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Prevalence of Depressive, Apathetic and Anxiety Symptoms in Long-Term Parkinson's Disease Patients After Deep Brain Stimulation: a Telephonic Cross-Sectional Study

Henrique Pereira Carneiro

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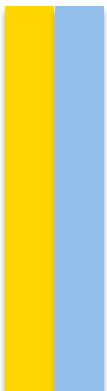

Prevalence of depressive, apathetic and anxiety symptoms in long-term Parkinson's disease patients after deep brain stimulation: a telephonic cross-sectional study

Artigo Original

Dissertação de candidatura ao grau de Mestre em Medicina submetido ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto. Junho 2026

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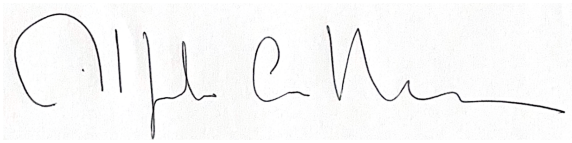

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RESUMO

Introdução/Objetivos: A Doença de Parkinson (DP) é uma doença neurodegenerativa que se pode manifestar clinicamente com sintomas não motores, entre os quais sintomas neuropsiquiátricos (nomeadamente depressão, ansiedade e apatia) que contribuem significativamente para a diminuição da qualidade de vida. Apesar da Estimulação Cerebral Profunda (ECP) configurar uma terapêutica eficaz para as complicações motoras da DP, o seu papel na evolução destes sintomas permanece pouco claro. Este estudo teve como objetivo estabelecer a prevalência de sintomas depressivos, ansiosos e apáticos em doentes com DP submetidos a ECP, bem como identificar possíveis associações clínicas, cirúrgicas e de enquadramento temporal da doença.

Metodologia: Estudo observacional, transversal e unicêntrico. Procedeu-se à realização de entrevistas telefónicas e recolha retrospetiva de dados clínicos. Após uma amostra inicial de 119 doentes, foram incluídos 54 participantes com diagnóstico de DP e submetidos a STN-DBS. A avaliação neuropsiquiátrica foi efetuada através da aplicação do Beck Depression Inventory-II (BDI-II), da Starkstein's Apathy Scale (SAS) e da Hospital Anxiety and Depression Scale – Anxiety Subscale (HADS-A). Foram realizadas análises univariadas e regressão logística multivariável para identificação de fatores associados.

Resultados: Na população em estudo, observou-se uma prevalência de 46.3% de sintomas depressivos moderados a graves, 27.8% de sintomas ansiosos moderados a graves e 66.7% de apatia clinicamente significativa. Em análise multivariada, os sintomas depressivos associaram-se de forma significativa a uma idade mais avançada na inclusão (OR ajustado de 1.164, IC de 95% 1.022–1.326, p = 0.022), a uma melhoria funcional mais modesta a longo prazo (OR ajustado de 0.023, IC de 95% 0.001-0.931, p = 0.046) e à presença de sintomas ansiosos (OR ajustado de 76.222, IC de 95% 5.694-1020.340, p = 0.001). Por sua vez, os sintomas ansiosos apresentaram uma associação com a presença concomitante de sintomas depressivos (OR ajustado de 46.753, IC de 95% 3.668–595.994, p = 0.003). Não foram identificadas associações significativas entre apatia e as variáveis clínicas e cirúrgicas estudadas.

Conclusões: Os resultados obtidos sugerem que os sintomas neuropsiquiátricos são altamente prevalentes em doentes com DP após longos períodos de seguimento pós-DBS. Estudos prospetivos multicêntricos são necessários para clarificar os determinantes destes sintomas e o impacto da estimulação cerebral profunda a longo prazo.

Palavras-Chave: Doença de Parkinson, Estimulação Cerebral Profunda, Depressão, Apatia, Ansiedade

ABSTRACT

Introduction/Objectives: Parkinson's disease (PD) is a neurodegenerative disease that may manifest clinically with non-motor symptoms, among which neuropsychiatric symptoms (namely depression, anxiety and apathy) contribute significantly to a reduction in quality of life. Although Deep Brain Stimulation (DBS) constitutes an effective therapy for the motor complications of PD, its role in the evolution of these symptoms remains unclear. This study aimed to establish the prevalence of depressive, anxiety and apathy symptoms in PD patients submitted to DBS, as well as to identify possible clinical, surgical and disease-related temporal associations.

Methods: This was a single-center, cross-sectional observational study. Telephonic interviews were carried out and retrospective clinical data were collected. From an initial sample of 119 patients, 54 participants with a diagnosis of PD who had undergone STN-DBS were included. Neuropsychiatric assessment was performed through the administration of the Beck Depression Inventory-II (BDI-II), the Starkstein's Apathy Scale (SAS) and the Hospital Anxiety and Depression Scale – Anxiety Subscale (HADS-A). Univariate analyses and multivariable logistic regression were performed to identify associated factors.

Results: In the study population, the prevalence of moderate-to-severe depressive symptoms was 46.3%, moderate-to-severe anxiety symptoms 27.8%, and clinically significant apathy 66.7%. In multivariable analysis, depressive symptoms were significantly associated with older age at study inclusion (adjusted OR 1.164, 95% CI 1.022–1.326, p = 0.022), less favorable long-term functional improvement (adjusted OR 0.023, 95% CI 0.001–0.931, p = 0.046), and the presence of anxiety symptoms (adjusted OR 76.222, 95% CI 5.694–1020.340, p = 0.001). Anxiety symptoms were independently associated with the concomitant presence of depressive symptoms (adjusted OR 46.753, 95% CI 3.668–595.994, p = 0.003). No significant associations were identified between apathy and the studied clinical and surgical variables.

Conclusions: The results obtained suggest that neuropsychiatric symptoms are highly prevalent in PD patients after long periods of post-DBS follow-up. Multicenter prospective studies are required to clarify the determinants of these symptoms and the long-term impact of DBS.

Key-Words: Parkinson's disease, Deep Brain Stimulation, Depression, Apathy, Anxiety

ABBREVIATION LIST

AS - Apathy Scale
BDI-II - Beck Depression Inventory II
DBS - Deep Brain Stimulation
GPi - Globus Pallidus Internus
HADS-A - Hospital Anxiety and Depression Scale – Anxiety Subscale
IQR - Interquartile Range
LBs - Lewy Bodies
LEDD - Levodopa Equivalent Daily Dose
LFU - Last Follow-Up
MDS - Movement Disorder Society
MER - Microelectrode Recording
PD - Parkinson's Disease
SAS - Starkstein's Apathy Scale
SNpc - Substantia Nigra pars compacta
SPSS - Statistical Package for the Social Sciences
STN - Subthalamic Nucleus
STN-DBS - Subthalamic Nucleus Deep Brain Stimulation
ULSSA - Unidade Local de Saúde de Santo António
UPDRS - Unified Parkinson's Disease Rating Scale
UPDRS-I - Unified Parkinson's Disease Rating Scale – Part I (Non-Motor Experiences of Daily Living)
UPDRS-II - Unified Parkinson's Disease Rating Scale – Part II (Motor Experiences of Daily Living)
UPDRS-III - Unified Parkinson's Disease Rating Scale – Part III (Motor Examination)
UPDRS-IV - Unified Parkinson's Disease Rating Scale – Part IV (Motor Complications)

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative movement disorder, described for the first time more than 200 years ago. It is the second most common neurodegenerative disease in the world, with the fastest growing prevalence.[1, 2]

