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Pre-operative REM sleep behavior disorder and subthalamic DBS outcome in Parkinsons disease

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Franck Durif: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

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ABSTRACT

Objective: To determine whether Parkinson's disease (PD) patients eligible to subthalamic deep brain stimulation (STN-DBS) with probable REM sleep behavior disorder (RBD) preoperatively could be more at risk of poorer motor, non-motor and quality of life outcomes 12 months after surgery, compared to those without RBD.

Methods: We analyzed the preoperative clinical profile of 448 PD from a French multicentric prospective study (PREDISTIM), according to the presence or absence of probable RBD, based on the RBD Single Question and RBD Screening Questionnaire. Among the 215 PD patients with 12 months follow-up after STN-DBS, we compared motor, cognitive, psycho-behavioral profile and quality of life outcomes in patients with (preopRBD+) or without probable RBD preoperatively (preopRBD-).

Results: At preoperative evaluation, preopRBD+ were older (61 ± 7.2 vs. 59.5 ± 7.7 years; $p=0.02$), had less motor impairment (MDS-UPDRS III Off: 38.7 ± 16.2 vs. 43.4 ± 7.1 ; $p=0.03$) but more non-motor symptoms on daily living activities (MDS-UPDRS I: 12.6 ± 5.5 vs. 10.7 ± 5.3 ; $p<0.001$), more psycho-behavioral manifestations (ASBPD total: 7.7 ± 5.1 vs. 5.1 ± 0.4 ; $p=0.003$) and worse quality of life (PDQ39: 33 ± 12 vs. 29 ± 12 ; $p=0.03$), as compared to preopRBD-. Both preopRBD+ and preopRBD- had significant MDS-UPDRS IV score decrease (-37% and -33% respectively), MDS-UPDRS III "MedOff/StimOn" score decrease (-52% and -54%), and dopaminergic treatment decrease (-52% and -49%) after surgery, with no between group difference. There was no between group difference for cognitive and global quality of life outcomes.

Conclusions: In PD patients eligible to STN-DBS, the presence of probable RBD preoperatively is not associated with a different clinical outcome 1 year after neurosurgery.

Registration number: ClinicalTrials.gov: NCT02360683.

INTRODUCTION

Recent evidence suggests that Parkinson's disease (PD) patients with REM sleep behavior disorder (RBD) might exhibit a more severe phenotype,^{1,2} including greater motor disabilities and axial symptoms,^{3,4} dysautonomia,⁵ cognitive impairment,^{6,7} visual hallucinations,⁸ and impulse control disorders.^{9,10} Subthalamic nucleus Deep Brain Stimulation (STN-DBS) is a well-documented treatment for severe PD with motor fluctuations and dyskinesias.¹¹⁻¹³ However, some patients may demonstrate worsening of other symptoms following STN-DBS, such as apathy,¹² emergence of impulsive behaviors,¹² axial symptoms including freezing of gait, postural instability and dysarthria.¹⁴⁻¹⁷ Neuroimaging indicators have been proposed for guiding surgical decisions for DBS, such as connectivity profile,¹⁸ lower boundaries of T2-relaxometry in the STN reported to predict motor outcome,¹⁹ or accumbens nucleus volume reported as a marker of risk of cognitive decline after STN-DBS.²⁰ Yet, those tools are difficult to use in daily practice, and identifying PD patients at risk of negative outcomes after STN-DBS remains a challenge because there are currently few clinical indicators to determine patients most likely to benefit from this treatment.^{21,22} Up until recently, only two monocentric studies (conducted in 41 and 50 patients respectively) have assessed outcomes of PD patients with RBD undergoing STN-DBS, and reported conflicting results.^{23,24} The aim of this study was to investigate whether the presence of RBD before STN-DBS could impact motor, cognitive, psycho-behavioral and quality of life outcomes 12 months after STN-DBS, from a large French prospective cohort of PD patients, and to characterize the preoperative profile of PD patients with and without probable RBD.

MATERIALS AND METHODS

Patients:

This study was an ancillary analysis using data collected from the PREDISTIM cohort. PREDISTIM is an ongoing prospective multicentric cohort (Protocol 2013-A00193-42) sponsored by the University Hospital of Lille, conducted in 17 PD expert centers from the French clinical research network (NS-Park/F-CRIN). The primary objective was to study the predictive factors of the therapeutic response to STN-DBS on the long-term quality of life. Briefly, patients undergoing STN-DBS in each one of the participating centers were consecutively included into the study between 11/2013 and 09/2019. The inclusion criteria were a diagnosis of PD according to the United Kingdom Parkinson's Disease Brain Bank, disease duration ≥ 5 years, age between 18 and 75 years and indication of STN-DBS. Exclusion criteria included atypical parkinsonism, severe cognitive impairment, severe psychiatric disorders, acute levodopa motor response $< 30\%$ and contra-indications to surgery. Clinical data were collected at baseline, and then at one-year post-surgery.

Among 795 patients enrolled in the PREDISTIM cohort and awaiting STN-DBS at the time of the analysis (02/2019), 56% (n=448) completed RBD-SQ and/or RBD-1Q preoperatively and were included in our ancillary study. Indeed, RBD questionnaires were not initially part of the PREDISTIM study and this ancillary study began in 04/2015. The clinical and demographic characteristics of PD patients with (preopRBD+) and without (preopRBD-) probable RBD preoperatively were described in the whole population (n=448). Then we investigated the outcomes 12 months after STN-DBS, in terms of variations of motor, non-motor and quality of life scores compared to baseline, in a subset of patients (n=215) who had both pre- and postoperative evaluations (**Figure 1**).

