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sur l'évolution motrice, cognitive,
psycho-comportementale et sur la qualité de vie un an
après stimulation cérébrale profonde dans la Maladie de
Parkinson**

Elsa Besse-Pinot

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UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLOME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

Elsa BESSE-PINOT

Présentée et soutenue publiquement le 28 Mai 2020

Rôle prédictif de la présence de troubles du comportement en sommeil paradoxal en préopératoire sur l'évolution motrice, cognitive, psycho-comportementale et sur la qualité de vie un an après stimulation cérébrale profonde dans la Maladie de Parkinson

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Président du jury :

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1. INTRODUCTION

Préambule, contexte scientifique et clinique

La maladie de Parkinson représente la deuxième pathologie neurodégénérative après la maladie d'Alzheimer (1). Sa prévalence est estimée à 0.3/1000 dans la population générale des pays industrialisés (2) et concernerait 1% des sujets de plus de 60 ans (3). Son pronostic est grevé par la progression du handicap moteur et l'apparition dans 25 à 40 % des cas d'une démence, responsables d'une réduction de l'espérance de vie (4).

Historiquement, les études de neuropathologie ont mis en évidence une dégénérescence précoce des neurones dopaminergiques de la pars compacta de la substance noire, responsable des symptômes moteurs de la maladie associés à des dépôts anormaux de protéines alpha synucléines agrégées, formant des inclusions intra neuronales appelées corps de Lewy (5), (6). Plus tard, un schéma évolutif de la maladie a été proposé, comparable à celui des maladies à Prions, avec une progression rostro-caudale depuis le système nerveux périphérique jusqu'au système nerveux central (7). Ce modèle de progression rostro-caudale est néanmoins actuellement débattu. L'hypothèse actuelle est celle d'une atteinte neurodégénérative multi systémique hétérogène expliquant la coexistence de nombreux signes moteurs et non moteurs. Ce modèle a également permis d'expliquer l'existence d'une phase prodromale comportant une série de symptômes non moteurs tels que la constipation (8), l'anosmie (9), les troubles du comportement en sommeil paradoxal (TCSP) (10), la dysautonomie (11) ou la dépression (9), pouvant parfois précéder de plusieurs années l'apparition de la maladie. Ainsi, la triade parkinsonienne associant rigidité extra pyramidale, bradykinésie et tremblement de repos, s'explique par la déplétion dopaminergique des neurones de la substance noire se projetant sur le putamen dorsal du striatum. La dénervation dopaminergique mésolimbique et mésocorticale serait quant à elle à l'origine des troubles psycho-comportementaux et cognitifs tandis que la dénervation tubero-infundibulaire serait responsable de la dysautonomie (11) La dénervation intéresse également des systèmes non dopaminergiques comprenant l'atteinte des systèmes sérotoninergiques [14],

cholinergiques [15], noradrénergiques et adrénérgiques qui participerait respectivement à la genèse des troubles de l'humeur, des troubles du sommeil et troubles moteurs axiaux [16], symptômes qui s'avèrent alors non dopa-sensible.

Les troubles du comportement en sommeil paradoxal (TCSP) sont définis, selon la classification internationale des troubles du sommeil, comme des parasomnies du sommeil paradoxal et sont caractérisés par la perte de l'atonie musculaire, normalement présente, au cours du sommeil paradoxal, à l'origine d'une activité motrice involontaire semblant mimer le rêve (12). Les TCSP peuvent être idiopathiques ou associés à des pathologies neurologiques, essentiellement aux alpha-synucléopathies. Cependant, il a été montré que 81% des TCSP dit « idiopathiques » évoluent vers une alpha-synucléopathie après 16 ans de suivi, remettant en cause l'existence de forme idiopathiques (13). Alors que la prévalence des TCSP idiopathiques est faible, de l'ordre de 0.5 à 2 % (14,15) celle-ci est beaucoup plus élevée chez les patients atteints d'alpha-synucléinopathies, comprenant la maladie de Parkinson idiopathique, la démence à corps de Lewy (DCL) et l'atrophie multisystématisée (AMS) (16). Dans le cas de la maladie de Parkinson, la prévalence des TCSP irait de 19 à 70% (17).

Plusieurs études ont suggéré que la présence de TCSP dans la maladie de Parkinson pourrait constituer un sous-groupe distinct de patients avec un phénotype plus sévère, en particulier avec un déclin cognitif, des hallucinations et la présence plus marquée de troubles du contrôle des impulsions (18–20). Celle-ci pourrait également être associée à des symptômes axiaux plus importants et à une progression plus rapide des symptômes moteurs de la maladie (21), (22). La présence de TCSP chez les patients parkinsoniens pourrait donc conditionner le pronostic ainsi que la prise en charge, en suggérant par exemple une utilisation plus prudente des agonistes dopaminergiques chez ces patients-là, en raison du risque plus élevé d'hallucinations et de troubles du contrôle des impulsions.