Most cases occur sporadically (idiopathic PD), with macroscopic evidence of loss of the darkly pigmented area in the pars compacta neurons of the substantia nigra (SNpc) and in the locus coeruleus. This leads to a lack of dopaminergic input to the striatum with interrupted transmission to the thalamus and motor cortex, explaining the motor symptoms. There is also widespread cell loss in several other subcortical nuclei and multiple non-dopaminergic neurotransmitter systems, which is thought to account for some of the non-motor symptoms of PD. Microscopically, the pathological hallmark of PD is the Lewy bodies (LBs), protein aggregates within neuronal cell bodies which are immunoreactive for the protein α-synuclein.[3, 4]

PD is clinically characterized by parkinsonism, a motor syndrome including bradykinesia (a paucity and slowness of movement), rest tremor, muscular rigidity, shuffling gait and flexed posture. These manifestations can be accompanied by a variety of non-motor symptoms, including autonomic sensory, sleep, cognitive and psychiatric disturbances.[3]

The different available interventions aim to maintain motor function and avoid complications. Levodopa is the most effective symptomatic treatment however, with time, many patients develop motor complications such as fluctuations in motor response and involuntary movements known as dyskinesias.[5, 6]

Over the past decades, there has been a development in the surgical treatment of PD, more specifically the Deep Brain Stimulation (DBS), used for the first time in 1987 by Benabid and, later, in 1997 to replace thalamotomy in treating the characteristic tremor of PD.[6]

The DBS consists of the stereotactic implantation of stimulating electrodes into deep structures, such as the thalamus (nucleus ventrointermedius), globus pallidus (GPi) and subthalamic nucleus (STN) for chronic electrical stimulation. The STN has been the most extensively explored surgical target for DBS in the treatment of PD and is the most used. The current literature indicates there's no significant difference between cognitive, mood and behaviour aspects between STN-DBS and GPi-DBS. The mechanism of action of DBS remains controversial and is likely multifactorial.[7, 8]

Patients considered candidates for STN-DBS are those who meet diagnostic criteria for PD, are younger than 75 years and present with significant disability due to the diseases' motor complications. They should have had symptoms for more than 5 years, show a good response to medical treatment with levodopa and not exhibit significant cognitive impairment or severe uncontrolled psychiatric disorders. Few studies have reported a follow-up greater than five years

on PD patients treated with DBS. After a very long follow-up, more than 20 years post DBS, different ethical questions might emerge.[9, 10]

Neuropsychiatric symptoms are highly prevalent in PD and can represent some of the most debilitating aspects of the condition, leading to a decline in quality of life, a worse functional status and, therefore, an increased risk of death. At onset, depression and anxiety are the most frequent neuropsychiatric symptoms, however these symptoms can occur in any stage, appearing mostly in off periods.[11]

Studies show that apathy is particularly frequent, however it has been much less studied than other neuropsychiatric presentations. [15] Many of its characteristics remain poorly understood, most notably whether it constitutes a distinct clinical syndrome or a subcomponent of depression in PD. Recent studies have demonstrated that apathy and depression are separable entities; therefore, this distinction is assumed throughout the remainder of this work.[12]

No single mechanism has been identified to fully explain the relationship between these symptoms and PD. However, several overlapping mechanisms have been implicated in their pathophysiology. Among these are PD–associated dementia, as well as certain somatic therapies.[13]

An important concern about DBS is how it affects cognitive performance. Indeed, exclusion criteria include dementia or significant dysexecutive syndrome and depression or anxiety. In a clinical setting, cognitive impairment, depression and similar disorders are considered relative neurobehavioral contraindications to DBS, therefore, it is crucial to investigate these domains. Considering that DBS is a long-term stimulation therapy, it is important to understand what occurs in this setting as some effects might emerge over time.[10]

Early in the history of the method, reports of mental side effects were published, initially with reports of transient confusion and hallucinations. Further reports with disturbing side effects accumulated over time. While cognitive sequelae were studied in numerous papers but are generally conceived to have little impact on the quality of life, the field of psychiatric effects was more hesitantly explored. Hypomania is common following DBS in PD, as it may appear early postoperatively and lead to falsely positive improvements on mood and quality-of-life scales due to stimulation of the limbic system. While it typically subsides after a few weeks, longer-term neuropsychiatric effects such as depression and apathy may emerge and persist for years, significantly impacting patients and their families.[10, 14]

The Movement Disorder Society commissioned a task force to assess the different rating scales used in PD neuropsychiatric symptoms assessment and make clinical recommendations regarding their use. Relatively to depression, the Beck's Depression Inventory (BDI) is the most widely used and validated instrument in this population, whereas fewer data are available for the

remaining scales. Regarding apathy symptoms, Starkstein's Apathy Scale (AS) was identified as the only recommended scale. Many scales for anxiety assessment exist, but, according to the MDS, none of the reviewed can be recommended for use in PD populations since basic information on clinimetric properties is missing. Between them, the anxiety subscale of "The Hospital Anxiety and Depression Scale" (HADS) was evaluated independently and its internal consistency and reliability in PD patients was considered satisfactory.[15-17]

Given the relevance and impact of these symptoms, this study aimed to investigate the prevalence of depressive, apathy and anxiety symptoms in long-term PD patients that underwent DBS in a single center.

METHODS

This is a single-center, observational study with a cross-sectional telephonic assessment and retrospective clinical data collection. The study was conducted at the Department of Neurosurgery of Unidade Local de Saúde de Santo António, Porto, Portugal. The study protocol was submitted for approval to the Departamento de Ensino, Formação e Investigação (DEFI), the Responsável pelo Acesso à Informação (RAI) and the Ethics Committee of ULSSA/ICBAS. Following review, the study was approved under the reference "2026.097(076-CAC-079-CE)".

Every participant provided informed consent for the treatment of PD, for participation and for the use of their data for research purposes. Participants were informed of the study's objectives and confidentiality and anonymity were ensured throughout data collection, processing and analysis.

The study was conducted between September 2025 and June 2026 and each telephonic interview lasted approximately 10-20 minutes. Initial screening included 119 PD patients who had undergone DBS at Unidade Local de Saúde de Santo António. The inclusion criteria were as follows: (1) clinical diagnosis of PD; and (2) previous DBS surgery performed at Unidade Local de Saúde de Santo António before March 2024; Exclusion criteria were as follows: (1) refusal to provide informed consent; (2) failure to complete the interview due to severe speech impairment; (3) failure to be contacted after five telephone call attempts performed on different days and at different times; and (4) death before study inclusion.

