at the date of surgery; UPDRS-III scores and LEDD results at the preoperative appointment, and the 12/24-month follow-up appointment. It was calculated the time between symptom onset and surgery (age at the date of surgery - age at symptom onset), the difference between postoperative and preoperative LEDD results, and the benefits in UPDRS-III scores and LEDD results ($\frac{preoperative\ score/result - postoperativescore/result}{preoperative\ score/result} \times 100$).

Data Analysis

Descriptive Statistics provided means and standard deviations. Non-parametric tests, including Mann-Whitney and Independent-Samples Kruskal-Wallis, compared continuous and categorical independent variables, due to the small sample size. ANOVA for repeated measures compared 2 related variables. A p-value<0,05 was deemed statistically significant. Statistical analysis was conducted using the IBM SPSS Statistics 29 program for iOS.

Results

75 patients were considered. 63 belonged to the ND group and 12 to the D group, which included 8 in the DNMD subgroup and 4 in the DMD subgroup.

At the 12-month follow-up, out of the 12 dDBS patients, 66.7% had omnidirectional stimulation and 33.3% had at least one cerebral hemisphere with directional stimulation. Moreover, out of the DMD group, 2 patients had bilateral directional stimulation (50.0%), and 2 had unilateral directional stimulation (50.0%).

In the ND group, 30.2% of patients were women (n=19) and 69.8% were men (n=44); the mean age at symptom onset was 46.6 $\pm$ 1.1 years; the mean age at the date of surgery was 58.6 $\pm$ 1.0 years and the mean time between symptom onset and the date of surgery was 12.2 $\pm$ 0.6 years. 78.3% of patients did not have a family history of PD (n=47) and 21.7% did (n=13). (Table I and Fig. 1)

In the D group, 25.0% of patients were women (n=3) and 75.0% were men (n=9); the mean age at symptom onset was 47.1 $\pm$ 2.5 years; the mean age at the date of surgery was 57.1 $\pm$ 2.4 years and the mean time between symptom onset and the date of surgery was 10.0 $\pm$ 0.6 years. Also, 63.6% of patients did not have a family history of PD (n=7) and 36.4% did (n=4). (Table I and Fig. 1)

In the DNMD group, 12.5% of patients were women (n=1) and 87.5% were men (n=7); the mean age at symptom onset was 47.6 $\pm$ 2.9 years; the mean age at the date of surgery was 58.1 $\pm$ 2.6 years and the mean time between symptom onset and the date of surgery was 10.5 $\pm$ 0.8 years. Furthermore, 57.1% of patients did not have a family history of PD (n=4) and 42.9% did (n=3). (Table II and Fig. 2)

In the DMD group, 50.0% of patients were women (n=2) and 50.0% were men (n=2); the mean age at symptom onset was 46.0 $\pm$ 5.6 years; the mean age at the date of surgery was 55.0 $\pm$ 5.7 years and the mean time between symptom onset and the date of surgery was 9.0 $\pm$ 0.4 years. Additionally, 75.0% of patients did not have a family history of PD (n=3) and 25.0% did (n=1). (Table II and Fig. 2)

Comparing the ND *vs.* D groups, higher mean preoperative UPDRS-III scores were observed in the ND group (40.5 ± 1.2 *vs.* 34.2 ± 1.7; p-value=0.018) and mean 12/24-month follow-up UPDRS-III score was also higher in the ND group (16.3 ± 0.8 *vs.* 12.5 ± 1.9; p-value=0.038). The mean benefit in UPDRS-III scores was lower in the ND group, but no statistically significant associations were found (59.1% ± 1.9% *vs.* 64.1% ± 4.5%; p-value=0.184). Mean preoperative LEDD was lower in the ND group (1584.1 mg ± 57.7 mg *vs.* 1684.6 mg ± 88.6 mg) and mean 12-month follow-up LEDD was higher in the ND group (521.1 mg ± 32.9 mg *vs.* 479.2 mg ± 68.7 mg), but no statistically significant associations were found (p-value=0.359 and p-value=0.756, respectively). The mean difference between 12-month follow-up LEDD results and preoperative LEDD results was lower in the ND group (-1062.9 ± 62.0 *vs.* -1205.4 ± 116.3) and the lowest mean benefit in LEDD results occurred in the ND group (65.1% ± 2.4% *vs.* 70.3% ± 5.1%), although no statistically significant associations were found (p-value=0.349 and p-value=0.553, respectively).