La stimulation cérébrale profonde des noyaux subthalamiques (SCP-NST) a montré son efficacité pour le traitement de la MPI chez des patients présentant des fluctuations motrices sévères malgré une adaptation optimale du traitement médicamenteux (23). Elle consiste en l'implantation d'électrodes

au niveau du noyau sous-thalamique, qui sont reliées à un stimulateur réglable en intensité, en fréquence et en amplitude. Elle a prouvé son efficacité dans l'amélioration de la fonction motrice d'environ 50%, dans la diminution des complications motrices jusqu'à 70% et dans la réduction d'un peu plus de la moitié des doses de traitements dopaminergiques (24,25). Son effet sur la qualité de vie a également été bien démontré (26). Toutefois, il existe aussi des effets indésirables rencontrés au décours de la chirurgie. En dehors des rares complications directement liées à la procédure, les effets indésirables stimulo-induits concernent surtout l'apparition ou l'aggravation de troubles de la marche (freezing), de troubles posturaux (27) et d'une dysarthrie (24). Son effet sur les signes non moteurs reste à ce jour débattu. En effet, plusieurs publications rapportent une amélioration des symptômes hyper-dopaminergiques (28), qui serait essentiellement liée à la diminution du traitement dopaminergique, mais une aggravation de l'apathie et des troubles cognitifs (29). Néanmoins, il semble qu'il existe une grande variabilité dans ces résultats et ceci pourrait être directement lié au positionnement des électrodes de stimulation au sein du noyau subthalamique (30).

A l'heure actuelle, il reste difficile d'identifier en préopératoire les patients à risque d'une évolution péjorative après SCP-NST. Puisque les TCSP dans la maladie de Parkinson semblent associés à un plus fort risque de déclin cognitif (31), d'hallucinations (32), de trouble du contrôle des impulsions (33) et à des symptômes axiaux plus importants (21),(22), leur présence en préopératoire pourrait également être associée à de moins bons résultats de la stimulation cérébrale profonde subthalamique sur les signes moteurs et non moteurs. Or, les données de la littérature sur cette question sont rares et discordantes.

En effet, deux études (34) ,(35) ont évalué l'évolution après SCP-NST de patients présentant un TCSP en préopératoire (preopTCSP+) par rapport à des patients sans TCSP (preopTCSP-). D'un côté, Zibetti *et al* ont montré, sur une cohorte de 41 patients, que les patients présentant des preopTCSP+ avaient une évolution motrice significativement moins bonne 3 ans après SCP-NST, en particulier pour les symptômes axiaux (34). D'un autre côté, Bargiotas *et al* n'ont pas retrouvé de différence d'évolution

motrice 1 an après SCP-NST sur une cohorte de 50 patients, entre les patients avec et sans preopTCSP. Dans cette cohorte, il existait en revanche une amélioration des symptômes dépressifs, de l'apathie et des activités de la vie quotidienne chez les patients preopCSP+ comparativement aux patients preopTCSP-.

Hypothèses de travail et objectifs

Notre hypothèse est que la présence de TCSP en préopératoire chez les patients avec une maladie de Parkinson idiopathique, serait associée à une moins bonne évolution un an après SCP-NST sur le plan moteur, cognitif et psycho-comportemental, comparativement à des patients sans TCSP préopératoire.

L'objectif de notre étude est de comparer l'évolution des symptômes parkinsoniens moteurs, des complications motrices, des fonctions cognitives (efficacité globale, attention et mémoire de travail, mémoire épisodique, fonctions exécutives, fonctions visuospatiales, langage), des fonctions psycho-comportementales et de la qualité de vie 1 ans après la SCP-NST chez les patients parkinsoniens avec pTCSP+ par rapport aux patients pTCSP-.

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2. ARTICLE

Predictive role of REM sleep behavior disorder for subthalamic deep brain stimulation outcomes in Parkinson's disease

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Glossary:

PD = Parkinson Disease; **RBD** = Rapid eye movement sleep Behavior Disorder; **STN-DBS** = Subthalamic nucleus Deep Brain Stimulation; **LEDD** = Levodopa Equivalent Daily Dose; **UPDRS** = 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.

ABSTRACT

Backgrounds: Identifying PD patients at risk of negative outcomes after STN-DBS remains a challenge, and there are currently few clinical indicators allowing to target indications in patients that will most likely benefit of this treatment. Since the presence of REM sleep behavior disorder (RBD) in PD is associated with a more severe phenotype of the disease, we aimed to determine whether PD patients with RBD preoperatively (preop-RBD) could be more at risk of poorer motor and non-motor outcomes 12 months after STN-DBS

Methods: Data were obtained from the French multicentric cohort study Predi-Stim. Four hundred and forty-eight patients awaiting STN-DBS and screened for the presence of probable preop-RBD (RBD) were included. All these patients were assessed before STN-DBS, and 242 patients were also assessed 12 months after surgery. We compared parkinsonian symptoms, cognitive functions, psycho-behavioral profile, and quality of life between PD patients with (RBD+) and without probable preop-RBD (RBD-) at baseline and 12 months after DBS-STN.

Results: Among 448 PD patients at baseline, 242 (54%) were RBD+. Before surgery, RBD+ were older ($p= 0.02$), had better disabilities motor score ($p= 0.03$) but exhibited greater non-motor aspects of experiences of daily living ($p<0,001$) with more signs such as anxiety ($p=0.01$), depression ($p= 0.01$) and apathy ($p=0.01$), and poorer quality of life ($p= 0.03$), as compared to RBD-. Chronic bilateral STN-DBS improved parkinsonian symptoms and quality of life in both groups at 12 months, whereas it worsened cognitive function in both groups, with no between group differences of variation. At postoperative evaluation, LEDD dose was lower ($p= 0.05$) in RBD+ compared to RBD-. Hypodopaminergic symptoms did not differ anymore between group while and ICDs improved in RBD+ ($p=0.05$). Despite positive outcomes of psycho-behavioral, QoL remained poorer in RBD+ ($p= 0.04$).

Conclusions: The presence of RBD preoperatively is not associated with different motor and cognitive outcomes 1 year after STN-DBS, but seems to be associated with better psycho-behavioral outcomes, either for hypo-dopaminergic symptoms and ICDs, as compared to patients without RBD before surgery.