The telephonic interview consisted, firstly, of obtaining informed consent, followed by the administration of three different questionnaires - Beck Depression Inventory II (BDI-II), Starkstein's Apathy Scale (SAS) and Hospital Anxiety and Depression Scale - Anxiety Subscale (HADS-A). The interviewer was blinded to the patients' DBS outcomes and clinical evolution. The scales were chosen based on Movement Disorder Society (MDS) recommendations on depression, anxiety and apathy symptoms assessment in the context of PD.[15]

The BDI-II was originally designed as a self-report questionnaire, but it has also been validated as an telephonic interview-administered rating scale. It consists of 21 items, each scored from 0 to 3. According to the literature, a score of 0–13 indicates 'minimal' depressive symptoms, 14–19 'mild' symptoms, 20–28 'moderate' symptoms and 29–63 'severe' symptoms of depression. For the purpose of statistical analysis, the results were dichotomized into two groups: 'minimal-to-mild' symptoms (BDI-II <20) and 'moderate-to-severe' depressive symptoms (BDI-II ≥20), as performed previously in the literature. The Portuguese version of this scale was utilized by Campos et al.[18-20]

The HADS-A consists of 7 statements, scored on a four-point scale from 0 to 3. The recommended HADS-A cutoff is a score of 8, with 8-10 being considered 'mild', 11-14 is 'moderate' and 15-21 consists of 'severe' anxiety. The results of the application of this scale were then divided into two groups: 'normal-to-mild' symptoms (HADS-A <11) and 'moderate-to-severe' anxiety symptoms (HADS-A ≥11), as previously performed in the literature. The Portuguese version of this scale was utilized by Pereira et al in 2008, and the scale has been validated for telephonic use. [21-23]

Starkstein's Apathy Scale (SAS) consists of 14 items phrased as questions, each scored from 0 to 3. A total score equal or greater than 15 is considered clinically relevant for the diagnosis of apathy. For the purpose of statistical analysis, the results were dichotomized into two groups according to the absence or presence of clinically relevant apathy symptoms: SAS <15 and SAS ≥15, as previously performed in the literature. The Portuguese version of this scale was utilized by Guimarães et al. [24, 25]

After completion of the interviews, data collected from the telephone assessments and retrospective clinical data were entered into a data base built with Microsoft Excel. An inferential statistical analysis was performed with the software "Statistical Package for the Social Sciences" (SPSS) version 28.0, IBM. The threshold for statistical significance was set at $p<0.05$. The statistical tests used, together with the corresponding variables analysed, are presented in Table VI.

RESULTS

A total of 119 patients submitted to DBS for PD were initially identified. Of these, 33 were deceased at the time of inclusion and 13 could not be reached after five telephone attempts on different days and at different times. After successful contact, 12 presented with severe speech impairment that precluded a reliable interview and 7 refused participation. In summary, 54 patients completed the telephone interview and were included in the analysis, as is shown in Figure 1.

Retrospective patients' characteristics are summarized in Table I. The cohort was predominantly male, with 32 men (59.3%). Comorbidities are presented in Table I. A family history of PD was reported in 17 patients (31.5%), while 3 patients (5.5%) had a family history of essential tremor. The median age at symptom onset was 45 (IQR 11) and the median age at diagnosis was 46 years (IQR 13). At clinical onset, symptoms were right-sided in 27 patients (51.9%) and left-sided in 25 patients (48.1%). Motor fluctuations developed at a median age of 50 years (IQR 13), while dyskinesia occurred at a median age of 53.5 years (IQR 13). Median age at surgery was 56 years (IQR 12), corresponding to a median time from symptom onset of 11 years (IQR 5). At study inclusion, median age was 66 years (IQR 11), with a median time from symptom onset of 20 years (IQR 7) and a median time from surgery of 9 years (IQR 8). The median preoperative UPDRS-I, UPDRS-II, UPDRS-III, and UPDRS-IV scores were 1 (IQR 1), 20 (IQR 7), 38 (IQR 11), and 9 (IQR 3), respectively. The median preoperative levodopa equivalent daily dose (LEDD) was 1572 mg (IQR 610). Median last follow-up (LFU) was 6 years postoperatively (IQR 7).

All patients underwent bilateral STN-DBS and the median number of MER trajectories was 6 (IQR 2). No intraoperative complications were reported but postoperative complications occurred in 3 patients (5.6%), including one infection, one lead mispositioning associated with poor clinical outcome and one lead migration. All 3 cases required surgical reintervention. Directional leads were implanted in 16 patients (29.6%) and 11 (68.8%) of these were receiving bilateral ring mode stimulation at LFU. The surgical characteristics are summarized in Table II.

Longitudinal clinical outcomes after STN-DBS are presented in Table III. The assessment of non-motor experiences of daily living, with the UPDRS-I, remained stable after follow-up with a preoperative median score of 1 (IQR 1) and a median score of 1 (IQR 3) at LFU. Functional impairment, assessed by UPDRS-II, improved from a preoperative median of 20 (IQR 7) to 6 (IQR 5) at 1 year postoperatively and a median of 10.5 (IQR 6) at LFU, corresponding to a median reduction of 50% (IQR 36). Motor symptoms, assessed by UPDRS-III, decreased from a preoperative median score of 38 (IQR 11) to 12 (IQR 9) at 1 year and remained lower than baseline at the LFU, with a median score of 14 (IQR 9), corresponding to a median reduction of 58.5% (IQR 25). Motor complications assessed by UPDRS-IV decreased substantially after surgery from a preoperative

median score of 9 (IQR 3) to 1 (IQR 2) at 1 year and 1 (IQR 2) at LFU, corresponding to a median reduction of 85.7% (IQR 28). LEDD was substantially reduced after surgery from a preoperative median of 1572 mg (IQR 610) to 480 mg (IQR 300) at 1 year and 610 mg (IQR 360) at LFU, corresponding to a median reduction of 61.3% (IQR 28.9).

The results of the telephonic interview are presented in Table IV, together with data from the retrospective analysis regarding the proportion of patients receiving antidepressant and anxiolytic medication at LFU. As described, in our study population, 37 patients (68.5%) were receiving antidepressant treatment at LFU, while 33 patients (61.1%) were receiving anxiolytic medication. The distribution of BDI-II, HADS-A and SAS scores according to postoperative follow-up duration is presented in Table V.

Considering depression symptoms as assessed by the BDI-II, 15 patients (27.8%) scored within the minimal symptoms range, while 14 (25.9%) had mild, 14 (25.9%) moderate and 11 (20.4%) severe depressive symptoms. As described, patients were divided into two groups according to the results. Patients with moderate-to-severe depressive symptoms were older at inclusion [68 (IQR 6) vs 63 (IQR 12) years; p<0.001] and had higher preoperative total UPDRS-III scores [40 (IQR 11) vs 33 (IQR 10); p=0.027], as shown in Table VII. No other clinical or surgical variables differed significantly between groups. Patients with minimal-to-mild depressive symptoms had greater percentage reductions in total UPDRS-I [50% (IQR 100) vs 0.0% (IQR 83.3); p=0.039] and UPDRS-II [55% (IQR 12) vs 38.1% (IQR 28.4); p=0.026] from preoperative assessment to LFU. Furthermore, patients with moderate-to-severe depressive symptoms were significantly more likely to present concomitant moderate-to-severe anxiety symptoms (HADS-A ≥11) at LFU (56% vs 3.4%; p<0.001), as described in Table VIII. Moreover, no significant association was observed between a documented preoperative diagnosis of depressive syndrome and the presence of moderate-to-severe depressive symptoms (BDI-II ≥20; p = 0.632), moderate-to-severe anxiety symptoms (HADS-A ≥11; p = 0.711), or clinically relevant apathy (SAS ≥15; p = 0.934) at the time of study inclusion. No significant differences were observed between groups regarding antidepressant use (72% vs 65.5%; p=0.609) or anxiolytic use at LFU (64% vs 58.6%; p=0.686).