The objective of this ancillary study was to determine whether PD patients with probable RBD preoperatively could be more at risk of poorer motor, non-motor and quality of life outcomes 12 months after STN-DBS. Data from patients with preoperative screening of probable RBD were included into the analysis.

Standard Protocol Approvals, Registrations, and Patient Consents:

This study was approved from CPP (Comité de Protection des Personnes) Nord Ouest-IV Ethical Committee and registered in the ClinicalTrials.gov website (NCT02360683), and registered registered in the ClinicalTrials.gov website (NCT02360683). Patients gave written informed consent, the study was conducted according to the good clinical practice, local regulations and data collection was compliant with GDPR (General Data Protection Regulation) rules.

Study design and clinical scores:

The diagnosis of probable RBD was assessed preoperatively using for each patient both the RBD Single Question (RBD1Q) and RBD Screening Questionnaire (RBDSQ) scores, that are validated as sensitive and specific tools for detecting RBD in general population,^{25,26} and in PD.^{27,28}

Probable preoperative RBD (preopRBD+) was defined by a positive response for RBD single question (RBD1Q) and / or a score ≥ 6 on the RBD Screening Questionnaire (RBDSQ) at pre-operative evaluation.^{25,29}

Clinical assessments at each visit included collection of demographic data, parkinsonism, neuropsychological testing, quality of life questionnaires, medical and treatment history. Parkinsonism evaluation was performed using the Movement Disorder's Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS),³⁰ which assesses non-motor and motor experiences of daily living (MDS-UPDRS I, II), motor examination (MDS-UPDRS III) and motor complications (MDS-UPDRS IV). MDS-UPDRS part I-IV, part III was performed in OFF and ON state during a standardized acute levodopa challenge

At baseline, motor assessment was performed using MDS-UPDRS Part III in the “Off” state, after 12-hr withdrawal of antiparkinsonian medication (Med Off), and in the “On” state, after taking 1.5 times the usual morning Levodopa dose using dispersible Levodopa (Med On). Twelve months after surgery, the efficacy of STN-DBS and of Levodopa was assessed in the morning after at least 12hrs of withdrawal of antiparkinsonian medication using MDS-UPDRS Part III in three conditions: “medication off – stimulation off” (MedOff/ StimOff), “medication off – stimulation on” (MedOff/ StimOn), and “medication on – stimulation on” (MedOn/ StimOn).

Comparison between baseline and 12 months after surgery were performed for MDS-UPDRS III Off, defined by the conditions “Med Off” preoperatively vs “MedOff/ StimOff” postoperatively and for MDS-UPDRS III On, defined by the conditions “Med On” preoperatively vs “MedOn/ StimOn” postoperatively. The effect of chronic STN-DBS was also evaluated comparing MDS-UPDRS III in “Med Off” condition preoperatively vs. “MedOff/ StimOn” postoperatively. The axial score was defined as the sum of the following motor subscores: speech, gait, posture, postural stability (items 18, 28, 29 and 30 of the MDS-UPDRS Part III).³¹

Cognitive functions were assessed using 11 validated tests in PD, according to the French consensus for the evaluation of cognitive functions in PD,³² which included the following; Montreal Cognitive Assessment (MoCA) for global efficiency;³³ Symbol Digit Modalities Test (SDMT) for attention and working memory; Digit Span Forward and Backward, Subtests 16-item Free/Cued Recall Test and 10/36 Spatial Recall Test for episodic memory; Oral Letter–Number Sequencing task and D-KEFS Color–Word Interference Test for executive function; Benton Judgement of Line Orientation and CLOX clock-drawing test for visuospatial function; Boston Naming Test and Animal fluency test for language.

Regarding psycho-behavioral symptoms, we used the French version of Ardouin Scale of Behavior in Parkinson's Disease (ASBPD) to assess hypo- and hyperdopaminergic disorders,

non-motor fluctuations and impulse-control disorder (ICD) (compulsive eating, hobbyism, punding, compulsive shopping, pathological gambling, hypersexuality, dopaminergic addiction)³⁴. For this scale, higher scores indicate worse mood and behavioral disturbances.

The Parkinson's Disease Questionnaire (PDQ 39) scale was used to assess quality of life. PDQ39 summary index (PDQ39-SI) ranges from 0 to 100; the higher the score indicates worse quality of life.³⁵

The Levodopa Equivalent Daily Dose (LEDD) was provided for each patient taking account of levodopa treatments, dopamine agonists, and other antiparkinsonian drugs such as MAO-B inhibitors, COMT inhibitors and amantadine.³⁶

Statistical analysis

Continuous data were expressed as mean and standard-deviation or median and interquartile range, according to statistical distribution. The assumption of normality was assessed by the Shapiro-Wilk test. Regarding non-repeated measures (such as comparison of baseline features between preopRBD+ and preopRBD-), continuous variables were compared between groups by Student t-test or Mann-Whitney test when the assumptions of t-test were not met. The homoscedasticity was analyzed using the Fisher-Snedecor test. Categorical parameters were compared between groups using chi-squared or Fisher's exact tests.