Comparing the ND *vs.* DNMD *vs.* DMD groups, the mean preoperative UPDRS-III score was higher in the ND group (40.5 ± 1.2), followed by DMD (36.8 ± 3.7) and DNMD (32.9 ± 1.2). A statistically significant association was found between the ND and DNMD groups (adjusted p-value=0.045). Regarding DMD's postoperative UPDRS-III scores, 1 of 4 patients had a 12-month follow-up score and the other 3 had a 24-month follow-up score. The mean 12/24-month follow-up UPDRS-III score was higher in the DMD group (18.3 ± 3.4), followed by ND (16.3 ± 0.8) and DNMD (9.6 ± 1.4). Statistically significant associations were found (p=0.004), namely between the DMD and DNMD groups (adjusted p-value=0.029) and the ND and DNMD groups (adjusted p-value=0.005). The highest mean benefit in UPDRS-III scores happened in the DNMD group (70.3% ± 4.9%), followed by ND (59.1% ± 1.9%) and DMD (51.7% ± 5.5%). Statistically significant associations were found (p=0.011), particularly between the DMD and DNMD groups (adjusted p-value=0.021) and the ND and DNMD groups (adjusted p-value=0.029). The mean preoperative LEDD was higher in the DNMD group (1716.9 mg ± 85.6 mg) followed by DMD (1620.0 mg ± 223.8 mg), and ND (1584.1 mg ± 57.7 mg) and the mean 12-month follow-up LEDD was higher in the DMD group (667.5 mg ± 51.2 mg), followed by ND (521.1 mg ± 32.9 mg) and DNMD (385.0 mg ± 82.3 mg). No statistically significant associations were found (p-value=0.584 and p-value=0.138). The highest mean benefit in LEDD results occurred in the DNMD group (77.5 % ± 5.0%), followed by ND (65.1 ± 2.4 %) and DMD (56.0 ± 8.1%), but no statistically significant association was found (p-value=0.130).

Discussion

In oDBS, the leads consist of an electrode with 4 cylindrical contacts[25] and a diameter of approximately 1.3mm[26] spaced vertically along its length.[25] Its therapeutic efficacy depends on applying the stimulation field to the dorsolateral portion of the STN or its immediate surroundings.[27] However, the STN is a bi-convex, not spherical, nucleus in the basal ganglia[25,26], meaning the stimulation is unlikely to cover the target tissue needed to maximize the effect adequately. Thus, greater amplitudes are necessary and side effects may appear, resulting in decreased efficacy.[25]

dDBS aims to solve these problems using electrodes designed for a more spatially refined and asymmetrical stimulation.[28,29] Unlike oDBS leads, which move stimulation primarily along the vertical axis (Z axis), dDBS leads grant further anatomical-clinical explorations in the horizontal plane (along the X and Y axes). [30] Hence, it becomes possible to precisely control the volume of tissue activated (VTA)[31] and direct the energy towards the target and away from structures responsible for side effects.[32] This increases the effective range of stimulation that brings therapeutic advantages without causing deleterious effects: the therapeutic window. It, also, offers more programming flexibility[9] enabling effective outcomes at lower current amplitudes or allowing higher amplitudes without provoking unintended consequences.[31] The electrodes still have 4 cylindrical contacts spaced vertically but the 2 center ones are split into 3 segments, spanning approximately 120º and can all be activated simultaneously (simulating a ring electrode, and originating a spherical VTA identical to the omnidirectional stimulation) or individually or paired (generating a conical stimulation)[25,33].

Intuitively this increased ability to provide accurate and personalized stimulation seems advantageous, but it is offset by dDBS' programming complexity since there are 16 electrodes (8 per hemisphere) and numerous pulse width (20–500 μs), frequency (2–240 Hz), and amplitude (0–12.75 mA) combinations.[16,29] Theoretically, over 25000 are possible if tested for every possible configuration of stimulation parameters in depth (each level) and for each segmented contact, becoming unmanageable in clinical practice. To help neurologists reduce programming time, practice guidelines and assisted programming using patient-specific imaging and electrophysiological data including local field potentials should be elaborated.