A multivariable logistic regression analysis was performed including the variables that were significant, as exposed in Table IX. In the baseline model, age at inclusion remained independently associated with moderate-to-severe depressive symptoms (adjusted OR 1.099, 95% CI 1.009–1.196, p = 0.031), whereas the association with preoperative UPDRS-III score lost significance (adjusted OR 1.039, 95% CI 0.967-1.116, p = 0.293). In the model that incorporated both baseline and evolution variables, age at inclusion (adjusted OR 1.164, 95% CI 1.022–1.326, p = 0.022) and percentage variation in UPDRS-II score (adjusted OR 0.023, 95% CI 0.001–0.931, p = 0.046)

remained independently associated with moderate-to-severe depressive symptoms, whereas the association with percentage variation in UPDRS-I score lost significance (OR 1.160, 95% CI 0.583-2.306, p=0.672). When anxiety symptoms were included in the model, HADS-A ≥11 emerged as an independent association of moderate-to-severe depressive symptoms (adjusted OR 76.222, 95% CI 5.694–1020.340, p = 0.001).

Regarding anxiety symptoms assessed with the HADS-A, 34 patients (63%) scored within the normal range, 5 patients (9.3%) within the mild range, 9 patients (16.7%) expressed moderate anxiety symptoms and 6 (11.1%) had clinically severe anxiety symptoms. Overall, 15 patients (27.8%) expressed moderate to severe anxiety symptoms. Comparing the two statistical groups (Tables X and XI), patients with moderate-to-severe anxiety symptoms had a longer time from surgery to inclusion [12 (IQR 5) vs 8 (IQR 7) years; p=0.007]. In addition, a significant difference in the proportion of patients implanted with directional leads was observed between groups (p=0.022), with directional leads being less frequent among patients with moderate-to-severe anxiety symptoms. Patients with moderate-to-severe anxiety symptoms exhibited lesser postoperative percentage reductions in total UPDRS-II [-52.2% (IQR 34) vs -30.9% (IQR 42.7); p=0.037] and were more likely to have concomitant depressive symptoms (BDI ≥ 20) at LFU (93% vs. 28.2%; p<0.001). No significant differences were observed regarding antidepressant use (69.2% vs 66.7%; p=0.856) or anxiolytic use (66.7% vs 46.7%; p=0.177).

When performing the multivariable logistic regression analysis (Table IX), neither time from surgery to inclusion, implantation of directional leads nor percentage variation in UPDRS-II remained independently associated with moderate-to-severe anxiety symptoms. The presence of moderate-to-severe depressive symptoms (BDI-II ≥20) was independently associated with anxiety symptoms (adjusted OR 46.753, 95% CI 3.668–595.994, p = 0.003).

Clinically relevant apathy symptoms, defined by an SAS score ≥15, were observed in 36 patients (66.7%). Patients were subsequently divided into two groups according to the presence or absence of clinically relevant apathy. No statistically significant differences were observed between patients with and without clinically relevant apathy in the studied clinical and surgical variables, nor in percentage changes in clinical outcomes, as shown in Tables XII and XIII.

DISCUSSION

Non-motor symptoms are increasingly recognized as a major determinant of disability and, although, in many cases, they are more burdensome and prolonged than motor manifestations in PD, they are usually underrecognized.[23] Among these, neuropsychiatric symptoms are particularly relevant due to their high prevalence and impact on patients. No single mechanism has yet been identified that fully explains the relationship between these manifestations and PD, but current evidence suggests that multiple overlapping disease-related mechanisms contribute to their development.[26]

The present study aimed to assess the prevalence of depression, anxiety and apathy in PD long-term patients treated with DBS. These symptoms are among the most common non-motor manifestations of PD and are associated with reduced quality of life, increased disability and are key drivers for increased morbidity, as well as cost for society.[26, 27] Understanding their prevalence, clinical and surgical correlations in long-term DBS-treated patients is therefore essential for optimizing patient management, surgical techniques and timings and long-term follow-up strategies.

In the present cohort, 46.3% of the participants had moderate-to-severe depression symptoms, 27.8% had moderate-to-severe anxiety symptoms and 66.7% had clinically relevant apathy. These findings are broadly consistent with the existing literature on the subject, although reported prevalence rates vary greatly across studies.[28-31] Particularly noteworthy was the high proportion of patients receiving psychotropic medication at LFU, with 68.5% and 61.1% being treated with antidepressants and anxiolytics, respectively. Despite this, a substantial proportion of patients continued to experience clinically relevant neuropsychiatric symptoms. Furthermore, no significant association was observed between antidepressant or anxiolytic use at LFU and the presence of clinically significant depressive, anxiety and apathy symptoms. These findings highlight the persistent burden of neuropsychiatric manifestations in patients with PD following DBS and underscore the importance of their ongoing assessment and management in long-term follow-up.

Previous studies have suggested that neuropsychiatric outcomes may differ according to the DBS target, with GPi-DBS potentially having a less pronounced impact than STN-DBS. However, we could not assess this matter as every patient in our cohort underwent STN-DBS.[32] Moreover, depression seems to be particularly more common in PD patients with the LRRK2 G2019S mutation and in those with GBA mutations.[33] Unfortunately, genetic data were not available in our cohort and therefore this hypothesis could not be explored.

Regarding depression symptoms being associated with older age at inclusion, we conclude that this is a finding that may reflect the cumulative effects of disease progression and

ageing, as corroborated by Cong et al.[34] Although some authors have suggested that depression may be particularly associated with younger-onset PD and may even involve distinct pathophysiological mechanisms, our results did not support this hypothesis.[35, 36]

Furthermore, we were able to associate higher preoperative motor impairment and a subsequent less favourable long-term functional outcome, as shown by the progression of UPDRS-I and UPDRS-II, concluding that, in this cohort, depression appears to be related not only to disease progression and ageing, but also to poorer long-term functional benefit after DBS. This interpretation is in line with previous studies highlighting the close relationship between depressive symptoms, disability and quality of life in PD subjects.[34, 37, 38]

Following the findings regarding anxiety symptoms, we found that the presence of moderate-to-severe anxiety symptoms was associated with a longer time from surgery to inclusion, which may also reflect cumulative effects of disease progression and ageing.[39] Although the clinical significance of this finding remains uncertain, it warrants further investigation in larger cohorts. Previous studies have suggested that stimulation characteristics may influence neuropsychiatric outcomes. For example, Somma et al. reported less favourable anxiety outcomes when one or both electrodes were located in a more medial and/or anterior position within the subthalamic nucleus.[40] Although electrode location was not assessed in the present study, these findings highlight the potential importance of lead positioning and stimulation parameters in the development of anxiety symptoms after STN-DBS. Finally, our findings suggest a less favourable improvement in UPDRS-II scores that, similarly to depression, is in line with the literature.[37, 38, 41] It is worth noting that none of these variables remained independently associated with anxiety symptoms in the multivariable analysis, suggesting that their effects may be mediated by other factors.

A particularly relevant finding of the present study was the strong association observed between depressive and anxiety symptoms. In the multivariable logistic regression analyses, moderate-to-severe anxiety symptoms emerged as an independent predictor of moderate-to-severe depressive symptoms, while the presence of moderate-to-severe depressive symptoms was likewise independently associated with anxiety. These findings support the concept that depression and anxiety frequently coexist in patients with PD and may share common pathophysiological mechanisms.[23] From a clinical perspective, these results highlight the importance of systematically screening for anxiety in patients presenting depressive symptoms, and vice versa, particularly during long-term follow-up after STN-DBS.

Regarding clinically relevant apathy, we found that the prevalence of these symptoms in our cohort was high, affecting two-thirds of our study population, however, no statistically

significant differences were observed between groups in the clinical and surgical variables studied. It is plausible that apathy symptoms may have a substantial impact on quality of life, so this finding should not be overlooked and warrants further investigation in future studies.