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by the loss of normal muscular atonia during REM sleep, with complex motor behavior and dreaming (1). This disorder is frequently associated with Parkinson Disease (PD) and others α -Synucleinopathy (2–4), and can even be present several years before the onset of motor symptoms (5). Recent evidences suggest that PD patients with RBD, might exhibit a more severe phenotype with greater motor disabilities, especially for axial symptoms, and more non-motors signs such as impulse control disorders, hallucination and increased cognitive impairment (6,7).

Subthalamic nucleus Deep Brain Stimulation (STN-DBS) is a well-documented treatment for severe PD with motor fluctuations and levodopa-induced dyskinesias (LIDs), allowing a dramatic improvement of quality of life and motor symptoms and a reduction in Levodopa equivalent daily doses (LEDD) (7,8,11). STN-DBS has also be shown to be effective in improving non-motor symptoms such sensory, dysautonomic and cognitive fluctuations, but also neuropsychiatric fluctuations and impulse control disorders (10,11). However, some patients also demonstrate worsening of other symptoms following STN-DBS with increased apathy (10), increased axial symptoms including freezing of gait, postural instability and dysarthria (12), and could also impact non-motor features outcomes (12,13). Identifying PD patients at risk of negative outcomes after STN-DBS remains a challenge, and there are

currently few clinical indicators allowing to target indications in patients that will most likely benefit of this treatment. Since the presence of RBD in PD is associated with a more severe phenotype of the disease, including higher risk of postural instability and freezing of gait,(14,15) dysautonomia,(16) impaired cognitive profile,(17,18) visual hallucinations,(19) and impulse control disorders,(20,21) we hypothesized that PD patients with RBD preoperatively (preop-RBD) could be more at risk of poorer motor and non-motor outcomes after STN-DBS. Up to now, only few studies assessed outcomes of PD patients with preop-RBD undergoing STN-DBS but reported conflicting results : the first one, focusing on motor symptoms, reported less improvement for parkinsonian symptoms in PD patients with preop-RBD, one year and three years after STN-DBS (21); conversely, another study did not show any difference for motor outcomes after STN-DBS between PD patients with and without preop-RBD, but highlighted greater improvement of hypodopaminergic symptoms in PD patients with preop-RBD compared to patients without RBD (22).

Thus, the aim of this study was to investigate whether the presence of RBD before STN-DBS could impact the motor, cognitive, psycho-behavioral outcomes and quality of life in PD patients 12 months after STN-DBS.

MATERIALS AND METHODS

This is an ancillary study of a multicentric prospective study PREDI-STIM whose main objective is to identify the predictive factors of quality of life response after Deep Brain Stimulation of the Sub-Thalamic Nucleus in PD patients (clinicalTrial.gov n°NCT02360683).

Patients:

All patients included met the condition of the Movement Disorder Society Clinical Diagnostic Criteria for the diagnosis of Parkinson's Disease (24) and the standard surgical criteria defined by moderate to severe levodopa related motor fluctuations despite optimal treatment adjustment. Patients were not included if they had a contraindication to surgery : age greater than 75 years, atypical Parkinson's disease, course of the disease less than 5 years, severe cognitive impairment or dementia (MoCA score <24 and DSMIV criteria), parkinsonian psychosis, dopa-sensibility<30%, severe cerebral atrophy or MRI abnormality, presence of another serious terminal pathology. The study was approved by the ethics committee (CPP Nord-Ouest IV) and all patients gave their informed consent.

Study design and clinical scores:

The diagnosis of probable RBD (RBD) was assessed preoperatively using the RBD-1Q and RBDSQ scores, both validated as sensitive and specific tools for detecting RBD (25,26).

Patients were divided in two groups depending on the presence of preop-RBD screened with a positive response for RBD-1Q and / or a score ≥ 6 for RBDSQ at preoperative evaluation (preop-RBD) (25,27). The two groups were compared at baseline and 12 months after STN-DBS (postoperative evaluation).

Parkinsonism evaluation was performed using the Unified Parkinson's Disease Rating Scale (UPDRS) (5) which assess non-motor and motor experiences of daily living (UPDRS I, II), motor examination (UPDRS III) and motor complications (UPDRS IV).

At baseline motor assessment was performed using UPDRS Part III in the 'Off' state after 12-h 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 acute efficacy of STN-DBS and of Levodopa was assessed in the morning after at least 12 h of withdrawal of antiparkinsonian medication using UPDRS Part III in three

conditions: ‘medication off – stimulation off’ (Med Off / Stim Off), ‘medication off – stimulation on’ (Med Off / Stim On), and ‘medication on – stimulation on’ (Med On / Stim On).

Comparison between baseline and 12 months after surgery were performed for UPDRS III Off defined by the conditions “Med Off” preoperatively vs “Med Off / Stim Off” postoperatively and for UPDRS III On defined by the conditions “Med On” preoperatively vs “Med On / Stim On” postoperatively. The effect of chronic STN-DBS was also evaluated comparing UPDRS III in “Med Off” condition preoperatively vs “Med Off / Stim On” postoperatively.

Cognitive functions were assessed using 11 validated tests in Parkinson's disease according to the French consensus for the evaluation of cognitive functions in Parkinson's disease (28) : Montreal Cognitive Assessment (MoCA) (29) for global efficiency; 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. Cognitive results were not normalized thus, we could not realize between groups comparisons of absolute value. However, intra group comparisons were performed between baseline and follow up, as well as between-groups comparisons of the percentage of variations.

