BMJ Neurology Open

Subthalamic stimulation has acute psychotropic effects and improves neuropsychiatric fluctuations in Parkinson's disease

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To cite: Magalhães AD, Amstutz D, Petermann K, *et al*. Subthalamic stimulation has acute psychotropic effects and improves neuropsychiatric fluctuations in Parkinson's disease. *BMJ Neurology Open* 2024;**6**:e000524. doi:10.1136/bmjno-2023-000524

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjno-2023-000524).

Accepted 24 October 2023

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ABSTRACT

Background Subthalamic nucleus deep brain stimulation (STN-DBS) is a well-established treatment for motor complications in Parkinson's disease (PD). However, its effects on neuropsychiatric symptoms remain disputed. The aim of this study was to evaluate the effects of STN-DBS on neuropsychiatric symptoms in PD.

Methods We retrospectively assessed 26 patients with PD who underwent a preoperative levodopa challenge and postoperative levodopa and stimulation challenges 1 year after STN-DBS. Based on the Neuropsychiatric Fluctuations Scale, Neuropsychiatric State Scores and Neuropsychiatric Fluctuation Indices (NFIs) were calculated. Mixed-effects models with random effects for intercept were used to examine the association of Neuropsychiatric State Score and NFI with the different assessment conditions.

Results In acute challenge conditions, there was an estimated increase of 15.9 points in the Neuropsychiatric State Score in stimulation ON conditions (95% CI 11.4 to 20.6, p<0.001) and 7.6 points in medication ON conditions (95% CI 3.3 to 11.9, p<0.001). Neuropsychiatric fluctuations induced by levodopa, quantified with NFI, decreased by 35.54% (95% CI 49.3 to 21.8, p<0.001) 1 year after STN-DBS.

Conclusions Bilateral STN-DBS at therapeutic parameters has acute psychotropic effects similar to levodopa and can modulate and decrease levodopa-induced neuropsychiatric fluctuations.

INTRODUCTION

Non-motor symptoms affect most patients with Parkinson's disease (PD) and can have a higher impact on quality of life than motor signs.[1] Neuropsychiatric symptoms such as depression, anxiety and apathy have been associated with a dopaminergic deficit, whereas symptoms of euphoria and impulsivity have been linked to overstimulation of the mesolimbic pathways by dopaminergic medication.[2] Similar to motor fluctuations, neuropsychiatric fluctuations in response to dopaminergic medication may develop, with patients' moods changing frequently and abruptly between opposite emotional states.[2]

Subthalamic nucleus deep brain stimulation (STN-DBS) is a well-established treatment for motor complications in PD.[3] However, the STN not only integrates motor but also associative and limbic cortico-basal ganglia circuitries and STN-DBS can therefore affect cognition and behaviour.[4] While some studies have reported worsening in mood, anxiety and apathy after STN-DBS,[3] others have shown beneficial effects of STN-DBS on impulse control disorders (ICD) and neuropsychiatric fluctuations.[5]

To optimise symptom control and improve patients' quality of life, assessing neuropsychiatric fluctuations is of great importance but often neglected.[6] The tools that are typically used for their assessment are either not specifically designed to investigate neuropsychiatric symptoms in PD[7] or evaluate a longer retrospective time range[8] and therefore cannot detect acute symptoms experienced during neuropsychiatric fluctuations. The Neuropsychiatric Fluctuations Scale (NFS) is an easy-to-administer self-rating tool specifically designed to detect and quantify acute changes in neuropsychiatric symptoms in PD.[9]

Our study aimed to evaluate the acute effect of STN-DBS on the neuropsychiatric state and neuropsychiatric fluctuations in PD.

METHODS

Study design and participants

This retrospective observational single-centre study was approved by the local ethics committee (2020-02392). We screened 31 consecutive patients with PD who underwent bilateral STN-DBS at the University Hospital

Bern from July 2019 until June 2021. Patients were considered candidates for STN-DBS if they had disabling motor complications and at least a 30% improvement in motor symptoms with levodopa. We included patients with available comprehensive routine clinical care preoperative and 12-month postoperative assessments and excluded patients for whom informed consent for research or follow-up data were unavailable (online supplemental figure 1).