It is worth noting that a documented preoperative diagnosis of depressive syndrome was not associated with depressive, anxiety or apathy symptoms at LFU, however, this finding should be interpreted with caution, as only three patients in the cohort had a documented preoperative diagnosis.

When considering the findings of the present study, several limitations must be noted. First, this was a single-center study, which may limit the generalization of the results to other clinical settings and surgical approaches. Therefore, multicenter studies involving larger and more diverse cohorts would be valuable to confirm and strengthen the external validity of these findings. Another important limitation is the relatively small sample size, comprising only 54 participants, which inevitably reduced the statistical power of the analyses and limited the ability to detect weaker associations. Furthermore, the interval between surgery and study inclusion (median of 9 years, IQR 8), resulted in a relevant attrition of the original cohort due to mortality, with 33 patients (27.7% of the initially eligible population) passing before study inclusion, resulting in a possible survival bias. This observation is consistent with previously reported long-term survival data following STN-DBS patients with PD.[42]

The methodology adopted, using telephone interviews, also introduced several limitations. Given the advanced stage of disease in this cohort, reflected by a median time from symptom onset to inclusion of 20 years, a considerable number of patients presented severe dysarthria, precluding reliable participation in the interview. Moreover, although interviews were conducted by the same investigator, telephone-based assessments inherently involve a degree of subjectivity and may be susceptible to information bias.

It is important to acknowledge that the heterogeneity of follow-up duration represented an important limitation to this investigation, potentially affecting the interpretation of the findings and the robustness of the inferential analysis. Although the clinical records were consistently detailed and well organized, the retrospective nature of data collection may have introduced inaccuracies related to missing or incomplete information.

It’s relevant to consider the absence of preoperative and postoperative neuropsychiatric assessments, preventing conclusions being drawn regarding the long-term impact of DBS on the development or evolution of neuropsychiatric symptoms. Although information on psychotropic medication use was available and analyzed, medication data alone cannot be considered a reliable surrogate for a formal neuropsychiatric diagnosis. This is particularly relevant for anxiolytic

medications, whose use is common among patients with PD. Furthermore, the absence of a control group comprising non-DBS treated PD patients precludes direct comparisons between treatment strategies. Although comparative studies remain scarce and variable, there is evidence suggesting that long-term neuropsychiatric outcomes may not differ substantially between patients treated with STN-DBS and those receiving optimized medical therapy alone.[10, 43, 44]

CONCLUSION

This study shows that neuropsychiatric symptoms are highly prevalent among long-term PD patients after DBS. Moderate-to-severe depressive symptoms, moderate-to-severe anxiety symptoms and clinically relevant apathy were observed in a substantial proportion of the study's population, highlighting the persistent burden of non-motor manifestations even many years after surgery. These findings support the importance of systematic long-term neuropsychiatric assessment in PD patients treated with STN-DBS. Early identification and management of depression, anxiety and apathy may contribute to improved quality of life and overall clinical outcomes. Further multicenter longitudinal studies with larger cohorts and preoperative neuropsychiatric evaluation are needed to better understand the long-term impact of DBS on these symptoms and to identify modifiable risk factors.

APPENDICES

Table I: Summary of Clinical Characteristics.

*IQR, interquartile range. PD, Parkinson's Disease. UPDRS-I, first section of the Unified Parkinson's Disease Rating Scale. UPDRS-II, second section of the Unified Parkinson's Disease Rating Scale. UPDRS-III, third section of the Unified Parkinson's Disease Rating Scale. UPDRS-IV, fourth section of the Unified Parkinson's Disease Rating Scale. LFU, last follow-up. LEDD, levodopa equivalent daily dose. *Referring to diagnosis established previously to the inclusion of the participant in the study.*

Items	**Total (N=54)**
Age at symptom onset [median (IQR)], years; n=52	45 (11)
Age at diagnosis [median (IQR)], years; n=51	46 (13)
Age at first medication [median (IQR)], years; n=51	46 (13)
Age at first motor fluctuation [median (IQR)], years; n=50	50 (13)
Age at first dyskinesias [median (IQR)], years; n=50	53.5 (13)
Age at surgery [median (IQR)], years	56 (12)
Age at inclusion [median (IQR)], years	66 (11)
Time from symptom onset to surgery [median (IQR)], years; n=52	11 (5)
Time from symptom onset to inclusion [median (IQR)], years; n=52	20 (7)
Time from surgery to inclusion [median (IQR)], years	9 (8)
Male Gender [n (%)]	32 (59.3)
Comorbidities [n (%)]*	
Hypertension	15 (27.8)
Diabetes Mellitus	4 (7.4)
Dyslipidemia	11 (20.3)
Previous oncological disease	4 (7.4)
Depressive or anxiety syndrome	3 (5.5)
Family history of PD [n (%)]; n=49	17 (31.5)
Family history of essential tremor [n (%)], n=48	3 (5.5)
Laterality at clinical onset [n (%)], n=52	
Right	27 (51.9)
Left	25 (48.1)
Bilateral	0 (0.0)
Preoperative total UPDRS-I score [median (IQR)]	1 (1)
Preoperative total UPDRS-II score [median (IQR)]	20 (7)
Preoperative total UPDRS-III score [median (IQR)]	38 (11)
Preoperative total UPDRS-IV score [median (IQR)]	9 (3)
Preoperative *LEDD* [median (IQR)], mg	1572 (610)
LFU [median (IQR)], years post-op	6 (7)

Table II: Surgical characteristics, stimulation features and complications.
*STN-DBS, deep brain stimulation of the subthalamic nucleus. MER, microelectrode recording. IQR, interquartile range. LFU, last follow-up. *Percentage of those with directional leads implanted.*

Items	**Total (N=54)**
Patients with STN-DBS	54 (100.0)
Patients with bilateral STN-DBS [n (%)]	54 (100.0)
Number of MER trajectories per patient [median (IQR)]	6 (2)
Patients with intraoperative complications [n (%)]	0 (0.0)
Patients with postoperative complications [n (%)]	
Total	3 (5.6)
Infection	1 (1.9)
Lead mispositioning with poor clinical result	1 (1.9)
Lead migration	1 (1.9)
Requiring surgical reintervention	3 (5.6)
Patients with directional leads [n (%)]	16 (29.6)
Patients with bilateral ring mode stimulation at LFU [n (%*)], n=16	11 (68.8)

Table III: Effects of STN DBS during the off-medication condition (on-stimulation and off-medication).

UPDRS-I, first section of the Unified Parkinson's Disease Rating Scale. UPDRS-II, second section of the Unified Parkinson's Disease Rating Scale. UPDRS-III, third section of the Unified Parkinson's Disease Rating Scale. UPDRS-IV, fourth section of the Unified Parkinson's Disease Rating Scale LEDD, levodopa equivalent daily dose. IQR, interquartile range. LFU, last follow-up.