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) (30). The presence of impulse-control disorders (ICDs) was defined by a scores ≥ 2 for at least one of the following items: eating behavior, hobbyism, punding, compulsive shopping, pathological gambling,

hypersexuality, dopaminergic addiction (subscores 5, 7, 8, 10, 11, 12, or 13) (16). For these two scales, higher scores indicate greater apathy and severe 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; being the higher the score, the worse the quality of life (31).

The Levodopa Equivalent Daily Dose (LEDD) was automatically provided for each patient taking account of levodopa treatments, dopamine agonists, and other antiparkinsonian drugs such as MAO-B inhibitors, COMT inhibitors and amantadine (32).

Statistical analysis

Statistical analyses were performed using Stata software, version 15 (StataCorp, College Station, TX, US). The tests were two-sided, with a type I error set at 5%. 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 using the Shapiro-Wilk test. Concerning non-repeated measures, continuous variables were compared between groups by Student t-test or Mann-Whitney test when assumptions of t-test were not met. The homoscedasticity was analyzed using the Fisher-Snedecor's test. Categorical parameters were compared between groups using chi-squared or Fisher's exact tests. The relationships between continuous variables were studied estimating correlation coefficients (Pearson or Spearman, according to statistical distribution with the Sidak's type I error correction due to multiple comparisons). Random-effects models for correlated data were performed to measure time and group effects and their interaction time x group, taking into account between and within patient variability (subject as random-effect). 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 outcome. Then, multivariable analyses have been

performed using adjustment on covariates fixed according to the univariate results and to the clinical relevance.

RESULTS

Characteristics of the patients

Among 448 patients awaiting STN-DBS who completed RBD-SQ and/or RBD-1Q, 330 patients underwent surgery when carrying out study. Two hundred and six patients were excluded from analysis either because of missing data (n=25), still waiting for surgery (n=93) or did not reach 12 months follow up after surgery (n= 88). Thus, baseline analysis was conducted on 448 patients, while 12 months analysis and comparison between baseline and 12 months were performed on 242 patients. (**Supplemental data. Flow chart**)

Our total population had a mean age of 63.3 ± 7.4 years, with a sex ratio of 300 men for 148 women and disease duration was 11.0 ± 4.3 years at baseline. In the whole group, STN-DBS allowed a mean decrease of UPDRS III Off from 52%, of UPDRS IV from 36% and a decrease of dopaminergic treatments from 52% at postoperative evaluation (12 months after STN-DBS) compared to baseline.

Among 448 PD patients at baseline, 242 (54%) had probable preop-RBD (RBD+), while 206 did not have probable preop-RBD (RBD-). At baseline, RBD+ were older ($p= 0.02$), but did not differ from RBD- for sex ratio, and disease duration (**Table 1**). Motors symptoms, non-motors symptoms and quality of life of RBD+ and RBD- preoperatively and 12-months after STN-DBS are resumed in **Table 2 and Table 3**.

Parkinsonian, cognitive, psycho-behavioral symptoms and quality of life at baseline:

UPDRS III score assessed in “Med Off” condition was significantly lower in RBD+ compared to RBD- ($p=0,003$), but there was no significant difference between groups for the UPDRS III scores in “Med On” condition. UPDRS I score was higher in RBD+ ($p < 0.001$) compared to RBD-. There was no significant between-groups difference for UPDRS II scores neither for UPDRS IV scores, neither for total LEDD dose.

The two groups were comparable for MOCA scores at baseline.

ASBPD total score was significantly higher in RBD- groups ($p =0.03$). When considering specifically each part of scale, we noticed significant differences between groups with RBD+ who exhibited more apathy, ($p = 0.019$), anxiety ($p= 0.01$) and depression signs ($p = 0.001$). In contrast, hyperdopaminergic behaviors, neuropsychiatric fluctuation and ICD subscores did not differ between groups.

PDQ-39 SI score was significantly higher in RBD+ comparing to RBD- ($p= 0.03$), especially for “emotional well-being” ($p<0.01$), “communication” ($p=0.02$), “social support” (<0.01), “cognition” ($p<0.01$), and “bodily discomfort” ($p<0.01$) (**Figure 1A**).

Parkinsonian, cognitive, psycho-behavioral symptoms and quality of life 12 month after STN-DBS

Twelve months after STN-DBS, UPDRS III score assessed in “Med Off / Stim Off” condition was lower in RBD+ ($p= 0.04$) compared to RBD-, with lower LEDD ($p = 0.05$). UPDRS I scores, UPDRS II scores in “Med Off / Stim On” condition, UPDRS III scores in “Med Off / Stim On“ and “Med On / Stim On” condition, UPDRS IV scores, MOCA and ASBPD total scores and sub-scores were not different in RBD+ compared to RBD-after STN-DBS.

PDQ 39 SI, and cognition subscore were significantly higher in RBD+ (respectively $p=0.04$ and $p=0.01$) compared to RBD-, but no significant difference was found for other PDQ 39 dimensions (**Figure 1B**).

Parkinsonian, cognitive, psycho-behavioral symptoms and quality of life variations between baseline and postoperative evaluation at 12 months

STN-DBS allowed a mean decrease of UPDRS III Off scores by 53% in RBD- ($p<0.001$) and by 52.2 % in RBD+ ($p<0.01$), while no postoperative variation of UPDRS III On compared to baseline was observed in both groups. UPDRS I score significantly decreased by 16% ($p<0.01$) in RBD+ group, whereas no significant variation was observed in RBD- group.

UPDRS II Off and UPDRS IV scores significantly decreased in both groups (respectively $p = 0,01$ for RBD- and $p < 0,01$ for RBD +; $p < 0,01$ for RBD- and RBD +).