To compare baseline and one year after STN-DBS variations between preopRBD+ and preopRBD-, random-effects models were performed to measure time and group (preopRBD+ and preopRBD-) effects and their interaction time x group, taking into account between and within patient variability (subject as random-effect). This interaction corresponds to the difference of variation (absolute change between baseline and evaluation at M12) between preopRBD+ and preopRBD-. The normality of residuals from these models was studied using the Shapiro-Wilk test. When appropriate, a logarithmic transformation has been proposed to

achieve the normality of dependent outcomes. Then, multivariate analyses have been performed using adjustment on covariates fixed according to the univariate results and to the clinical relevance: age, sex, preoperative LEDD and preoperative MDS-UPDRS III off scores and baseline values of studied dependent outcomes. Random-effects models were also carried out to analyze intra-group variation for preopRBD+ and preopRBD- patients.

A sensitivity analysis was conducted to evaluate the statistical nature of missing data and their potential impact on results. More precisely, patients with and without follow-up at one year were compared for their baseline characteristics. As data were missing completely at random regarding each clinical variable, no imputation of data was applied.

Statistical analyses were performed using Stata software, version 15 (StataCorp, College Station, US). The tests were two-sided, with a type I error set at 5%. As analyses were exploratory, the individual p-values have been reported without applying systematically mathematical correction according to several works reported in the literature, but specific attention was given to the magnitude of differences and to clinical relevance.^{37,38} Indeed, it has been previously suggested that the choice and the number of tested hypotheses may be data dependent, which means that multiple significance tests can be used for descriptive purposes but not for decision making, regardless of whether multiplicity corrections are performed or not. Significant results based upon exploratory analyses should clearly be labeled as exploratory results. Conversely, the lack of multiple correction of the type I error cannot impact non-significant results.³⁹

Data availability:

The data that supports the findings of this study are available from the corresponding author, upon reasonable request.

RESULTS

Characteristics of the patients

Among 795 PD patients enrolled in the PREDISTIM cohort and awaiting STN-DBS, 448 completed RBDSQ and/or RBD1Q preoperatively. Out of them 330 patients underwent surgery at the time of our study, and 215 had a postoperative evaluation 12 months after STN-DBS (**Figure 1**).

Demographic and clinical profile of PD candidates to STN-DBS at preoperative evaluation according to the presence of probable RBD preoperatively.

We characterized the demographical and clinical profile of RBD+ and RBD- preoperatively in the whole group (n=448) (300 males; mean age: 63.3 ± 7.4 years; mean disease duration: 11.0 ± 4.3 years). Among 448 PD patients at baseline, 242 (54%) were preopRBD+, while 206 were preopRBD-. Motor symptoms, non-motor symptoms and quality of life of preopRBD+ and preopRBD- patients before STN-DBS are presented in **Table 1**.

PreopRBD+ were older ($p=0.02$), with a higher MDS-UPDRS I score ($p<0.001$) and lower MDS-UPDRS III score assessed in “MedOff” condition ($p=0.003$) compared to preopRBD-.

Regarding psycho-behavioral characteristics, ASBPD total score was significantly higher in preopRBD+ compared to preopRBD- ($p=0.03$). When considering each dimension of the scale, we observed higher scores in preopRBD+ for hypodopaminergic symptoms ($p<0.001$).

In contrast, non-motor fluctuations, hyperdopaminergic behaviors (including ICD subscores) did not differ between groups.

PDQ-39 SI score was significantly higher in preopRBD+ compared to preopRBD- ($p=0.03$), specifically for “emotional well-being” ($p<0.01$), “communication” ($p=0.02$), “social support” ($p<0.01$), “cognition” ($p<0.01$), and “bodily discomfort” ($p<0.01$) subscores.

Clinical outcomes of PD patients after STN-DBS according to the presence of probable RBD preoperatively

The analysis of clinical scores at 12 months and variation of scores between baseline and 12 months were performed on 215 patients (142 males; mean age: 60.3 ± 7.1 years; mean disease duration: 11.4 ± 4.4 years). To rule out different profile of this sample compared to the whole group, we compared demographic and clinical characteristics of both groups (**Table 2**). The groups with and without follow up at 12 months were comparable for all clinical data except for MDS-UPDRS I that was lower and MOCA that was greater in the group with a post-operative assessment (respectively 11.1 ± 5.1 vs 12.2 ± 5.7 ; $p=0.003$ for MDS-UPDRS I and 26.8 ± 2.3 vs 25.8 ± 3.2 ; $p<0.001$ for MOCA), although non-significant clinical size effect.

Among 215 PD patients who were assessed both preoperatively and 12 months after STN-DBS, 122 (57%) were preopRBD+, while 93 (43%) were preopRBD-. Parkinsonian, cognitive, psycho-behavioral symptoms, treatment doses and quality of life score variations between baseline and postoperative evaluation at 12 months depending on the presence of preopRBD are presented in **Table 3, 4, 5, 6**.

STN-DBS resulted in a mean decrease of MDS-UPDRS III MedOff scores compared to baseline (defined as the chronic effect of stimulation), by 52 % in preopRBD+ ($p<0.01$) and by 54 % in preopRBD- ($p<0.001$), with no between group difference (**Table 3**). MDS-UPDRS IV score significantly decreased by 37% ($p<0.01$) in preopRBD+, and by 33% ($p<0.01$) in preopRBD- with no between group difference. STN-DBS also led to a LEDD

total reduction compared to baseline in both groups (preopRBD+: -52%, $p < 0.01$ preopRBD-: -49%, $p < 0.01$), with no between group difference.

MDS-UPDRS I and MDS-UPDRS II significantly decreased in both groups, yet no between group difference of variation was observed. MoCA score decreased both in preopRBD- ($p < 0.05$) and in preopRBD+ ($p < 0.05$) after STN-DBS, yet without any significant group differences.