Assessments

At 1-year follow-up, 8 out of the 26 included patients underwent postoperative acute levodopa challenge while keeping stimulation ON, resulting in two conditions: Medication-OFF/Stimulation-ON (Med-OFF/Stim-ON) and Medication-ON/Stimulation-ON (Med-ON/Stim-ON). The remaining 18 patients additionally underwent an acute stimulation challenge, resulting in four conditions: Medication-OFF/Stimulation-ON (Med-OFF/Stim-ON), Medication-OFF/Stimulation-OFF (Med-OFF/Stim-OFF), Medication-ON/Stimulation-OFF (Med-ON/Stim-OFF) and Medication-ON/Stimulation-ON (Med-ON/Stim-ON).

The levodopa challenge was performed after withdrawal for more than 48 hours of dopamine agonists and more than 8 hours of levodopa formulations, with patients receiving a suprathreshold dose of levodopa plus benserazide corresponding to 150% of their morning levodopa equivalent dose. Medication ON was rated when the patient and examiner agreed that a stable medication ON condition was attained. Stimulation OFF and ON were rated earliest at 30 min after changing the condition.

Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III scores, the Parkinson's Disease Questionnaire (PDQ-39), MDS-UPDRS parts I, II and IV and the Montreal Cognitive Assessment (MoCA) scores were obtained.

Neuropsychiatric fluctuations were assessed using the NFS.[9] The NFS consists of 20 items derived from several neuropsychiatric tools that have been shown to best describe subjective neuropsychiatric symptoms in patients with PD. Each item is rated by the patient from 0 (does not describe how I feel right now) to 3 (describes a lot of how I feel right now). Ten items correspond to typical ON symptoms (such as well-being, increased motivation and mania), and 10 items correspond to typical OFF symptoms (such as depression, anxiety and apathy), resulting in two subscores (ON items and OFF items) ranging from 0 to 30.[9] We used the NFS scores to compute a new Neuropsychiatric State Score:

$$\textit{Neuropsychiatric State Score} = \textit{Score ON items} + \left(30 - \textit{Score OFF items}\right)$$

This Neuropsychiatric State Score correlates positively with the magnitude of ON neuropsychiatric symptoms and ranges from 0 to 60, where 0 translates to a predominance of OFF neuropsychiatric symptoms and 60 to a predominance of ON neuropsychiatric symptoms (ie, elevated mood).

To quantify the severity of neuropsychiatric fluctuations, we computed the Neuropsychiatric Fluctuation Index (NFI):

$$NFI = 100 * \left(1 - \frac{\textit{Neuropsychiatric State Score OFF condition}}{\textit{Neuropsychiatric State Score ON condition}}\right)$$

The NFI is a percentage change score that quantifies the modification of neuropsychiatric symptoms (ie, the percentage change in neuropsychiatric symptoms).

Statistical Analysis

Descriptive statistics were computed for demographic and clinical characteristics using frequency for categorical variables and mean and SD for continuous variables. Random forest imputation was performed for missing data (online supplemental table 1). Mixed-effects models with random effects for intercept were used to examine the association between the Neuropsychiatric State Score or NFI and the different assessment conditions. Sex, disease duration and levodopa challenge dose were used as covariates, as indicated. Statistical analysis was performed using R V.4.1.3 and RStudio V.2022.02.1.[10]

RESULTS

The demographic and clinical characteristics of patients are shown in table 1. At 1-year follow-up, motor symptoms improved under STN-DBS (MDS-UPDRS parts III and IV scores), quality of life (PDQ-39 Summary Index) improved by 19.9% and levodopa equivalent daily dose (LEDD) was reduced by 60.2% (table 1).