MOCA score compare to baseline decreased in RBD- ($p < 0.05$) and in RBD+ ($p < 0.05$). There was no significant change whatever the group for attentional, instrumental and memory functions assessed by the use of 11 cognitive tests (**Supplemental Table 4**).

ASBPDP total score, hyperdopaminergic behaviors and neuropsychiatric fluctuation subscores significantly decreased in both groups. While, hypodopaminergic subscore worsened in RBD- ($p = 0.03$), it tended to be improved in RBD+ ($p = 0.65$).

PDQ39 SI scores decreased by 16% in RBD- ($p < 0.01$) and by 8% in RBD+ ($p < 0.01$). Considering sub scores, “Activities of daily living”, “bodily discomfort” and “Stigma” significantly decreased in both groups (respectively $p < 0,01$ for RBD- and RBD+; $p < 0,01$ for RBD- and RBD+; $p < 0,01$ for RBD- and RBD+) whereas “Cognition” sub score only decreased in RBD+ ($p < 0,01$) (**Figure 2**).

Finally, when comparing the percentage of variation from baseline to 12 months between groups, no significant difference was found and multivariate analysis adjusted on age, sex, LEDD and UPDRS III Off scores confirmed the provided results (**Supplemental Table 5**).

DISCUSSION

Among PD candidates to STN-DBS, RBD+ patients are older, present milder motor symptoms, but poorer non motor aspects of experiences of daily living with more hypodopaminergic psycho-behavioral symptoms and decreased quality of life compared to RBD- at preoperative evaluation. Twelve months after STN-DBS, RBD+ show milder motor symptoms when “Med Off / Stim Off” and no difference when “Med Off / Stim On”, with a smaller postoperative LEDD dose, compared to RBD-. In spite of a greater postoperative decrease of total LEDD in RBD+, there is no longer between group difference for hypodopaminergic symptoms 12 months after STN-DBS. Indeed, hypodopaminergic symptoms worsen after STN-DBS in RBD- while they remain unchanged in RBD+. ICDs improve postoperatively in RBD+, while they remain unchanged in RBD-. Quality of life appears poorer in RBD+ before surgery compared to RBD- and, even if it improves in both groups similarly, remains poorer in RBD+12 month after STN-DBS.

To our knowledge, this is the first study to assess motor and non-motor outcomes of STN-DBS depending on the presence of probable preop-RBD in such a large multicentric cohort of PD patients. So far, two prospective studies compared the outcome of PD patients with and without preop-RBD and reported conflicting results. The first one, was conducted on 41 PD patients who underwent STN-DBS and were screened for probable preop-RBD (12% of patients) using a semistructured clinical interview.(22) This study focused on motor outcomes one years and

three years after STN-DBS. The second one assessed motor and non-motor outcomes, and was conducted on 50 PD patients who underwent surgery. In that latter study, preop-RBD diagnosis was confirmed by a night-polysomnography (48% of patients).(23)

Those studies did not report any significant difference at baseline in motor symptoms assessed by UPDRS III Off between PD patients with and without preop-RBD, whereas in our study RBD+ patients have better motor performance than RBD-. These findings are surprising since studies generally report greater motor disabilities and more axial involvement in PD patients with RBD (33,34). Yet, it is likely that we selected as candidates for surgery a specific subgroup of PD patients with RBD because those with axial signs such as freezing of gait or postural instability were not meeting STN-DBS criteria, thereby excluding a large range of PD with associated RBD. The relatively low percentage of PD with preop-RBD observed in our study (54%) and in previous ones (12% and 48%), compared to the generally observed prevalence of RBD in PD population (60%) reinforces this hypothesis.(35) Moreover, the use of UPDRS III scores might not allow to assess axial symptoms, while the use of composite axial score, such as Zibetti *et al* did, highlighted difference in severity of axial symptoms between groups.(36)

The first study mentioned above investigated whether groups exhibited differences in the percentage of improvement of motor symptoms between baseline and postoperative evaluation (at 1 and 3 years) with STN stimulation alone or in combination with levodopa treatment. (22) They reported less improvement of UPDRS III scores in PD patients with preop-RBD, but only for “Med On/ Stim On” condition, whilst no difference compared to patients without preop-RBD for “Med Off /Stim On” condition. This can be partly explained by the presence of increased axial features in PD patients with preop-RBD in this study, which are less likely to

be improve with dopaminergic medication. The second one compared UPDRS II and UPDRS III scores absolute values at baseline (« Med On » condition), and postoperatively (“Med On / Stim On” condition one year after surgery). (23) After STN-DBS, UPRDS III On score improved significantly in both groups, but the change was comparable between the two groups, unlike reported in the aforementioned study. Moreover, UPDRS II On score did significantly improved in PD patient with preop-RBD contrary to PD patients with preop-RBD. Those apparently conflicting results are probably explained by the heterogeneity of methodology used to assess motors outcomes in these different studies.

Otherwise, while previous studies did not show any difference in the post-operative treatment variation between groups, we highlight greater decrease in dopaminergic treatment in RBD+ compare to RBD-. The postoperative decreased dopaminergic treatment in RBD+ cannot be explained by a better efficiency of stimulation alone on motor symptoms since these patients are not different from RBD- in “Med Off/ Stim On” condition (**Table 2. Supplemental Figure 3**). Neither do they differ for treatment induced complications such as dyskinesia/ fluctuations (UPDRS IV) or ICDs symptoms. Yet RBD- present increased hypodopaminergic symptoms after DBS-STN, whereas RBD+ stay stable on this aspect, which could explain the relative lack of decrease of treatment in the RBD- group, in an attempt to prevent worsening of this psycho-behavioral manifestation.