Regarding psycho-behavioral features, hyperdopaminergic total subscores significantly decreased in both groups, with no between group difference. There was no postoperative variation of hypodopaminergic total subscore in the preopRBD+ group, while it significantly worsened in preopRBD- ($p = 0.03$), however there was no significant between group difference. ASBP total score, and non-motor fluctuation sub-scores significantly decreased in both groups (**Table 4**).

PDQ39 SI scores significantly decreased in preopRBD- (-16%, $p < 0.01$) and in preopRBD+ (-8%, $p < 0.01$), with no between group difference. “Activities of daily living”, and “Stigma” subscores significantly decreased in both groups, whereas “Cognition” and “communication” sub-scores only decreased in preopRBD+ ($p < 0.01$), although none of these variations significantly differed between groups. “Bodily discomfort” was the only quality of life sub-score that, whilst significantly decreasing in both groups, decreased more significantly in the preopRBD+ group ($p = 0.04$) (**Table 5**).

At baseline, there was no difference between preopRBD+ and preopRBD- for any cognitive assessment except for CLOX copy for which preopRBD+ patients presented statistically better scores compared to preopRBD- ($p = 0.003$), although this difference was not clinically

significant since scores were in the normal range for both groups. There was no significant between group difference for postoperative variation of attentional, instrumental and memory functions assessed by the 11 cognitive tests, neither was there any between group difference at postoperative evaluation for these tests (**Table 6**).

Multivariate analysis taking into account the effect of age, sex, LEDD and MDS-UPDRS III Off scores at preoperative evaluation confirmed that there was no difference of variation 12 months after DBS-STN between preopRBD+ and preopRBD- for MDS-UPDRS II, IV, MoCA, ASPBD total and subtotal scores (**Table 7**).

DISCUSSION

Among PD candidates to STN-DBS, preopRBD+ patients were older, with milder motor symptoms, but with poorer non-motor aspects of daily living, more hypodopaminergic psycho-behavioral symptoms and decreased quality of life compared to preopRBD- at preoperative evaluation. Twelve months after STN-DBS, both preopRBD+ and preopRBD- had MDS-UPDRS IV score decrease (-37% and -33% respectively), MDS-UPDRS III MedOff decrease (-52% and -54%), and total LEDD decrease (-52% and -49%) after surgery, with no between group difference. There was no between group difference for cognitive, psycho-behavioral and global quality of life outcomes.

To our knowledge, this is the first study to assess motor and non-motor outcomes of STN-DBS depending on the presence of probable preoperative RBD in a large multicentric cohort of PD patients. So far, two prospective studies assessed the outcome of PD patients with and without preopRBD and reported conflicting results. The first one was conducted on 41 PD patients screened for probable preoperative RBD (12% of patients) using a semi-structured

clinical interview.²³ The second one was conducted on 50 PD patients, and RBD diagnosis was confirmed preoperatively by a night-polysomnography (48% of patients).²⁴

These studies did not report any significant difference between PD patients with and without preopRBD at baseline for motor symptoms assessed with UPDRS III Off, whereas in our study preopRBD+ patients had better motor performance than preopRBD-. These findings are in contrast with the concept that PD patients with RBD have usually greater motor disabilities and more axial impairment.^{40,41} Since we observed no difference at baseline for composite axial signs between preopRBD+ and preopRBD-, it is possible that we selected a subgroup of PD patients with RBD as good candidates for surgery, because those with axial signs such as freezing of gait or postural instability were not meeting STN-DBS criteria, thereby excluding a range of PD patients with associated RBD. Conversely, Zibetti *et al* suggested that more severe axial symptoms preoperatively in PD patients with preopRBD could account for the lower percentages of improvement of motor symptoms after STN stimulation that they reported in this group at 1 and 3 years.²³

The second study compared UPDRS II and UPDRS III absolute scores at baseline (“Med On” condition), and postoperatively (“MedOn /StimOn” condition 12 months after STN-DBS) in PD patients with and without PSG-confirmed RBD.²⁴ Aligned with our results, they report a significant improvement of UPDRS III On score in both groups, without between group difference. Moreover, UPDRS II On score did significantly improve in preopRBD+ whereas it remained stable in preopRBD-.²⁴

Global psycho-behavioral outcomes after STN-DBS did not differ between groups and total ASBPD score was improved in both groups. These results are in line with Bargiotas *et al* study showing that PD patients with RBD have greater apathy and depression symptoms than those without RBD at baseline, whereas no difference remained one year after STN-DBS.²⁴ In

the whole population of PD, the effect of STN-DBS on psycho-behavioral hypodopaminergic symptoms is debated, with studies reporting improvement,^{15,42} and others describing worsening.^{16,43–45}

Previous studies did not assess hyperdopaminergic outcomes after STN-DBS in PD patients with and without preop-RBD. The lack of association with ICD preoperatively in our study in the RBD+ group goes against the described association between RBD and ICDs in PD, and could be due to the selection of a non-representative “less severe” subgroup of PD patients with RBD as candidates for STN-DBS.^{46,47} Both groups improved after surgery for total hyperdopaminergic ASBPD, and for ICD subscores.