In the preoperative assessment, the mean Neuropsychiatric State Score was higher in the medication-ON condition compared with the medication-OFF condition (Med-OFF mean (SD) of 19.16 (12.02) vs Med-ON mean of 42.58 (11.53)) (figure 1A, online supplemental figure 2). At 1-year follow-up, the mean Neuropsychiatric State Score was higher in stimulation-ON conditions (Med-OFF/Stim-OFF 14.56 (12.13) vs Med-OFF/Stim-ON 33.23 (12.64); Med-ON/Stim-OFF 24.83 (14.33) vs Med-ON/Stim-ON 39 (11.93)). The Neuropsychiatric State Score in Med-ON/Stim-ON moderately correlated (r=−0.48) with the PDQ-39 Summary Index but did not explain much of the variability of the data (p=0.007, R^2=0.235) (online supplemental figure 3). Using a mixed-effects model, we estimated an increase of 15.9 points in the Neuropsychiatric State Score when changing from the Stim-OFF condition to the Stim-ON condition (95% CI 11.4 to 20.6, p<0.001) and 7.6 points when changing from the Med-OFF condition to the Med-ON condition (95% CI 3.3 to 11.9, p<0.001) (figure 1A). Comparing the preoperative and postoperative acute levodopa challenges, we estimated an increase of 4.9 points in the Neuropsychiatric State Score per 100 mg of levodopa in the preoperative challenge (95% CI 2.9 to 6.9, p<0.001) compared with an increase of 3.7 points per 100 mg of levodopa postoperatively (95% CI 1.8 to 5.6, p<0.001) (figure 1A).

Table 1 Demographic characteristics at baseline and clinical characteristics at preoperative and 12-month postoperative assessments

Demographic characteristics	Value	
Sex (M/F)	16/10	
Age at onset, years (mean (SD))	50.2 (7.5)	
Disease duration, years (mean (SD))	10.3 (5.4)	
Education, years (mean (SD))	13.4 (3.7)	
Clinical characteristics	**Preoperative mean (SD)**	**Postoperative mean (SD)**
LEDD-total (mg/day)	1140.4 (477.0)	453.5 (338.1)
LEDD-LDopa (mg/day)	871.5 (362.0)	358.8 (321.6)
LEDD-DA (mg/day)	172.7 (228.6)	75.4 (80.4)
Number of daily levodopa intake	5.7 (1.8)	3.9 (2.5)
Levodopa challenge dose	342.3 (113.7)	211.5 (57.1)
MDS-UPDRS part IA	4.6 (2.2)	3.3 (3.3)
Depressed mood (MDS-UPDRS part IA)	1.0 (0.5)	1.0 (0.9)
Anxious mood (MDS-UPDRS part IA)	0.8 (0.9)	0.8 (0.9)
Apathy (MDS-UPDRS part IA)	1.0 (0.9)	0.6 (0.7)
Dopamine dysregulation syndrome (MDS-UPDRS part IA)	0.6 (0.7)	0.1 (0.3)
MDS-UPDRS part IB	9.6 (3.7)	7.7 (3.4)
MDS-UPDRS part III	Med-ON: 15.2 (7.2) Med-OFF: 38.3 (11.9)	Stim-ON/Med-ON: 17.4 (11.2) Stim-ON/Med-OFF: 29.8 (15.6)
MDS-UPDRS part IV	8.0 (3.1)	4.0 (2.9)
MoCA	27.2 (2.3)	25.8 (3.5)
STN-DBS stimulation parameters	–	Amplitude (mA): 2.6 (0.8) Frequency (Hz): 130 (0) Pulse width (µs): 60 (0)
PDQ-39 Summary Index Score	26.6 (12.7)	21.3 (12.8)

Demographic characteristics, LEDD-total, LEDD-LDopa, LEED-DA, number of daily levodopa intake, MDS-UPDRS parts I and IV, MoCA, STN-DBS stimulation parameters and PDQ-39 Summary Index Score refer to a chronic assessment. Levodopa challenge dose and MDS-UPDRS part III refer to acute challenge assessments.
LEDD, levodopa equivalent daily dose; LEDD-DA, LEDD-dopamine agonist; LEDD-LDopa, LEDD levodopa; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; Med-OFF, Medication-OFF; Med-ON, Medication-ON; MoCA, Montreal Cognitive Assessment ; PDQ-39, Parkinson's Disease Questionnaire; Stim-ON/Med-OFF, Stimulation-ON/Medication-OFF; Stim-ON/Med-ON, Stimulation-ON/Medication-ON; STN-DBS, subthalamic nucleus deep brain stimulation.