Regarding cognitive functions, there is no difference between groups at baseline and 12 months after surgery. However, RBD+ exhibit poorer subjective assessment in cognitive dimension of PDQ39 compared to RBD-, either before or after surgery. This suggest a more severe impact of a similar cognitive impairment in RBD+ on daily life functioning. Previous studies assessing

STN-DBS outcome of PD with RBD did not investigate cognitive functions, but the cognitive dimension of PDQ39 assessed by Bargiotas *et al*, was worst in RBD+ preoperatively, in line with our results, but did not differ compared to RBD- after STN-DBS. These discrepancies could be explained by a clear improvement in depression scores after STN-DBS in Bargiotas *et al* study, whereas no significant postoperative variation of depression score was observed in our study. Thus, alleviation of depressive symptoms may have diminished the negative impact of cognitive impairment in daily life functioning in that previous study.

Even if RBD+ have greater apathy, anxiety and depression preoperatively, they have no postoperative variation of severity for these symptoms, whereas RBD- patients worsen for total hypo-dopaminergic subscore. This finding suggests no deleterious effect of surgery on hypo-dopaminergic symptoms in RBD+, in spite of a greater decrease of dopaminergic treatment in that subgroup. These data are in line with Bargiotas *et al* study showing that RBD+ have greater apathy and depression symptoms than RBD- at baseline, whereas no difference remained one year after STN-DBS. (23) Altogether, hypodopaminergic symptoms appear to be relatively preserved from worsening in RBD+ patients after DBS-STN compared to RBD-. In the general population of PD, the effect of STN-DBS on hypodopaminergic symptoms is debated, with studies reporting improvement (13,37) and others describing worsening (38–41) of hypo-dopaminergic signs, and the postoperative decrease of dopaminergic treatment is not likely to solely explain the increase of apathy that can occur after STN-DBS (42). Thus, predictive factor for the occurrence of hypo-dopaminergic outcomes such as apathy after surgery are of crucial importance, and the presence of RBD before STN-DBS could indicate a reduced risk for such an evolution.

In regard to hyperdopaminergic symptoms, we found no between-group difference preoperatively, but our results reveal a postoperative decrease of ICDs in RBD+ whereas no significant variation for the presence of ICDs is reported after STN-DBS for RBD-. 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 for the RBD+ group goes against the generally described association between RBD and ICDs in PD (35), and could be due to the selection of a non-representative “less severe” subgroup of PD patients with RBD as candidates for DBS-STN. The decrease of ICDs after STN-DBS in the PD-RBD+ group compared to the RBD- could be related to greater reduction of dopaminergic treatment in the RBD+ group.

In both groups, global QoL improve after surgery, yet it remains worst in RBD+ either pre or post operatively compare to RBD-. One of our assumptions to explain that lack of improvement, is that even if surgery seems to provide benefit effect on non-motors signs especially hypodopaminergic signs, in RBD+, some others symptoms not clearly emphasized by UPDRS I such as dysautonomia, other sleep-wake disorders, could remain debilitating on daily life functioning. The use of another scale such as NMSS could have highlighted difference (43).

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 assigned. Yet, the screening of probable RBD was conducted using a validated scale with 72.6% of sensitivity, 65.7% of specificity for the diagnosis of RBD.(44) Furthermore, the limited access to video-polysomnography in clinical practice did not allow to perform this exam 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 (45,46). Indeed, RBD symptoms may fluctuate along the evolution of PD (47) but in spite of these clinical variations, a specific long-term trait is associated with RBD, probably in relation with a specific pattern of neurodegeneration in those patients, and is what we aimed to assess 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 postoperatively results. However, we noted in our whole population an improvement of 52% for motor 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 close to generally observed motor improvement, pleads for the correct location of the effective contacts (8,11).

CONCLUSION:

Altogether, our results suggest that the presence of preop-RBD is not associated with different motor and cognitive outcomes 1 year after STN-DBS, but could indicate relatively better psycho-behavioral outcomes, as RBD+ patients appear to be relatively spared from hypo-dopaminergic worsening and present a decrease of ICDs, as compared to RBD-. STN-DBS improves quality of life in PD patients regardless to the presence of preop-RBD but does not allow to erase the difference observed between those groups before surgery, suggesting other factors leading to worse quality of life are associated with RBD. 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 :

| Table 1: Clinical and Demographic features of PD patients with and without RBD preoperatively | | | |
|--|------------------------|-------------------------|----------------|
| Characteristics | pRBD + (n= 242) | pRBD – (n = 206) | p Value |
| Sex (male : female) | 169 : 73 | 131 : 75 | 0.16 |
| Age (yr) | 61.0 ± 7.2 | 59.5 ± 7.7 | 0.02 |
| LEDD (mg/day)^a | 1330 [1074-2252] | 1324 [963-1696] | 0,58 |
| Dopamine-Agonist therapy (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 |
| Abbreviations: PD = Parkinson Disease; RBD = Rapid eye movement sleep Behavior Disorder; LEDD = Levodopa Equivalent Daily Dose | | | |
| ^a : The dose of levodopa equivalent medication was calculated as the dose of dopamine agonist plus levopoda | | | |

Table 2: Parkinsonian and cognitive symptoms at baseline and after bilateral subthalamic deep brain stimulation in PD patients with and without RBD preoperatively.