No between group difference was found for cognitive outcomes 12 months after surgery. Previous studies assessing STN-DBS outcome of PD with RBD did not investigate detailed cognitive functions, but only cognitive dimension of PDQ39. In the study of Bargiotas *et al*, no between-group difference was observed after STN-DBS for cognitive dimension of PDQ39. These findings probably reflect the selection of a specific subgroup of RBD+ patients fulfilling criteria for DBS STN, with better cognitive profile compared to what is generally reported in RBD patients. Indeed, cognitive impairment have been reported in PD patients with RBD compared to PD Patients without RBD and with controls,⁴⁸ and more particularly visuo-perceptive alterations seem to be specifically associated with RBD either idiopathic or secondary to PD.⁶ Moreover, preopRBD+ and preopRBD- patients did not differ for attentional tasks at baseline nor at postoperative evaluation, but both groups presented a significant postoperative decrease compared to baseline for SDMT, with no between group difference for variation. Our results are in line with attention/concentration impairment previously reported after STN DBS,⁴⁹ and suggest that preopRBD+ patients fulfilling STN

DBS criteria do not have a greater risk for increased attentional impairment one year after surgery compared to preopRBD-.

In both groups, global quality of life improves after surgery with no between group differences. However, while preopRBD+ have worse global quality of life preoperatively, it does not differ from preopRBD- 12 months after STN-DBS.

A number of limitations of this study must be identified. First, the lack of polysomnography confirmed diagnosis of RBD could lead to some PD patients having been mis-classified. Yet, in order to increase the sensitivity of the clinical diagnosis, two different screening tools were combined to detect the presence of symptoms of RBD, namely the RBD1Q and the RBDSQ. The latter showed a moderate to high sensitivity and specificity (0.842 and 0.962 respectively) using a cut-off ≥ 6 .²⁸ Furthermore, the limited access to video-polysomnography in clinical practice limited this examination on such an important multicentric cohort. Another limitation is that RBD status of patients was not controlled after STN-DBS, though STN-DBS has been reported to have an effect on RBD symptoms and could modify their prevalence postoperatively.^{50,51} Indeed, RBD symptoms may fluctuate along the evolution of PD,⁽⁴⁷⁾ but in spite of these clinical variations, the loss of muscle atonia during REM sleep, which is the polysomnographic feature of RBD, appears to be a long lasting marker in PD.⁵² Thus, a specific long-term trait seems to be associated with RBD, possibly in relation with a specific pattern of neurodegeneration, leading us to assess RBD as a predictor for STN-DBS outcome in that study. The lack of data regarding the location of electrodes and stimulation parameters should also be acknowledged and could interfere with postoperative results. However, we noted in our whole population an improvement of 52% for motor MDS-UPDRS scores in the “Off” medication state, a reduction of 36% for dyskinesia and a reduction of antiparkinsonian

drugs by approximately 36% after STN-DBS. Those results are close to the classically observed motor improvements of STN-DBS treatment, justifying the correct location of electrodes in this population.¹¹ It should also be acknowledged that, whilst we report the largest cohort available as of yet in a study focusing on the predictive role of probable RBD before STN-DBS, there are limits as to the inferences that this study will support given the limited sample of baseline patients with 12 months follow up. Moreover, these results are based on an early analysis one year after STN-DBS, and the follow up of the whole cohort three and five years after surgery will bring more light on the question of the long-term motor and non-motor prognosis associated with the presence of preoperative probable RBD.

CONCLUSION:

Altogether, our results suggest that the presence of probable RBD preoperatively is not associated with different motor, cognitive and global quality of life outcomes 1 year after STN-DBS. Total psycho-behavioral symptoms were also similarly improved in both groups. STN-DBS improves quality of life in PD patients regardless of the presence of preopRBD. Thus, although the presence of RBD has been previously reported to be associated with a more severe phenotype of PD, it does not seem to constitute a marker of risk of poor outcome after surgery in PD patients eligible to STN-DBS. Further studies, assessing long-term outcomes associated with the presence of RBD preoperatively 3 years and 5 years after surgery, will improve our comprehension of the specific prognosis associated with the presence of RBD in PD candidates to STN-DBS.

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Tables and Figures

Characteristics	preopRBD+ (n= 242)	preopRBD- (n = 206)	p
Sex (male : female)	169 : 73	131 : 75	0.16
Age (yr)	61.0 ± 7.2	59.5 ± 7.7	0.02
Total LEDD (mg/day)	1330 [1074-2252]	1324 [963-1696]	0,58
Dopamine-Agonist LEDD (mg/day)	240 [150-356]	300 [160-460]	0.06
Duration of disease (yr)	11.3 ± 4.5	10.8 ± 4.1	0.32
Duration since onset motor complications (yr)	6.0 ± 3.6	5.9 ± 3.4	0.78
MDS-UPDRS I (score 0 to 16)	12.6 ± 5.5	10.7 ± 5.3	<0.001
MDS-UPDRS II (score 0 to 52)	18.6 ± 8.8	18.5 ± 8.5	0.98
MDS-UPDRS III Off (score 0 to 108)	38.7 ± 16.2	43.4 ± 7.1	0.003
MDS-UPDRS III On (score 0 to 108)	9.1 ± 7.1	10.1 ± 7.6	0.24
MDS-UPDRS IV (score 0 to 23)	8.6 ± 3.5	8.4 ± 3.4	0.60
Axial Score On (score 0 to 16)	1.1 ± 1.6	1.0 ± 1.5	0.58
Axial Score Off (score 0 to 16)	4.5 ± 3.8	5.0 ± 3.9	0.23
MoCA (score 0 to 30)	26.3 ± 2.7	26.4 ± 3.1	0.64
ASBPD total (score 0 to 84)	7.7 ± 5.1	5.1 ± 0,4	0.003
Hypodopaminergic disorders subscore (score 0 to 20)	3.1 ± 2.5	2.8 ± 2.3	<0.001
Neuropsychiatric fluctuations subscore (score 0 to 8)	1.4 ± 1.5	0.7 ± 1.2	0.52
Hyperdopaminergic disorders subscore (score 0 to 56)	3.1 ± 2.9	0.8 ± 1.8	0.39
ICD subscore (score 0 to 28)	0.6 ± 1.1	0.5 ± 0.8	0.33
PDQ 39 Summary Index (score 0 to 100)	33±12	29±12	0.03
Mobility	37±20	36±22	0.53
Activites of daily living	37±19	38±20	0.60
Emotional well-Being	37±18	29±17	<0.01
Communication	28±19	24±18	0.02
Social support	15±18	10±15	<0.01
Cognition	34±16	23±15	<0.01
Stigma	35±23	33±23	0.20
Bodily Discomfort	49±21	41±20	<0.01