Scores	**Pre-op (n=54)**	**1 year post-op (n=43)**	**2 years post-op (n=45)**	**5 years post-op (n=33)**	**10 years post-op (n=12)**	**15 years post-op (n=3)**	**LFU (n=54)**
Total UPDRS-I [median (IQR)]	1 (1)	1 (1)	1 (2)	1 (3)	1 (1)	1 (1)	1 (3)
Percentage variation from pre-op at LFU [median (IQR)]							-33 (67)
Total UPDRS-II [median (IQR)]	20 (7)	6 (5)	8 (3)	10 (4)	14 (9)	23 (7)	10.5 (6)
Percentage variation from pre-op at LFU [median (IQR)]							-50 (36)
Total UPDRS-III [median (IQR)]	38 (11)	12 (9)	13 (11)	15 (7)	17 (13)	29 (6)	14 (9)
Percentage variation from pre-op at LFU [median (IQR)]							-58.5 (25)
Total UPDRS-IV [median (IQR)]	9 (3)	1 (2)	1 (3)	2 (4)	1 (3)	2 (5)	1 (2)
Percentage variation from pre-op at LFU [median (IQR)]							-85.7 (28.0)
LEDD [median (IQR)], mg	1572 (610)	480 (300)	470 (340)	560 (280)	685 (450)	380 (220)	610 (360)
Percentage variation from pre-op at LFU [median (IQR)]							-61.3 (28.9)

Table IV: Neuropsychiatric assessment at LFU.
BDI-II, Beck Depression Inventory-II. HADS-A, Hospital Anxiety and Depression Scale - Anxiety Subscale. SAS, Starkstein's Apathy Scale. LFU, last follow-up.

Score	**Total (N=54)**
BDI-II depression symptoms severity category [n (%)]	
minimal (score 0-13)	15 (27.8)
mild (score 14-19)	14 (25.9)
moderate (score 20-28)	14 (25.9)
severe (score 29-63)	11 (20.4)
HADS-A anxiety symptoms severity category [n (%)]	
normal (score 0-7)	34 (63.0)
mild (score 8-10)	5 (9.3)
moderate (score 11-14)	9 (16.7)
severe (score 15-21)	6 (11.1)
SAS >14 [n (%)]	36 (66.7)
Patients on antidepressant medication at LFU [n (%)]	37 (68.5)
Patients on anxiolytic medication at LFU [n (%)]	33 (61.1)

Table V: Comparison of neuropsychiatric scores according to LFU postoperatively.

BDI-II, Beck Depression Inventory-II. HADS-A, Hospital Anxiety and Depression Scale - Anxiety Subscale. SAS, Starkstein's Apathy Scale. LFU, last follow-up. IQR, interquartile range.

Scores	**LFU = 1 year post-op (n=2)**	**LFU = 2 years post-op (n=7)**	**LFU = 3 years post-op (n=3)**	**LFU = 4 years post-op (n=4)**	**LFU = 5 years post-op (n=6)**	**LFU = 6 years post-op (n=3)**	**LFU = 7 years post-op (n=5)**	**LFU = 8 years post-op (n=3)**	**LFU = 9 years post-op (n=2)**	**LFU = 10 years post-op (n=2)**
BDI-II, [median (IQR)]	17 (NA)	19 (21)	18 (NA)	14 (9)	24.5 (3)	5 (NA)	17 (9)	20 (NA)	16 (NA)	14 (NA)
HADS-A, [median (IQR)]	6.5 (NA)	7 (NA)	4 (NA)	0.5 (NA)	6 (6)	1 (NA)	7 (9)	2 (NA)	6.5 (NA)	1.5 (NA)
SAS, [median (IQR)]	11.5 (NA)	23 (11)	21 (NA)	25.5 (7)	20 (10)	12 (NA)	11 (5)	18 (NA)	16.5 (NA)	12.5 (NA)

(cont.)	**LFU = 11 years post-op (n=3)**	**LFU = 12 years post-op (n=4)**	**LFU = 13 years post-op (n=2)**	**LFU = 14 years post-op (n=3)**	**LFU = 15 years post-op (n=2)**	**LFU = 16 years post-op (n=2)**	**LFU = 17 years post-op (n=1)**
BDI-II, [median (IQR)]	23 (NA)	27.5 (10)	20 (NA)	12 (NA)	18.5 (NA)	23.5 (NA)	31 (NA)
HADS-A, [median (IQR)]	10 (NA)	11.5 (NA)	10.5 (NA)	1 (NA)	8.5 (NA)	10 (NA)	12 (NA)
SAS, [median (IQR)]	21 (NA)	24.5 (7)	29 (NA)	11 (NA)	21 (NA)	23 (NA)	1 (NA)

Table VI: Statistical tests used in the inferential analysis.
*The significance threshold was set at p < 0.05. Statistical analyses were performed using SPSS software (version 28.0, IBM). BDI-II, Beck Depression Inventory-II; HADS-A, Hospital Anxiety and Depression Scale - Anxiety Subscale; SAS, Starkstein's Apathy Scale; LEDD, Levodopa Equivalent Daily Dose; LFU, Last Follow-Up; MER, Microelectrode Recording; STN-DBS, Subthalamic Nucleus Deep Brain Stimulation; UPDRS, Unified Parkinson's Disease Rating Scale. *For variables that did not conform to a normal distribution, as determined by the Shapiro-Wilk test.*

Statistical Test	Variables
Pearson's Chi-square teste	Arterial hypertension, diabetes mellitus, dyslipidemia, previous oncological disease, preoperative depressive syndrome, preoperative anxiety syndrome, male gender, family history of Parkinson's disease, family history of essential tremor, side of symptom onset, postoperative complications, infection, lead mispositioning with poor clinical outcome, lead migration, requiring surgical reintervention, directional lead implantation, bilateral ring mode stimulation at LFU, patients on antidepressant medication at LFU, patients on anxiolytic medication.
Mann-Whitney U test*	Age at symptom onset, age at diagnosis, age at first motor fluctuation, age at first dyskinesia, age at surgery, age at inclusion, time from symptom onset to surgery, time from symptom onset to inclusion, time from surgery to inclusion, preoperative total UPDRS-III score, preoperative LEDD, percentage variation in UPDRS-I, percentage variation in UPDRS-II, percentage variation in UPDRS-III, percentage variation in UPDRS-IV, percentage variation in LEDD, LFU duration, number of MER trajectories per patient.
Logistic Regression Analysis	All multivariable analyses presented in the study.

Table VII: Comparison of clinical and surgical variables according to moderate-to-severe depressive symptoms at telephone assessment.

*BDI-II, Beck Depression Inventory-II. IQR, interquartile range. UPDRS-I, first section of the Unified Parkinson's Disease Rating Scale. UPDRS-II, second section of the Unified Parkinson's Disease Rating Scale. UPDRS-III, third section of the Unified Parkinson's Disease Rating Scale. UPDRS-IV, fourth section of the Unified Parkinson's Disease Rating Scale. LEDD, levodopa equivalent daily dose. MER, microelectrode recording. LFU, last follow-up. * The specific statistical tests used to compare the two groups are detailed in Table VI. **Percentage of those with directional leads implanted.*

Independent variables	**BDI-II <20 (n=29)**	**BDI-II ≥20 (n=25)**	***p****
Age at first symptoms, [median (IQR)], years, n=52	43 (12)	48 (11)	0.305
Age at surgery, [median (IQR)], years	53 (12)	61 (12)	0.137
Age at inclusion, [median (IQR)], years	63 (12)	68 (6)	**<0.001**
Time from first symptoms to surgery, [median (IQR)] years, n=52	11 (5)	11 (4)	0.850
Time from first symptoms to inclusion, [median (IQR)] years, n=52	20 (7)	21 (6)	0.532
Time from surgery to inclusion, [median (IQR)] years	8 (6)	9 (6)	0.488
Preoperative total UPDRS-I, [median (IQR)]	1 (2)	1 (2)	0.252
Preoperative total UPDRS-II, [median (IQR)]	18 (7)	20 (8)	0.476
Preoperative total UPDRS-III, [median (IQR)]	33 (10)	40 (11)	**0.027**
Preoperative total UPDRS-IV, [median (IQR)]	9 (2)	8 (3)	0.516
Preoperative LEDD, [median (IQR)]	1675 (535)	1505 (600)	0.375
Number of MER trajectories, [median (IQR)]	6 (2)	6 (2)	0.919
Patients with postoperative complications, [n (%)]	1 (6.7)	2 (5.1)	0.643
Patients with directional leads, [n (%)]	11 (37.9)	5 (20.0)	0.150
Patients with ring mode stimulation at LFU, [n (%**)] n=16	7 (63.6)	4 (80.0)	0.513

Table VIII: Comparison of clinical outcome percentage variation according to moderate-to-severe depressive symptoms at telephone assessment.