| | pRBD+ | | | pRBD- | | | p | p [†] | p [‡] |
|----------------------------------|--------------------------------|-------------------------------|------------------------|-------------------------------|-------------------------------|------------------------|-----------------|----------------|----------------|
| | Baseline | 12 months | % change from baseline | Baseline | 12 months | % change from baseline | | | |
| UPDRS I | 12.6 ± 5.5 (n = 232) | 10.1 ± 5.1 * (n = 101) | -16% [-43; 25] | 10.7 ± 5.3 (n = 195) | 10.0 ± 5.4 (n = 76) | -11% [-42; 25] | <0.01 | 0.93 | 0.07 |
| UPDRS II Off | 18.6 ± 8.8 (n = 211) | 15.8 ± 8.0 * (n = 92) | -15% [-10; 11] | 18.5 ± 8.5 (n = 182) | 15.6 ± 8.2 * (n = 66) | -13% [-45; 30] | 0.98 | 0.11 | 0.89 |
| UPDRS III Off^a | 38.7 ± 16.2 (n=232) | 40.8 ± 15.9 (n = 103) | 2.7% [-17; 33] | 43.4 ± 7.1 (n = 200) | 48.3 ± 18.1 (n= 76) | 1.7% [-18; 41] | 0.003 | 0.04 | 0.92 |
| UPDRS III On^b | 9.1 ± 7.1 (n = 190) | 10.0 ± 7.3 (n = 104) | 15% [-45; 50] | 10.1 ± 7.6 (n = 151) | 10.7 ± 8.7 (n= 77) | 0% [-44; 100] | 0.24 | 0.95 | 0.95 |
| UPDRS IV | 8.6 ± 3.5 (n = 226) | 5.4 ± 3.2 * (n = 74) | -37% [-67; -9] | 8.4 ± 3.4 (n = 193) | 5.8 ± 3.1 * (n= 60) | -33% [-54; 10] | 0.60 | 0.47 | 0.45 |
| MOCA | 26.3 ± 2.7 (n = 216) | 25.4 ± 3.8 * (n = 92) | 3% [-10; 0] | 26.4 ± 3.1 (n = 188) | 25.4 ± 3.1 * (n = 75) | 4% [-9;-2] | 0.64 | 0.95 | 0.97 |
| LEDD totale | 1330 [1074-2252] (n=212) | 550 * [280-1050] (n=83) | -52% [-77; -25] | 1324 [963-1696] (n=177) | 774 * [486-1098] (n=66) | -49% [-66; -17] | 0.58 | 0.05 | 0.017 |

Abbreviations: UPDRS= Unified Parkinson's disease Rating Scale; LARS = Lille Apathy Rating Scale; MoCA = Montreal Cognitive Assessment; LEDD = Levodopa Equivalent Daily Dose.

UPDRS III range from 0 to 108, with higher scores indicating worse functioning. UPDRS-II range from 0 to 52, with higher scores indicating worse activities of daily living functioning. UPDRS-IV, range from 0 to 23, with higher scores indicating worse levodopa-induced complications UPDRS-I, range from 0 to 16, with higher scores indicating worse emotion and cognition functioning. MoCA range from 0 to 30, with higher scores indicating worse functioning. LARS range from -36 to 36, with higher scores indicating greater apathy.

UPDRS III Off^a were assessed "in Med Off" condition at baseline and in "Med Off/ Stim Off" condition 12 months after surgery

UPDRS III On^b were assessed "in Med On" condition at baseline and in "Med On/ Stim On" condition 12 months after surgery

*: p< 0.05 for within group comparison of absolute values between baseline and 12 months after DBS-STN

P : between group comparisons of absolute values at baseline

p[†] : between group comparisons of absolute values 12 months after DBS-STN

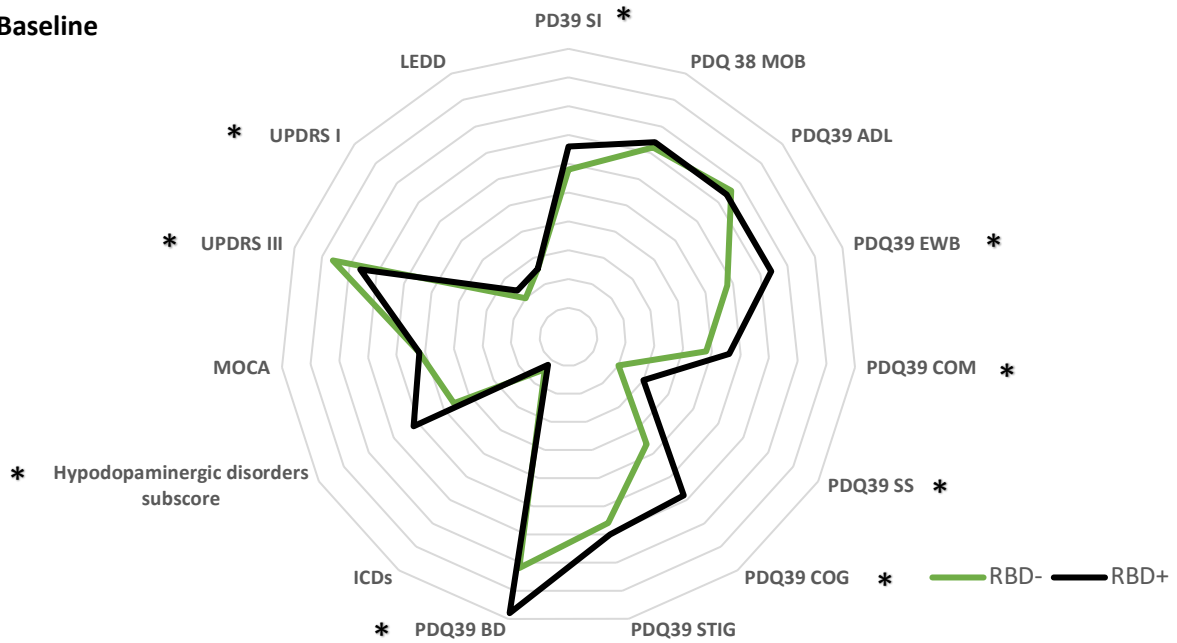
p[‡]: between-group comparisons of variation between baseline and 12 months after DBS-STN