The NFI was higher in the preoperative assessment than after STN-DBS for Med-OFF/Stim-ON to Med-ON/Stim-ON (preoperative Med-OFF to Med-ON NFI mean 49 (40.22), postoperative Med-OFF/Stim-ON to Med-ON/Stim-ON NFI mean 13.46 (27.87)) (figure 1B). Using a mixed-effects model and correcting for sex, disease duration and preoperative and postoperative levodopa challenge dose, postoperative NFI decreased by 35.54% compared with the preoperative NFI (95% CI 49.3 to 21.8, p<0.001), reflecting an improvement in neuropsychiatric fluctuations (figure 1C).

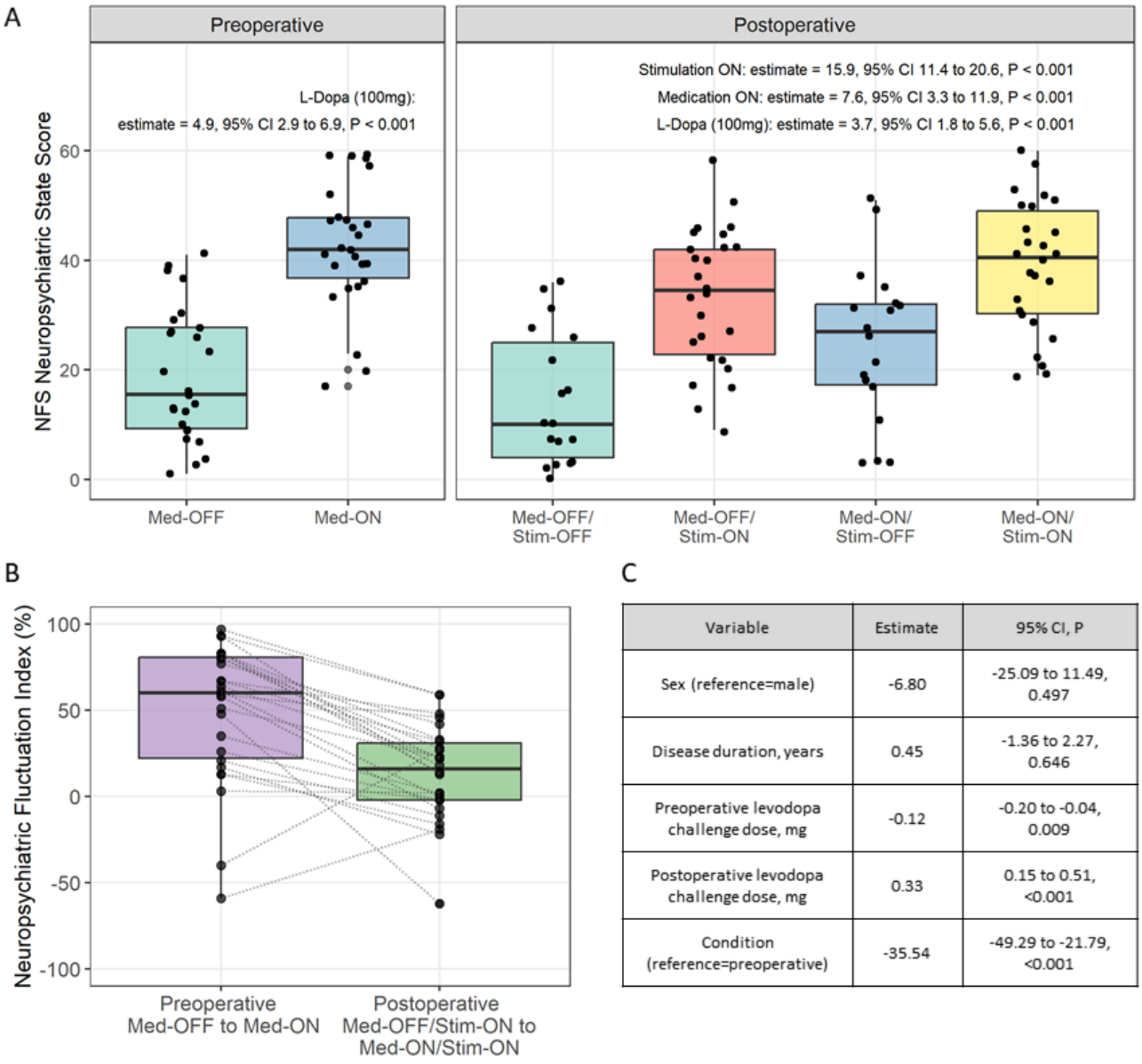
DISCUSSION

In this retrospective study, neuropsychiatric fluctuations during levodopa and stimulation challenge tests were quantified using the NFS,[9] from which we computed the Neuropsychiatric State Score and NFIs.