Additionally, dDBS' leads are more expensive than oDBS ones, limiting availability in many centers, or to a minor percentage of patients per center, often depending on hospital vendors' contracts.[17,22,31,34] In ULSSA, dDBS' electrodes cost 120% more than oDBS', costing the hospital around 3300€ *vs*. 1500€, respectively. Besides, dDBS requires more complex and time-consuming programming (at least twice), therefore it would be beneficial to identify the best-segmented level so dDBS can reach the efficiency of oDBS programming.[17,26] It remains unclear how often, when, and for what reasons dDBS is used in clinical practice. [28,29,32,35]

While interpreting this study's findings, these limitations should be considered: the smaller dDBS' sample size (n=12) *vs*. the oDBS' (n=63); the lack of some variables in some patients due to the study's retrospective character; the obtained data belonging exclusively to patients from one neurologist and one hospital in Portugal, and therefore they can have been influenced by factors related to the subjective character of the decisions, the institution, and/or the country, since there are no common worldwide programming guidelines for dDBS and different strategies and algorithms are used. Furthermore, considering the patients were selected between 2009 and 2022, encompassing 14 years, the evolution of the surgical team's and the neurologist's experience, the protocols, and the technology used could have interfered with the clinical outcomes. The same logic can be applied to the change in the stereotactic head frame from the Leksell G® to the Leksell Vantage® since December 2021. Despite its limitations, this study provides important insights and serves as a valuable base for future studies.

Compared to the D group, the ND group had lower mean preoperative LEDD (1584.1 mg ± 57.7 mg *vs*. 1684.6 mg ± 88.6 mg) and higher mean 12-month follow-up LEDD (521.1 mg ± 32.9 mg *vs*. 479.2 mg ± 68.7 mg), resulting in a smaller difference between these 2 variables (-1062.9 mg ± 62.0 mg *vs*. -1205.4 mg ± 116.3 mg) and a lower mean benefit in LEDD results (65.1% ± 2.4% *vs*. 70.3% ± 5.1%). No statistically significant associations were found, suggesting directionality does not directly affect LEDD results. However, Pintér D. *et al*. found statistically significant differences that were lower in the omnidirectional stimulation group (−519.9 mg ± 376.9 mg *vs*. −742.6 mg ± 550.7 mg; p-value=0.015).[9] Koivu M. *et al*. obtained statistically significant benefits in LEDD results of 42.7% and 35.4% at 6 and 18 months, respectively, compared to baseline results in dDBS patients, which were lower than this study's results (70.3% ± 5.1%).[11] Karl J. A. *et al*. studied LEDD reductions in dDBS patients at 3, 12, 24, and 36 months and obtained a lower reduction than this study (-580 mg ± 575 mg; -620 mg ± 607; -556 mg ± 647 mg; -528 mg ± 488 mg *vs*. -1205.4 mg ± 116.3 mg).[32]

Regarding UPDRS-III scores, patients submitted to oDBS had, priorly, worse motor symptoms than the ones submitted to dDBS, since its mean preoperative UPDRS-III scores were higher (40.5 ± 1.2 *vs*. 34.2 ± 1.7). The mean 12/24-month follow-up UPDRS-III score was also higher in the ND group (16.3 ± 0.8 *vs*. 12.5 ± 1.9), meaning the mean benefit in UPDRS-III scores was lower in the ND group (59.1% ± 1.9% *vs*. 64.1% ± 4.5%). However, no statistically significant association between both groups was found, challenging the attribution of this difference to directionality.

Other studies, also, support the benefit of UPDRS-III scores in dDBS patients. Eleopra E. *et al*. found a mean benefit in UPDRS-III scores of 37.5% in 11 dDBS patients at a 12-month follow-up (medication OFF/stimulation ON) which is lower than this study's (64.1% ± 4.5%).[36] However, Koivu M. *et al*.'s mean benefit in UPDRS-III scores of dDBS patients at an 6-month follow-up is lower than this study's at the 12-month follow-up (44.0% *vs*. 64.1% ± 4.5%).[11] Pintér D. *et al*., Schnitzler A. *et al*., and Dembek T.A. *et al*. also evaluated the preoperative and postoperative UPDRS-III scores in a medication off-state and found no statistically significant differences.[9,26,27]

Despite these studies' findings, it is crucial to understand that not all dDBS patients have directional stimulation during follow-up. Only comparing the subgroups DMD and DNMD would provide clarity on whether directionality positively influences the patients' clinical outcomes.