Table 1: Clinical and demographical features of PD patients candidates to STN-DBS at preoperative assessment, according to the presence of probable RBD.

MDS-UPDRS= Movement Disorder's Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; LEDD = Levodopa Equivalent Daily Dose; ASBPD = Ardouin Scale of Behavior in Parkinson's Disease; ICD = Impulse control disorders; PDQ-39 = Parkinson's disease Questionnaire 39.

Characteristics	Patients without postoperative 12 months follow up (n= 233)	Patients with postoperative 12 months follow up (n=215)	<i>p</i>
Age (yr)	60.3 ± 7.7	60.3 ± 7.1	0.93
Sex (male : female)	158 :75	142 :73	0.69
Probable RBD	120 (51.5%)	122 (56.7%)	0.27
Total LEDD (mg/day)	1442 [965-1588]	1541 [1000-1746]	0.16
Dopamine-Agonist LEDD (mg/day)	368 [150-374]	370 [160-420]	0.22
Duration of disease (yr)	10.7 ± 4.1	11.4 ± 4.4	0.11
Duration since onset motor complications (yr)	5.8 ± 3.5	6.1 ± 3.5	0.38
MDS-UPDRS I (score 0 to 16)	12.2 ± 5.7	11.1 ± 5.1	0.03
MDS-UPDRS II (score 0 to 52)	18.8 ± 9.7	18.2 ± 7.3	0.93
MDS-UPDRS III Off (score 0 to 108)	39.8 ± 17.1	42 ± 16.2	0.05
MDS-UPDRS IV (Score 0 to 23)	8.2 ± 3.5	8.8 ± 3.3	0.05
Axial Score On (score 0 to 16)	4.8±4.0	4.6±3.7	0.93
Axial Score Off (score 0 to 16)	1.1±1.4	1.1±1.8	0.55
MOCA (score 0 to 30)	25.8 ± 3.2	26.8± 2.3	0.005
ASBPD total ((score 0 to 84)	6.87 ± 4.7	7.65 ± 5.1	0.12
PDQ39 (score 0 to 100)	30.5 ± 13.10	31.2 ± 11.2	0.58

Table 2. Preoperative clinical and demographic features of PD candidates to STN-DBS, according to the presence of a postoperative follow up 12 months after surgery. RBD: REM sleep behavior disorder; LEDD = Levodopa Equivalent Daily Dose MDS-UPDRS= Movement Disorder's Society Unified Parkinson's Disease Rating Scale; PD = Parkinson Disease; RBD = Rapid eyes movement sleep Behavior Disorder; MoCA: Montreal cognitive assesemnt; ASBPD: Ardouin scale of behavior in Parkinson's disease; PDQ39: Parkinson's disease quality of life 39 scale

	preopRBD+ (n = 122)			preopRBD- (n= 93)			p	p‡
	Baseline	12 months	% change from baseline	Baseline	12 months	% change from baseline		
MDS-UPDRS I (score 0 to 16)	11.7 ± 5.1	10.1 ± 5	-16% [-43; 25]*	10.2 ± 4.8	10.0 ± 5.3	-11% [-42; 25]	0.03	0.14
MDS-UPDRS II (score 0 to 52)	18.3 ± 7.2	15.8 ± 8	-15% [-10; 11]*	18 ± 7.4	15.7 ± 8.2	-13% [-45; 30]*	0.80	0.57
MDS-UPDRS III (score 0 to 108)								
Med Off preop vs. MedOff/StimOff postop	39.7 ± 15.2	40.7 ± 15.9	2.7% [-17; 33]	45.1 ± 17.1	48 ± 18.2	1.7% [-18; 41]	0.01	0.63
Med On preop vs. MedOn/StimOn post op	10.1 ± 7.1	9.9 ± 7.2	15% [-45; 50]	10.2 ± 7	10.5 ± 8.6	0% [-44; 100]	0.78	0.64
Med Off preop vs. MedOff/StimOn postop	39.7 ± 15.2	20 ± 11.4	-52 % [-28; 65]*	45.1 ± 17.1	23. ± 13.6	-54% [-25; 67]*	n.a.	0.28
MDS-UPDRS IV (score 0 to 23)	8.9 ± 3.4	5.4 ± 3.2	-37% [-67; -9]*	8.7 ± 3.1	5.8 ± 3.1	-33% [-54; 10]*	0.77	0.43
MoCA (score 0 to 30)	26.9 ± 2.4	25.4 ± 3.7	-3% [-10; 0]*	26.8 ± 2.4	25.4 ± 3.1	-4% [-9; -2]*	0.90	0.85
Total LEDD (mg/day)	1341 [998-1750]	799 [486 - 1098]	-52% [-77; -25]*	1333 [1000-1740]	562 [280- 1050]*	-49% [-66; - 17]*	0.75	0.22