In order to assess the acute psychotropic effects of STN-DBS, we calculated a Neuropsychiatric State Score. During the stimulation and levodopa challenges, we observed that the Neuropsychiatric State Score was higher in stimulation-ON than stimulation-OFF and in medication-ON than medication-OFF. This suggests that STN-DBS by itself can have acute psychotropic effects similar to those induced by levodopa. Therefore, the NFS can be used to separately measure the acute and direct psychotropic effects of both levodopa and STN-DBS and can be useful for titrating drug and stimulation treatments.

The NFI, a percentage change score quantifying the modification of neuropsychiatric symptoms based on the NFS, was also calculated. We compared preoperative and 1-year postoperative levodopa-induced neuropsychiatric fluctuations. In our model, corrected for sex, disease duration and levodopa challenge dose, postoperative NFI

Figure 1



Variable	Estimate	95% CI, P
Sex (reference=male)	-6.80	-25.09 to 11.49, 0.497
Disease duration, years	0.45	-1.36 to 2.27, 0.646
Preoperative levodopa challenge dose, mg	-0.12	-0.20 to -0.04, 0.009
Postoperative levodopa challenge dose, mg	0.33	0.15 to 0.51, <0.001
Condition (reference=preoperative)	-35.54	-49.29 to -21.79, <0.001

Figure 1 (A) Neuropsychiatric State Score computed for the 26 patients in the medication-ON, medication-OFF and stimulation-ON conditions and 18 patients in the stimulation-OFF conditions. Estimates, 95% CI and p values were computed using a mixed-effects model. (B) NFI was computed for the 26 patients in the medication-ON, medication-OFF and stimulation-ON conditions and 18 patients in the stimulation-OFF conditions. 95% CI and p values were computed using a mixed-effects model with the variables stated in (C). (C) Parameter estimates, 95% CI and p-value for the mixed-effects model for the outcome NFI. NFI, Neuropsychiatric Fluctuation Index.

decreased by 35.54% compared with the preoperative NFI. This proposes that NFI might be useful in assessing the severity of neuropsychiatric fluctuations and suggests that STN-DBS can improve neuropsychiatric fluctuations. STN-DBS could modulate neuropsychiatric fluctuations by allowing a decrease in dopaminergic treatment and by its stable psychotropic effects being better tolerated than the pulsatile psychotropic effects of levodopa.[5]

Our findings that STN-DBS per se has psychotropic effects may seem counterintuitive when considering previous reports of apathy as a long-term side effect of STN-DBS.[11] However, it is important to distinguish between the acute and chronic effects of STN-DBS and to consider neuropsychiatric changes related to postoperative dopaminergic medication decrease and ensuing desensitisation. Most previous studies evaluating the effect of STN-DBS on neuropsychiatric symptoms were performed with long-term follow-up and used instruments that evaluate neuropsychiatric symptoms in a retrospective manner over timeframes of 1 month.[12] These have allowed an assessment of the chronic effects of STN-DBS that may not result solely from a direct effect of STN-DBS

but could be due to a combination of factors including postoperative medication management, postoperative dopaminergic desensitisation and disease progression.[11] Previous reports, which have assessed the short-term effects of STN-DBS, have used instruments adapted from other applications and have shown conflicting results. Whereas mood assessed with a visual analogue scale[13] and the Addiction Research Centre Inventory true/false questionnaire[14] has improved in the stimulation-ON condition, mood assessed using the Profile of Mood States rating scale was shown to remain stable during a stimulation challenge.[15] In the current study, we show that, in an acute challenge, STN-DBS at therapeutic stimulation parameters can induce direct psychotropic effects similar to an acute levodopa challenge. Moreover, at 1-year follow-up, STN-DBS can improve neuropsychiatric fluctuations induced by levodopa. This could be in part due to a desensitisation of the psychotropic effects of levodopa, which is supported by our finding that the estimated increase per 100 mg of acute levodopa in the Neuropsychiatric State Score is higher preoperatively than postoperatively and is likely to contribute to the reported improvement in impulse control behaviours with chronic STN-DBS.[5 11] Our findings also suggest that future clinical trials should consider neuropsychiatric fluctuations when selecting patients for STN-DBS in addition to current motor criteria. The NFS is a quick-to-administer scale that can be used repeatedly to assess neuropsychiatric symptoms in real time without relying on retrospective accounts from patients and caregivers.

