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

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ABSTRACT
Background Subthalamic nucleus deep brain stimulation (SN-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 7.6 points in medication ON conditions (95% CI 3.3 to 11.9, p<0.001) and a higher impact on quality of life than motor fluctuations.

INTRODUCTION
Non-motor symptoms affect most patients with Parkinson’s disease (PD) and can have a non-motor 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 does not only integrates motor but also associative and limbic cortico-basal ganglia circuits 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 PD7 or evaluate a longer retrospective time range8 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 ON and OFF 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. 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. We used the NFS scores to compute a new Neuropsychiatric State Score:

\[ \text{Neuropsychiatric State Score} = \text{Score ON items} + (30 - \text{Score OFF items}) \]

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):

\[ \text{NFI} = 100 \times \left(1 - \frac{\text{Neuropsychiatric State Score OFF condition}}{\text{Neuropsychiatric State Score ON condition}}\right) \]

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-ON mean (SD) of 19.16 (12.02) vs Med-OFF 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-ON 14.56 (12.13) vs Med-OFF/Stim-OFF 33.23 (12.64); Med-ON/Stim-ON 24.83 (14.33) vs Med-ON/Stim-OFF 39.11 (11.93)) The Neuropsychiatric State Score in Med-ON/Stim-ON moderately correlated with the PDQ-39 Summary Index but did not explain much of the variability of the data (p=0.007, R²=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).
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, 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
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.

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.\(^1\) 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.\(^2\) 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. 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 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. 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 post-operatively and is likely to contribute to the reported improvement in impulse control behaviours with chronic STN-DBS.

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 blind 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. 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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