Table 3: Parkinsonian, cognitive symptoms and quality of life before and after bilateral STN-DBS in 215

PD patients, according to the presence of probable RBD preoperatively

*MDS-UPDRS= Movement Disorder's Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; LEDD = Levodopa Equivalent Daily Dose; PDQ-39 = Parkinson's disease Questionnaire 39; *: significant variation compared to baseline; p: between group comparisons of absolute values at baseline; p‡: between-group comparisons of variation between baseline and 12 months after DBS-STN;*

	preopRBD+		preopRBD-		p	p‡
	Baseline	12 months	Baseline	12 months		
ASBPD (score 0 to 84)	8.05 ± 5.2	6.14 ± 4.70*	7.12 ± 4.8	5.09 ± 3.9*	0.14	0.98
Hypodopaminergic disorders subscore (score 0 to 20)	3.16 ± 2.36	3.01 ± 2.07	2.26 ± 1.9	2.87 ± 2.3*	0.003	0.06
Non-motor fluctuations subscore (score 0 to 8)	1.41 ± 1.45	0.78 ± 1.19*	1.49 ± 1.29	0.66 ± 1.2*	0.46	0.68
Hyperdopaminergic disorders subscore (score 0 to 56)	3.47±3.27	2.35±3.25*	3.36±3.20	1.55±2.10*	0.61	0.26
ICD subscore (score 0 to 28)	0.91 ± 1.17	0.64 ± 1.14*	0.70 ± 1.04	0.47 ± 0.76	0.11	0.68

Table 4: Ardouin scale of behavior in PD before and after bilateral STN-DBS in 215 PD patients, according to the presence of probable RBD preoperatively.

ASBPD = Ardouin Scale of Behavior in Parkinson's Disease, ICD = impulse control disorders; *: $p < 0.05$ for within group comparison of absolute values between baseline and 12 months after STN-DBS; *: significant variation compared to baseline; p: between group comparisons of absolute values at baseline; p‡: between-group comparisons of variation between baseline and 12 months after DBS-STN

	preopRBD+ (n=122)			preopRBD- (n=93)			p	p‡
	Baseline	12 months	%	Baseline	12 months	%		
Summary Index (score 0 to 100)	32.7 ± 11.8	30.1 ± 12.4	-8% [-31; 13]*	29.1 ± 10.0	25.6 ± 13.2	-16% [-50; 7]*	0.04	0.48
Mobility	38.2 ± 21.1	36.7 ± 22.1	-4% [-32; 42]	37.5 ± 19.3	32.4 ± 21.3	-21% [-46; 33]	0.70	0.29
Activities of daily living	38.2 ± 19.6	30.5 ± 18.4	-20% [-42; 23]*	39.7 ± 18.8	27.2 ± 17.5	-30% [-67; 10]*	0.76	0.20
Emotional well-Being	35.6 ± 17.1	33.4 ± 17.6	-11% [-33; 38]	31.0 ± 16.6	30.7 ± 18.2	0% [-33; 37]	0.04	0.49
Communication	26.8 ± 19.3	30.7 ± 20.6	0% [-40; 67]*	25.1 ± 18.5	25.6 ± 19.7	0% [-50; 50]	0.59	0.28
Social support	14.1 ± 16.4	16.2 ± 17.9	0% [-100; 50]	9.2 ± 13.9	13.3 ± 17.7	-50% [-100; 25]	0.01	0.66
Cognition	34.6 ± 16.8	28.2 ± 18.1	-13% [-57; 14]*	24.8 ± 14.8	22 ± 15.7	-8% [-62; 50]	0.0001	0.19
Stigma	35.2 ± 22.3	25.4 ± 20.1	-33% [-67; 0]*	34.4 ± 22.6	21.4 ± 19.7	-37% [-89; 0]*	0.79	0.33
Bodily Discomfort	50.6 ± 21.1	36.1 ± 20.6	-26% [-50; 0]*	39.6 ± 18.5	32.2 ± 21.2	-25% [-60; 25]*	0.0001	0.048

Table 5: Quality of life before and after bilateral STN-DBS in 215 PD patients, according to the presence of RBD preoperatively. PDQ-39 = Parkinson's disease Questionnaire 39 for quality of life; *: significant variation compared to baseline; p: between group comparisons of absolute values at baseline; p‡: between-group comparisons of variation between baseline and 12 months after DBS-STN