This study has several limitations. There were no blinding or control groups. Additionally, it is important to acknowledge the limited availability of preliminary data from an ongoing validation study (NCT04366804), which does, however, suggest acceptable psychometric properties of the NFS.[9] Another limitation is the retrospective design. Due to a change in clinical routine, the first eight patients were only assessed postoperatively with an acute levodopa challenge (without stimulation challenge). Furthermore, because acute levodopa challenge doses were based on the current levodopa equivalent dose, preoperative and postoperative levodopa challenge doses were different, even if suprathreshold in both conditions, thus limiting the comparison between preoperative and postoperative conditions.

In conclusion, using a quick and easy-to-use self-rating tool, we show that an acute challenge of STN-DBS at therapeutic stimulation parameters has acute psychotropic effects similar to an acute levodopa challenge. At 1-year follow-up, STN-DBS modulates the psychotropic effects of levodopa and decreases neuropsychiatric fluctuations.

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Acknowledgements We thank Sue Zürcher, Saranya Saravanamuthu, Eva Bernhard, Julia Mathier and Margret Mäder for their help in the assessment of patients and Anita Zenger for study coordination.

Contributors 1. Research project: A. Conception, B. Organisation and C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique. ADM: 1A, 1B, 1C, 2A, 2B, and 3A. DA: 1A, 1B, 1C, 2A, 2C, and 3B. KP: 1A, 1B, 1C, 2A, 2C and 3B. ID: 1A, 1B, 1C and 3B. MS: 1A, 1B, 1C, 2A, 2C and 3B. MEMG: 1A, 1C and 3B. MLL: 1A, 1C and 3B. JW: 1A, 1C and 3B. SMC: 1A, 1C and 3B. AAD: 1A, 1C and 3B. GT: 1A, 1C and 3B. AN: 1A, 1C and 3B. CP: 1A, 1C and 3B. CRB: 1A and 3B. PMM: 1A and 3B. PK: 1A, 1B, 1C, 2A, 2C and 3B.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests ADM reports grants for attending meetings outside the submitted work by the European Academy of Neurology, the International Parkinson and Movement Disorder Society, Roche and Novartis. DA reports a research grant from Parkinson Schweiz outside the submitted work. MS reports travel expenses to attend scientific meetings from Boston Scientific outside the submitted work. GT reports funding from the Swiss National Science Foundation (project number: PZ00P3 202166) outside the submitted work. MMG reports funding from Fondation Bertarelli outside the submitted work. PMM was part of the team developing the Neuropsychiatric Fluctuations Scale. PMM reports honoraria from Bial for participation in a course and from the International Parkinson and Movement Disorder Society for activities during the International Congress 2022 and for directing the Clinical Outcome Assessment Programme outside the submitted work.PK was part of the team developing the Neuropsychiatric Fluctuations Scale. PK reports research or educational grants from the Swiss National Science Foundation (FNS 323530_177577/FNS 2020 32003BL_1 97 709–1/FNS 33IC30_198772), ROGER DE SPOELBERCH Foundation, Bertarelli Foundation, Annemarie Opprecht Foundation, Parkinson Schweiz, Michael J Fox Foundation, Aleva Neurotherapeutics, Boston Scientific, Medtronic, GE Healthcare, Idorsia, paid to employing institution; lecturing fees to employing institution from Boston Scientific, Bial, Advisis; travel expenses to scientific meetings from Boston Scientific, Zambon, Abbvie.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Bern Cantonal Ethics Committee (Amendement to 2020-02392). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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1. LEGENDS FOR SUPPLEMENTAL FILES

Supplementary Figure Legends

Supplementary Figure 1: A – Diagram of the patients included in the study.