*BDI-II, Beck Depression Inventory-II. UPDRS-I, first section of the Unified Parkinson's Disease Rating Scale. UPDRS-II, second section of the Unified Parkinson's Disease Rating Scale. UPDRS-III, third section of the Unified Parkinson's Disease Rating Scale. UPDRS-IV, fourth section of the Unified Parkinson's Disease Rating Scale. LEDD, levodopa equivalent daily dose. LFU, last follow-up. IQR, interquartile range. * The specific statistical tests used to compare the two groups are detailed in Table VI.*

Independent variables	**BDI-II <20 (n=29)**	**BDI-II ≥20 (n=25)**	***p****
Total UPDRS-I percentage variation from pre-op at LFU, [median (IQR)]	-50 (100)	0.0 (83.3)	**0.039**
Total UPDRS-II percentage variation from pre-op at LFU, [median (IQR)]	-55 (12)	-38.1 (28.4)	**0.026**
Total UPDRS-III percentage variation from pre-op at LFU, [median (IQR)]	-66.7 (19.3)	-52.9 (25.0)	0.163
Total UPDRS-IV percentage variation from pre-op at LFU, [median (IQR)]	-77.8 (30.4)	-85.7 (28.0)	0.717
LEDD percentage variation from pre-op at LFU, [median (IQR)]	-61.3 (34.4)	-64.6 (22.3)	0.759
HADS-A ≥11 at LFU, [n (%)]	1 (3.4)	15 (56)	**<0.001**
SAS ≥15 at LFU, [n (%)]	17 (58.6)	19 (76)	0.177
Patients on antidepressant medication at LFU [n (%)]	19 (65.5)	18 (72.0)	0.609
Patients on anxiolytic medication [n (%)]	17 (58.6)	16 (64.0)	0.686

Table IX: Multivariable logistic regression models for factors associated with moderate-to-severe depressive and anxiety symptoms at LFU.

*BDI-II, Beck Depression Inventory-II; HADS-A, Hospital Anxiety and Depression Scale – Anxiety Subscale; UPDRS-I, Unified Parkinson's Disease Rating Scale Part I; UPDRS-II, Unified Parkinson's Disease Rating Scale Part II; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; LFU, last follow-up; OR, odds ratio; CI, confidence interval; PD, Parkinson's disease. *The specific statistical tests used to compare the two groups are detailed in Table VI.*

Logistic regression model	**Adjusted OR (95% CI)**	***p****
BDI-II ≥20 at LFU		
Model 1: pre-op and surgical variables		
Age at inclusion	1.099 (1.009-1.196)	**0.031**
Total UPDRS-III pre-op	1.039 (0.967-1.116)	0.293
Model 2: model 1 variables plus PD evolution variables		
Age at inclusion	1.164 (1.022-1.326)	**0.022**
Total UPDRS-III pre-op	1.101 (0.996-1.217)	0.059
Total UPDRS-I percentage variation from pre-op at LFU	1.160 (0.583-2.306)	0.672
Total UPDRS-II percentage variation from pre-op at LFU	0.023 (0.001-0.931)	**0.046**
Model 3: model 2 variables plus HADS-A ≥11 at LFU		
Age at inclusion	1.177 (1.030-1.345)	**0.017**
Total UPDRS-III pre-op	1.053 (0.964-1.150)	0.252
Total UPDRS-I percentage variation from pre-op at LFU	0.604 (0.290-1.252)	0.174
Total UPDRS-II percentage variation from pre-op at LFU	0.843 (0.009-81.931)	0.942
HADS-A ≥11 AT LFU	76.222 (5.694-1020.340)	**0.001**
HADS-A ≥11 at LFU		
Model 1: preop and surgical variables		
Time from surgery to inclusion	1.170 (0.955-1.433)	0.129
Patients with directional leads	0.348 (0.026-4.599)	0.423
Model 2: model 1 variables plus PD evolution variables		
Time from surgery to inclusion	1.152 (0.927-1.432)	0.203
Patients with directional leads	0.382 (0.027-4.419)	0.477
Total UPDRS-II percentage variation from pre-op at LFU	0.216 (0.010-4.169)	0.282
Model 3: model 2 variables plus BDI-II ≥20 at LFU		
Time from surgery to inclusion	1.337 (0.969-1.846)	0.077
Patients with directional leads	1.054 (0.044-25.061)	0.477

Table IX (continued):

Total UPDRS-II percentage variation from pre-op at LFU	1.190 (0.027-52.335)	0.928
BDI-II ≥20 at LFU	46.753 (3.668-595.994)	**0.003**

Table X: Comparison of clinical and surgical variables according to moderate-to-severe anxiety symptoms at telephone assessment.

*HADS-A, Hospital Anxiety and Depression Scale - Anxiety Subscale. IQR, interquartile range. UPDRS-I, first section of the Unified Parkinson's Disease Rating Scale. UPDRS-II, second section of the Unified Parkinson's Disease Rating Scale. UPDRS-III, third section of the Unified Parkinson's Disease Rating Scale. UPDRS-IV, fourth section of the Unified Parkinson's Disease Rating Scale. LEDD, levodopa equivalent daily dose. MER, microelectrode recording. LFU, last follow-up. * The specific statistical tests used to compare the two groups are detailed in Table VI. **Percentage of those with directional leads implanted.*

Independent variables	**HADS-A <11 (n=39)**	**HADS-A ≥11 (n=15)**	***p****
Age at first symptoms, [median (IQR)], years, n=52	47 (11)	43 (12)	0.181
Age at surgery, [median (IQR)], years	59 (14)	54 (14)	0.163
Age at inclusion, [median (IQR)], years	66 (11)	66 (11)	0.932
Time from first symptoms to surgery, [median (IQR)] years, n=52	11 (5)	11 (4)	0.438
Time from first symptoms to inclusion, [median (IQR)] years, n=52	20 (8)	21 (6)	0.103
Time from surgery to inclusion, [median (IQR)] years	8 (7)	12 (5)	**0.007**
Preoperative total UPDRS-I, [median (IQR)]	1 (1)	2 (3)	0.564
Preoperative total UPDRS-II, [median (IQR)]	18 (7)	20.5 (4)	0.384
Preoperative total UPDRS-III, [median (IQR)]	36 (10)	40 (12)	0.436
Preoperative total UPDRS-IV, [median (IQR)]	9 (2)	9 (5)	0.516
Preoperative LEDD, [median (IQR)]	1585 (545)	1555 (850)	0.992
Number of MER trajectories, [median (IQR)]	6 (1)	6 (2)	0.311
Patients with postoperative complications, [n (%)]	2 (5.1)	1 (6.7)	0.825
Patients with directional leads, [n (%)]	15 (38.5)	1 (6.7)	**0.022**
Patients with ring mode stimulation at LFU, [n (%**) n=16]	10 (66.7)	1 (100.0)	0.486

Table XI: Comparison of clinical outcome percentage variation according to moderate-to-severe anxiety symptoms at telephone assessment.