	preopRBD+ (n = 122)			preopRBD- (n= 93)			p	p [†]	p [‡]
	Baseline	12 months	% change from baseline	Baseline	12 months	% change from baseline			
Attention									
SDMT (score 0 to 150)	42.4 ± 9.3	37.9 ± 9.8	-11% [-22; 1]*	44.9 ± 10.5	39.3 ± 10.3	-13 [-22; -2]*	0.12	0.37	0.50
Memory									
<i>Digit Span Forward and Backward</i>									
Digit Span Forward (Score 0 to 16)	9.1 ± 2.37	8.6 ± 2.01	-8% [-17; 11]	9 ± 2.25	8.7 ± 2.04	0 [-17; 12]	0.81	0.79	0.61
Digit Span Backward (Score 0 to 16)	7.2 ± 2.17	6.7 ± 1.96	0% [-20; 14]*	7.5 ± 2.50	6.9 ± 2.28	-11 [-24; 14]	0.45	0.53	0.63
<i>Subtests 16-item Free/Cued Recall Test</i>									
Total free recall trial (Score 0 to 48)	15.3 ± 0.99	15.1 ± 1.16	0% [-6; 0]	15 ± 1.90	14.7 ± 1.85	0 [-7; 0]	0.33	0.09	0.24
Total cued recall score (Score 0 to 48)	45.8 ± 3.39	43.7 ± 6.17	-2% [-6; 2]*	45.6 ± 4.6	43.2 ± 6.7	0 [-8; 0]*	0.76	0.58	0.51
<i>10/36 Spatial Recall Test</i>									
Total free recall score (Score 0 to 30)	14.12 ± 5.64	14.29 ± 4.90	0% [-23; 29]	14.6 ± 4.46	13.8 ± 4.33	0 [-33; 27]	0.52	0.60	0.21
Delayed free recall trial (Score 0 to 10)	5.31 ± 2.18	5.3 ± 3.18	0% [-39; 34]	5.24 ± 2.17	4.95 ± 1.93	0 [-40; 50]	0.84	0.42	0.58
Executive function									
<i>D-KEFS Color-Word Interference Test</i>									
Inhibition (nb errors)	1.37 ± 1.62	2.03 ± 0.27	-2% [-48; 86]*	1.49 ± 1.76	2.41 ± 3.29	-2.5% [-40; 86]*	0.55	0.64	0.78
inhibition/switching (nb errors)	1.91 ± 1.84	2.20 ± 1.94	4,6% [-55; 93]	1.93 ± 2.27	2.42 ± 1.61	6,8% [-45; 73]	0.32	0.73	0.74
<i>Oral Letter-Number Sequencing task</i>									
Baseline task (s.)	6.91 ± 2.38	7.28 ± 3.01	0% [-14; 27]	7 ± 2.8	8 ± 2.93	12,5% [-9; 33]*	0.83	0.15	0.11
alternating task (s.)	39.8 ± 21.8	43.2 ± 22.2	8,8% [-10; 37]	39.4 ± 26	40.4 ± 20.5	8,8% [-9; 33]	0.93	0.44	0.77
errors (nb)	0.76 ± 1.10	0.69 ± 1.11	-55% [-100; 33]	0.53 ± 0.96	0.7 ± 1.07	-66,6% [-100; 0]	0.97	0.62	0.77

<i>Switching cost</i>	6.34 ± 4.22	6.46 ± 3.43	10.1% [-15; 45]	6.2 ± 4.05	5.4 ± 2.77	0.75% [-37; 25]	0.84	0.06	0.22
Language									
<i>Animal fluency test (1 min)</i>	21.5 ± 5.3	18.2 ± 5.2	-13% [-33; 0]*	21.5 ± 5.7	18.6 ± 6.22	-13.3% [-30; 2]*	0.96	0.67	0.60
<i>Boston Naming test (score 0 to 15)</i>	12.5 ± 2.17	12.52 ± 2.13	0% [-7; 8]	12.24 ± 2.71	12.0 ± 2.88	0% [-13; 7]	0.53	0.21	0.17
Visuospatial function									
<i>CLOX clock drawing</i>									
<i>Draw (score 0 to 15)</i>	13.3 ± 1.77	13.27 ± 1.74	0% [-8; 8]	13.16 ± 2.18	12.87 ± 2.07	0% [-7; 8]	0.70	0.22	0.90
<i>Copy (score 0 to 15)</i>	14.37 ± 1.0	14.07 ± 1.0	0% [-7; 0]*	13.73 ± 1.43	13.75 ± 1.16	0% [-7; 8]	0.003	0.10	0.16
<i>Benton Judgment of Line Orientation test (score 0 to 15)</i>	12.1 ± 2.06	12.2 ± 2.48	0% [-8; 15]	12.2 ± 2.01	11.5 ± 0.31	0% [-15; 8]*	0.80	0.09	0.052

Table 6: Cognitive functions 12 months before and after bilateral STN-DBS in 215 PD patients, according to the presence of probable RBD preoperatively. *SDMT= Symbol Digit Modalities Test; *: significant variation compared to baseline; p: between group comparisons of absolute values at baseline; p‡: between-group comparisons of variation between baseline and 12 months after DBS-STN*

	Coef.	P> z 	[95% Conf. Interval]
MDS-UPDRS I	-1.140	0.18	[-2.819; 0.537]
MDS-UPDRS II	-0.019	0.77	[-2.945; 2.191]
MDS-UPDRS IV	-0.191	0.75	[-1.393; 1.012]
MoCA	-0.345	0.38	[-1.129; 0.438]
ASBPD total score	-0.043	0.94	[-1.299; 1.211]
Hypodopaminergic disorders subscore	-0.679	0.05	[-1.375; 0.016]
Neuropsychiatric fluctuations subscore	0.109	0.59	[-0.298; 0.518]
Hyperdopaminergic disorders subscore	-1.588	0.25	[-2.272; 0.903]
ICD	0.055	0.74	[-0.279; 0.391]

Table 7. Multivariate analysis of between group comparison of variation between baseline and 12 months after STN-DBS adjusted on age, sex, preoperative LEDD and preoperative MDS-UPDRS III off scores.

MDS-UPDRS= Movement Disorder's Society Unified Parkinson's disease Rating Scale; LARS = Lille Apathy Rating Scale; MoCA = Montreal Cognitive Assessment; LEDD = Levodopa Equivalent Daily Dose; ASBPD = Ardouin Scale of Behavior in Parkinson's Disease; ICD = Impulse control disorders; PDQ-39 = Parkinson's disease Questionnaire for quality of life.

Figure 1. Flow-Chart of the study