Supplementary Figure 2: A – Subscore for the ON items of NFS computed for the 26 patients in the medication ON, medication OFF and stimulation ON conditions and 18 patients in the stimulation OFF conditions. **B** – Subscore for the OFF items of NFS computed for the 26 patients in the medication ON, medication OFF and stimulation ON conditions and 18 patients in the stimulation OFF conditions.

Supplementary Figure 3: A – Correlation of postoperative Neuropsychiatric State score in Med-ON/Stim-ON and postoperative MDS-UPDRS part IV score. **B** – Correlation of postoperative Neuropsychiatric State Score in Med-ON/Stim-ON and postoperative PDQ-39 score. Abbreviations: PDQ-39, The Parkinson's Disease Questionnaire

Magalhães AD, *et al. BMJ Neurol Open* 2024; 6:e000524. doi: 10.1136/bmjno-2023-000524

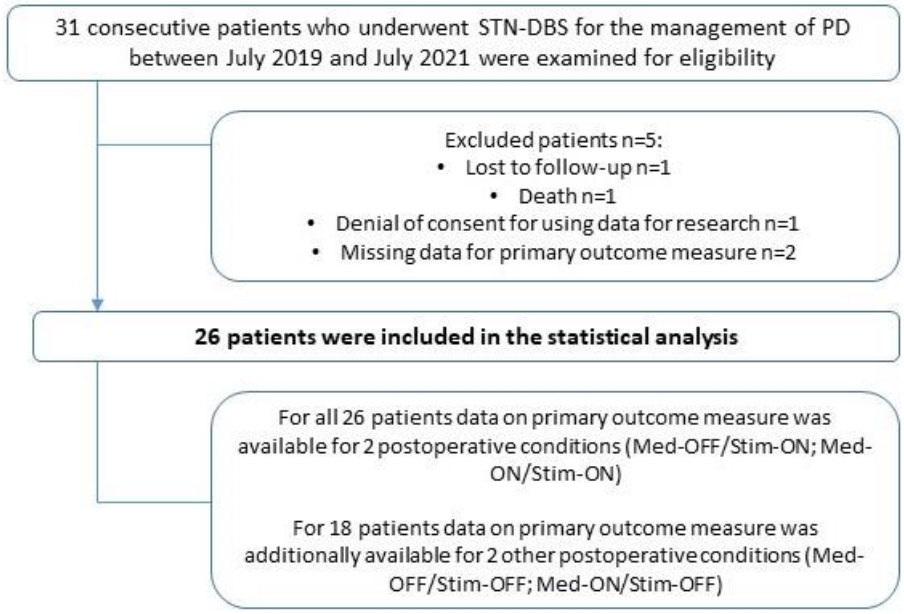
SUPPLEMENTARY TABLE 1

Supplementary Table 1: Items with missing data for demographic characteristics at baseline and clinical characteristics at preoperative and 12-month postoperative assessments. Abbreviations: MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; STN-DBS, Subthalamic Nucleus Deep Brain Stimulation; PDQ-39, Parkinson's Disease Questionnaire.