In this study, out of the 12 dDBS patients, 2 (16.7%) had bilateral directional stimulation, 2 (16.7%) had unilateral directional stimulation, and 8 (66.7%) had bilateral omnidirectional stimulation at the 12-month follow-up. Therefore, the percentage of dDBS patients with bilateral omnidirectional stimulation at the 12-month follow-up was already higher than the percentage that Koivu M. *et al.* had at a 6 or 18-month follow-up (66.7% *vs.* 24.8% *vs.* 29.5%, respectively).[11] Similarly, Dembek T.A. *et al.* had a lower percentage of bilateral omnidirectional stimulation at the 3 or 6-month follow-up than this study (20.0% *vs.* 66.7%) and a higher percentage of bilateral or unilateral directional stimulation (80.0% vs. 33.3%). [27]

By comparing ND *vs.* DNMD *vs.* DMD, the mean preoperative LEDD was higher in the DNMD group (1716.9 mg $\pm$ 85.6 mg) followed by DMD (1620.0 mg $\pm$ 223.8 mg), and ND (1584.1 mg $\pm$ 57.7 mg). The mean 12-month follow-up LEDD was higher in the DMD group (667.5 mg $\pm$ 51.2 mg), followed by ND (521.1 mg $\pm$ 32.9 mg) and DNMD (385.0 mg $\pm$ 82.3 mg). This means that the highest mean benefit in LEDD results occurred in the DNMD group (77.5 % $\pm$ 5.0%), followed by ND (65.1 $\pm$ 2.4 %) and DMD (56.0 $\pm$ 8.1%). However, no statistically significant associations were found.

Regarding the mean 12/24-month follow-up UPDRS-III score, a statistically significant association was found between directionality and higher scores. Contrary to this study, Koivu M. *et al.*, observed that patients' UPDRS-III scores were lower with directional stimulation than with omnipolar stimulation ($p = 0.012$). The highest mean benefit in UPDRS-III scores occurred in the DNMD group (70.3% $\pm$ 4.9%), followed by ND (59.1% $\pm$ 1.9%) and DMD (51.7% $\pm$ 5.5%). Statistically significant associations were found between the DMD and DNMD groups and the ND and DNMD groups. Thus, ULSSA's perspective suggests directional stimulation does not guarantee the best UPDRS-III outcomes, raising some questions: "Is awake surgery methodology enough to have higher benefits in UPDRS-III scores? Would it be different if the patient had global anesthesia and was asleep?"; "Should all centers invest in dDBS since it requires an increased investment of human, time, and financial resources, not only for the patient but also for the center itself?" and "Since the sample size was small, were these lower or similar benefits caused by external factors?". This study did not analyze electrode deviations, therefore "Did DMD patients have worse-positioned electrodes, to begin with, and directionality came as a solution to avoid side effects? Did it optimize the benefit in UPDRS-III scores, but without an ideal result being achieved?". Another question is "Since the mean benefit in UPDRS-III scores in patients with omnidirectional stimulation is already high (59.1 $\pm$ 1.9% in ND and 70.3% $\pm$ 4.9% in DNMD), does it become more difficult to obtain a superior benefit with directional electrodes?".

To address these questions, a new study should be conducted, either with future data from this hospital or from multiple hospitals with similar surgical and follow-up methodologies as ULSSA's. This would increase the dDBS patient pool, reducing sample size limitations. Also, electrode deviations should be analyzed to eliminate possible confounding factors.

Conclusion

Most dDBS patients had omnidirectional stimulation at the 12-month follow-up and ULSSA's experience suggests similar benefits between the ND and D groups, meaning that dDBS does not outperform oDBS. Additionally, of dDBS patients, the ones that had at least one cerebral hemisphere with directional stimulation at the 12-month follow-up (DMD) had worse outcomes. Regarding LEDD results, no association between directionality and its benefit was found.

These findings enhance the importance of standardizing the dDBS surgery protocols and creating programming and follow-up guidelines to reduce its subjectivity and allow a more accurate comparison between patients' benefits.

Appendix

Table I – Means of the continuous variables that describe the disease-specific, and medication-specific data of the study population when considering 2 groups.

ND – non-directional, meaning patients submitted to oDBS; D – directional, meaning patients submitted to dBDS; UPDRS-III – part III of the Unified Parkinson's Disease Rating Scale; LEDD – levodopa equivalent daily dose.

ND has n=63 (except on variables age at the date of surgery and time between symptom onset and surgery, where n=62), D has n=12 (note that 9 patients had a 12-month follow-up UPDRS-III score and 3 a 24-month follow-up score).

A p-value < 0.05 was considered as statistically significant.