*HADS-A, Hospital Anxiety and Depression Scale - Anxiety Subscale. UPDRS-I, first section of the Unified Parkinson's Disease Rating Scale. UPDRS-II, second section of the Unified Parkinson's Disease Rating Scale. UPDRS-III, third section of the Unified Parkinson's Disease Rating Scale. UPDRS-IV, fourth section of the Unified Parkinson's Disease Rating Scale. LEDD, levodopa equivalent daily dose. LFU, last follow-up. IQR, interquartile range. * The specific statistical tests used to compare the two groups are detailed in Table VI.*

Independent variables	**HADS-A <11 (n=39)**	**HADS-A ≥11 (n=15)**	***p****
Total UPDRS-I percentage variation from pre-op at LFU, [median (IQR)]	0 (133.3)	-50.0 (66.7)	0.826
Total UPDRS-II percentage variation from pre-op at LFU, [median (IQR)]	-52.2 (34.0)	-30.9 (42.7)	**0.037**
Total UPDRS-III percentage variation from pre-op at LFU, [median (IQR)]	-60.5 (18.6)	-50.0 (39.6)	0.379
Total UPDRS-IV percentage variation from pre-op at LFU, [median (IQR)]	-85.7 (30.4)	-85.7 (28.0)	0.928
LEDD percentage variation from pre-op at LFU, [median (IQR)]	-59.0 (27.6)	-66.4 (34.2)	0.676
BDI-II ≥20 at LFU, [n (%)]	11 (28.2)	14 (93)	**<0.001**
SAS ≥15 at LFU, [n (%)]	26 (66.7)	10 (66.7)	1.000
Patients on antidepressant medication at LFU [n (%)]	27 (69.2)	10 (66.7)	0.856
Patients on anxiolytic medication [n (%)]	26 (66.7)	7 (46.7)	0.177

Table XII: Comparison of clinical and surgical variables according to clinically relevant apathy symptoms at telephone assessment.

*SAS, Starkstein's Apathy Scale. IQR, interquartile range. UPDRS-I, first section of the Unified Parkinson's Disease Rating Scale. UPDRS-II, second section of the Unified Parkinson's Disease Rating Scale. UPDRS-III, third section of the Unified Parkinson's Disease Rating Scale. UPDRS-IV, fourth section of the Unified Parkinson's Disease Rating Scale. LEDD, levodopa equivalent daily dose. MER, microelectrode recording. LFU, last follow-up. * The specific statistical tests used to compare the two groups are detailed in Table VI. **Percentage of those with directional leads implanted.*

Independent variables	**SAS <15 (n=18)**	**SAS ≥15 (n=36)**	***p****
Age at first symptoms [median (IQR)], years; n=52	44.5 (14)	46.5 (12)	0.102
Age at surgery [median (IQR)], years	54.5 (15)	58.5 (14)	0.313
Age at inclusion [median (IQR)], years; n=52	65 (13)	67 (11)	0.144
Time from first symptoms to surgery [median (IQR)], years; n=52	11 (6)	11 (5)	0.850
Time from first symptoms to inclusion [median (IQR)], years; n=52	20 (8)	20 (8)	0.550
Time from surgery to inclusion [median (IQR)], years	8 (7)	10 (8)	0.468
Preoperative total UPDRS-I [median (IQR)]	1 (1)	1 (2)	0.279
Preoperative total UPDRS-II [median (IQR)]	20.5 (8)	19 (7)	0.433
Preoperative total UPDRS-III [median (IQR)]	38 (8)	37 (12)	0.805
Preoperative total UPDRS-IV [median (IQR)]	9 (3)	9 (3)	0.591
Preoperative LEDD [median (IQR)]	1737 (430)	1462 (630)	0.130
Number of MER trajectories [median (IQR)]	6 (1)	6 (2)	0.180
Patients with postoperative complications [n (%)]	0 (0.0)	3 (8.3)	0.208
Patients with directional lead [n (%)]	6 (33.3)	10 (27.8)	0.673
Patients with ring mode stimulation at LFU [n (%**)], n=16	4 (66.7)	7 (70.0)	0.889

Table XIII: Comparison of clinical outcome percentage variation according to clinically relevant apathy symptoms at telephone assessment.

*SAS, Starkstein's Apathy Scale. UPDRS-I, first section of the Unified Parkinson's Disease Rating Scale. UPDRS-II, second section of the Unified Parkinson's Disease Rating Scale. UPDRS-III, third section of the Unified Parkinson's Disease Rating Scale. UPDRS-IV, fourth section of the Unified Parkinson's Disease Rating Scale. LEDD, levodopa equivalent daily dose. LFU, last follow-up. IQR, interquartile range. * The specific statistical tests used to compare the two groups are detailed in Table VI.*

Independent variables	**SAS <15 (n=18)**	**SAS ≥15 (n=36)**	***p****
Total UPDRS-I percentage variation from pre-op at LFU, [median (IQR)]	-50.0 (150.0)	-16.7 (66.7)	0.529
Total UPDRS-II percentage variation from pre-op at LFU, [median (IQR)]	-51.0 (28.8)	-48.0 (37.1)	0.599
Total UPDRS-III percentage variation from pre-op at LFU, [median (IQR)]	-65.7 (25.8)	-57.2 (26.3)	0.518
Total UPDRS-IV percentage variation from pre-op at LFU, [median (IQR)]	-72.5 (28.9)	-87.5 (16.7)	0.208
LEDD percentage variation from pre-op at LFU, [median (IQR)]	-61.3 (12.2)	-62.7 (33.8)	0.676
BDI-II ≥20 at LFU, [n (%)]	6 (33.3)	19 (52.8)	0.177
HADS-A ≥11 at LFU, [n (%)]	5 (27.8)	10 (27.8)	1.000
Patients on antidepressant medication at LFU [n (%)]	10 (55.6)	27 (75.0)	0.147
Patients on anxiolytic medication [n (%)]	11 (61.1)	22 (61.1)	1.000

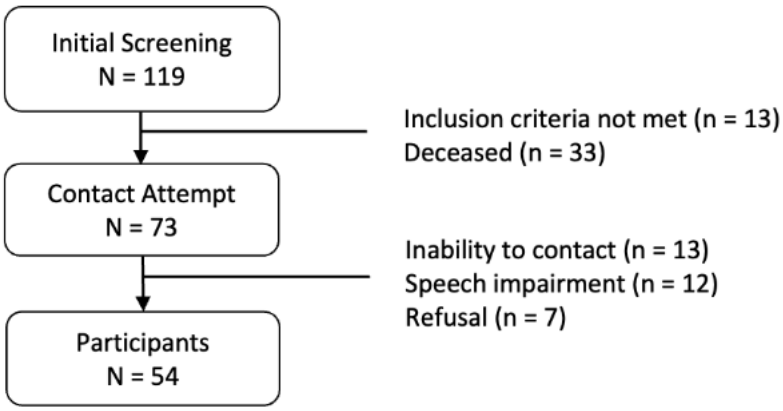

Figure 1: Flowchart of recruitment, follow-up and application of the questionnaires

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