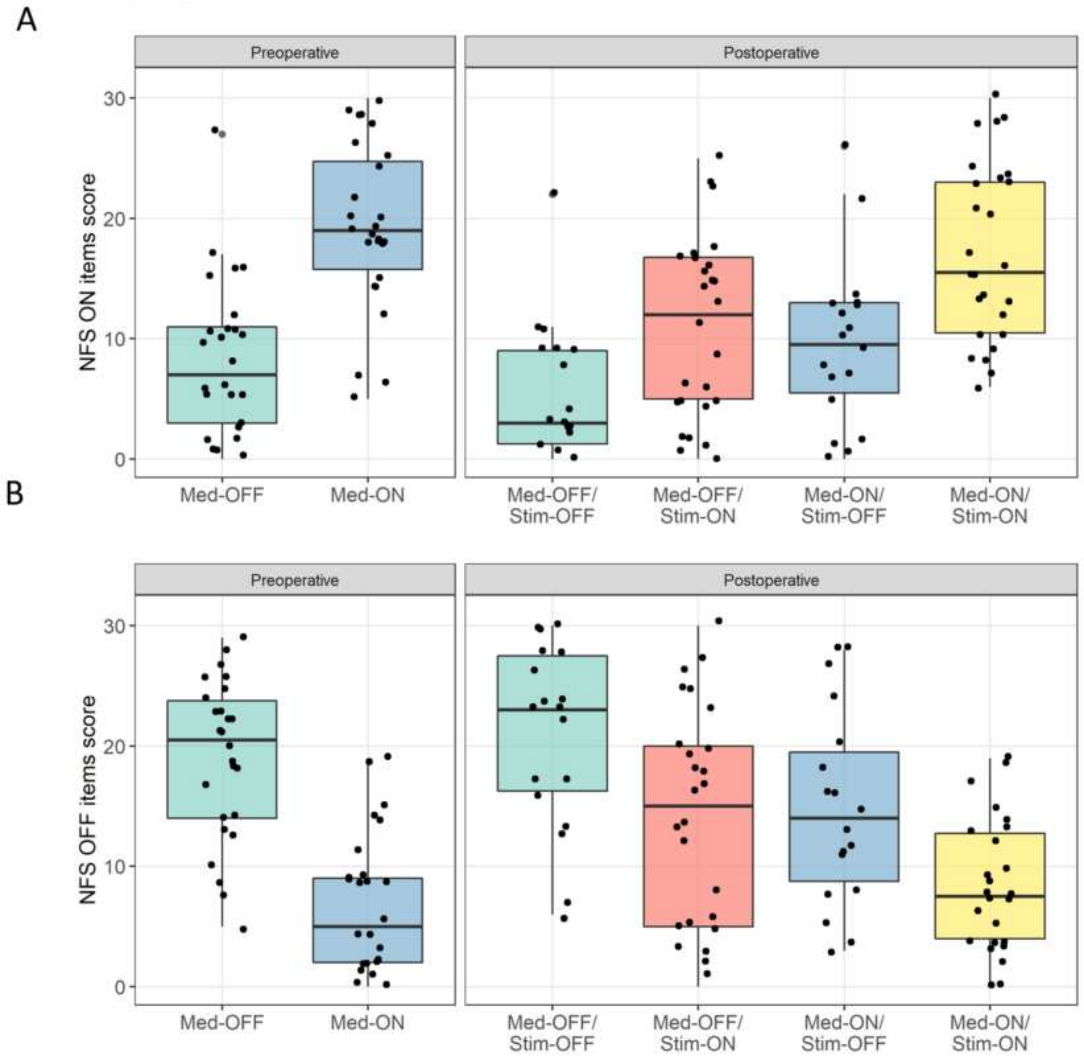
Demographic characteristics	**Missing data (%)**	
Sex (M/F)	0	
Age at onset	0	
Disease duration	0	
Education	1 (3.8)	
Clinical characteristics	**Preoperative** **Missing data (%)**	**Postoperative** **Missing data (%)**
Levodopa equivalent daily dose total [LEDD-total (mg/day)]	0	0
Levodopa equivalent daily dose levodopa [LEDD-LDopa (mg/day)]	0	0
Levodopa equivalent daily dose dopamine agonist [LEDD-DA (mg(day)]	0	0
Number of daily levodopa intake	0	0
Levodopa challenge dose	0	0
MDS-UPDRS part IA	3 (1.9)	12 (7.7)
Depressed mood (MDS-UPDRS part IA)	0	2 (7.7)

Anxious mood (MDS-UPDRS part IA)	0	2 (7.7)
Apathy (MDS-UPDRS part IA)	0	2 (7.7)
Dopamine dysregulation syndrome (MDS-UPDRS partIA)	0	2 (7.7)
MDS-UPDRS part IB	0	14 (7.7)
MDS-UPDRS part III	0	0
MDS-UPDRS part IV	4 (2.6)	12 (7.7)
MoCA	0	1 (3.8)
STN-DBS stimulation parameters	0	0
PDQ-39 Summary Index Score	22 (2.2)	6 (0.6)

SUPPLEMENTARY FIGURE 1



SUPPLEMENTARY FIGURE 2



SUPPLEMENTARY FIGURE 3