Variables	Mean ± SD		p-value
	ND (n=63)	D (n=12)	
Age at symptom onset (years)	46.6 ± 1.1	47.1 ± 2.5	0.965
Age at the date of surgery (years)	58.6 ± 1.0	57.1 ± 2.4	0.537
Time between symptom onset and surgery (years)	12.2 ± 0,6	10.0 ± 0.6	0.140
Preoperative UPDRS-III scores	40.5 ± 1.2	34.2 ± 1.7	**0.018**
12/24-month follow-up UPDRS-III scores	16.3 ± 0.8	12.5 ± 1.9	**0.038**
Benefit in UPDRS-III scores (percentage)	59.1 ± 1.9	64.1 ± 4.5	0.184
Preoperative LEDD results (mg)	1584.1 ± 57.7	1684.6 ± 88.6	0.359
12-month follow-up LEDD results (mg)	521.1 ± 32.9	479.2 ± 68.7	0.756
Benefit in LEDD results (percentage)	65.1 ± 2.4	70.3 ± 5.1	0.553
Difference between 12-month follow-up LEDD results and preoperative LEDD results (mg)	-1062.9 ± 62.0	-1205.4 ± 116.3	0.349

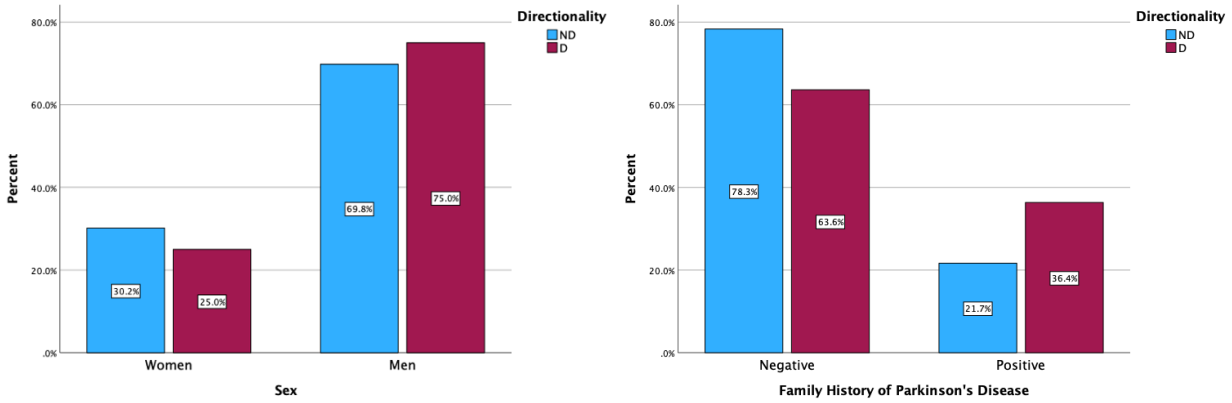


Figure 1 – Categorical variables that describe the sociodemographic and disease-specific data of the study population when 2 groups are considered.

ND – non-directional, meaning patients submitted to oDBS; D – directional, meaning patients submitted to dBDS.

ND has n=63 (except on variable family history of PD, where n=60); D has n=12 (except on variables family history of PD).

Table II – Means of the continuous variables that describe the sociodemographic, disease-specific, and medication-specific data of the study population when considering 3 groups.

ND – non-directional, meaning patients submitted to oDBS; DNMD – patients submitted to dBDS who did not have directional stimulation at the 12-month follow-up; DMD - patients submitted to dBDS who had at least one of the cerebral hemispheres with directional stimulation at the 12-month follow-up; UPDRS-III – part III of the Unified Parkinson's Disease Rating Scale; LEDD – levodopa equivalent daily dose.

ND has n=63 (except on variables age at the date of surgery and time between symptom onset and surgery, where n=62), DNMD has n=8 and DMD has n=4 (note that 1 patient had a 12-month follow-up UPDRS-III score and 3 a 24-month follow-up score).

A p-value < 0.05 was considered as statistically significant.

Variables	Mean ± SD			
	ND (n=63)	**DNMD (n=8)**	**DMD (n=4)**	**p-value**
Age at symptom onset (years)	46.6 ± 1.1	47.6 ± 2.9	46.0 ± 5.6	0.974
adjusted p-value	ND *vs.* DNMD = 1.000; ND *vs.* DMD = 1.000; DNMD *vs.* DMD = 1.000			
Age at the date of surgery (years)	58.6 ± 1.0	58.1 ± 2.6	55.0 ± 5.7	0.759
adjusted p-value	ND *vs.* DNMD = 1.000; ND *vs.* DMD = 1.000; DNMD *vs.* DMD = 1.000			
Time between symptom onset and surgery (years)	12.2 ± 0,6	10.5 ± 0,8	9.0 ± 0.4	0.197
adjusted p-value	ND *vs.* DNMD = 1.000; ND *vs.* DMD = 0.256; DNMD *vs.* DMD = 0.902			
Preoperative UPDRS-III scores	40.5 ± 1.2	32.9 ± 1.7	36.8 ± 3.7	**0.044**
adjusted p-value	ND *vs.* DNMD = 0.045; ND *vs.* DMD = 1.000; DNMD *vs.* DMD = 1.000			
12/24-month follow-up UPDRS-III scores	16.3 ± 0.8	9.6 ± 1.4	18.3 ± 3.4	**0.004**
adjusted p-value	ND *vs.* DNMD = 0.005; ND *vs.* DMD = 1.000; DNMD *vs.* DMD = 0.029			
Benefit in UPDRS-III scores (percentage)	59.1 ± 1.9	70.3 ± 4.9	51.7 ± 5.5	**0.011**
adjusted p-value	ND *vs.* DNMD = 0.045; ND *vs.* DMD = 1.000; DNMD *vs.* DMD = 1.000			
Preoperative LEDD results (mg)	1584.1 ± 57.7	1716.9 ± 85.6	1620.0 ± 223.8	0.584
adjusted p-value	ND *vs.* DNMD = 0.905; ND *vs.* DMD = 1.000; DNMD *vs.* DMD = 1.000			
12-month follow-up LEDD results (mg)	521.1 ± 32.9	385.0 ± 82.3	667.5 ± 51.2	0.138
adjusted p-value	ND *vs.* DNMD = 1.000; ND *vs.* DMD = 0.243; DNMD *vs.* DMD = 0.148			
Benefit in LEDD results (percentage)	65.1 ± 2.4	77.5 ± 5.0	56.0 ± 8.1	0.130
adjusted p-value	ND *vs.* DNMD = 0.366; ND *vs.* DMD = 0.731; DNMD *vs.* DMD = 0.161			

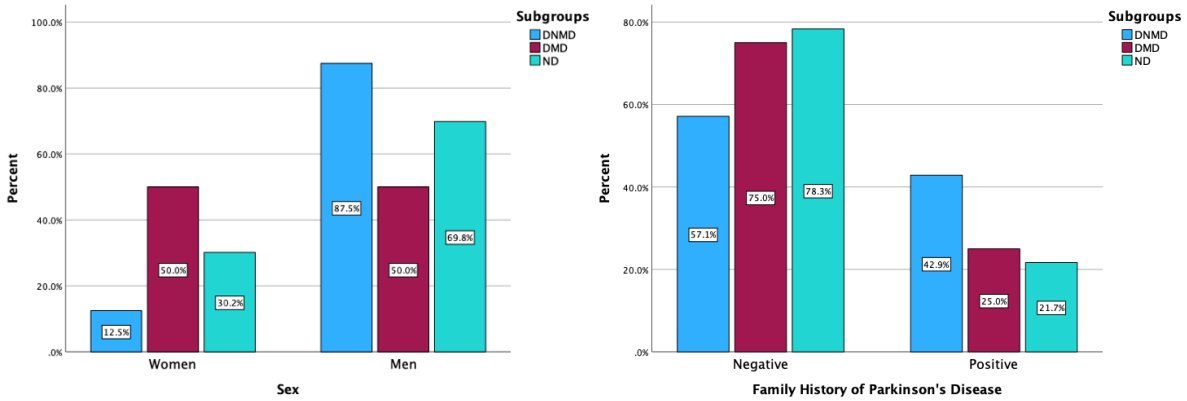


Figure 2 – Categorical variables that describe the sociodemographic and disease-specific data of the study population.

ND – non-directional, meaning patients submitted to oDBS; DNMD – patients submitted to dBDS who did not have directional stimulation at the 12-month follow-up (DNMD); DMD - patients submitted to dBDS who had at least one of the cerebral hemispheres with directional stimulation at the 12-month follow-up.

ND has n=63 (except on variable family history of PD, where n=60); DNMD has n=8 (except on variables family history of PD) and DMD has n=4.

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Data Availability

No additional data is available.

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**