Table 3: Behavioural outcomes at baseline and after bilateral subthalamic nucleus deep brain stimulation in PD patients with and without RBD preoperatively.

| | pRBD+ | | pRBD- | | p | p [†] | p [‡] |
|---|-----------------------|------------------------|-----------------------|-----------------------|-------------------|----------------|----------------|
| | Baseline (n = 230) | 12 months (n = 101) | Baseline (n = 193) | 12 months (n = 74) | | | |
| ASBPD | 7.7 ± 5.1 | 6.0 ± 0.5 * | 6.6 ± 4.6 | 5.1 ± 0.4 * | 0.003 | 0.15 | 0.80 |
| Hypodopaminergic disorders subscore | 3.1 ± 2.5 | 2.9 ± 2.1 | 2.3 ± 2.0 | 2.8 ± 2.3 * | > 0.001 | 0.68 | 0.06 |
| Depressed mood | 0.6 ± 0.8 | 0.67 ± 0.8 | 0.41 ± 0.7 | 0.56 ± 0.1 | 0.001 | 0.38 | 0.32 |
| Anxiety | 1.0 ± 0.9 | 0.73 ± 0.8 * | 0.77 ± 0.9 | 0.67 ± 0.9 | 0.01 | 0.68 | 0.17 |
| Irritability to aggressiveness | 0.34 ± 0.6 | 0.25 ± 0.50 | 0.28 ± 0.5 | 0.29 ± 0.6 | 0.30 | 0.64 | 0.32 |
| Hyperemotionality | 0.83 ± 0.86 | 0.75 ± 0.7 | 0.65 ± 0.7 | 0.76 ± 0.9 | 0.02 | 0.97 | 0.17 |
| Apathy | 0.36 ± 0.7 | 0.56 ± 0.8* | 0.22 ± 0.5 | 0.54 ± 0.8 * | 0.019 | 0.80 | 0.46 |
| Neuropsychiatric fluctuations subscore | 1.4 ± 1.5 | 0.8 ± 1.2 * | 1.3 ± 1.3 | 0.7 ± 1.2 * | 0.52 | 0.51 | 0.81 |
| Non-motor fluctuation OFF | 0.90 ± 0.9 | 0.53 ± 0.8 * | 0.80 ± 0.8 | 0.48 ± 0.9 * | 0.25 | 0.73 | 0.78 |
| Non-motor fluctuation ON | 0.56 ± 0.7 | 0.29 ± 0.6 * | 0.53 ± 0.7 | 0.19 * | 0.72 | 0.26 | 0.59 |
| Hyperdopaminergic disorders subscore | 3.1 ± 2.9 | 1.2 ± 2.6* | 2.8 ± 3.0 | 0.8 ± 1.8* | 0.39 | 0.74 | 0.31 |
| Hypomanic mood | 0.12 ± 0.3 | 0.11 ± 0.4 | 0.07 ± 0.3 | 0.1 ± 0.4 | 0.5 | 0.81 | 0.46 |
| Psychotic signs | 0.29 ± 0.5 | 0.13 ± 0.3 | 0.12 ± 0.3 | 0.12 ± 0.5 | > 0.001 | 0.92 | 0.08 |
| Nocturnal hyperactivity | 0.42 ± 0.8 | 0.2 ± 0.5* | 0.43 ± 0.8 | 0.09 ± 0.4* | 0.96 | 0.12 | 0.45 |
| Diurnal somnolence | 0.67 ± 0.7 | 0.51 ± 0.6 | 0.61 ± 0.7 | 0.46 ± 0.8 | 0.41 | 0.70 | 0.992 |
| Eating behaviour | 0.45 ± 0.6 | 0.46 ± 0.8 | 0.39 ± 0.7 | 0.36 ± 0.7 | 0.32 | 0.44 | 0.98 |
| Creativity | 0.19 ± 0.5 | 0.08 ± 0.3 | 0.28 ± 0.6 | 0.09 ± 0.3 * | 0.10 | 0.73 | 0.25 |
| Hobbysm | 0.25 ± 0.6 | 0.24 ± 0.6 | 0.25 ± 0.6 | 0.02 ± 0.2* | 0.99 | 0.001 | 0.035 |
| Punding | 0.14 ± 0.3 | 0.15 ± 0.3 | 0.12 ± 0.4 | 0.07 ± 0.2 | 0.64 | 0.19 | 0.73 |
| Risk task behaviour | 0.09 ± 0.3 | 0.07 ± 0.3 | 0.09 ± 0.3 | 0.09 ± 0.3 | 0.95 | 0.6 | 0.59 |
| Compulsive shopping | 0.10 ± 0.3 | 0.10 ± 0.4 | 0.10 ± 0.4 | 0.05 ± 0.2 | 0.89 | 0.38 | 0.53 |
| Pathological gambling | 0.09 ± 0.3 | 0.03 ± 0.2 * | 0.08 ± 0.3 | 0.02 ± 0.2 | 0.92 | 0.91 | 0.6 |
| Hypersexuality | 0.17 ± 0.5 | 0.05 ± 0.3* | 0.14 ± 0.4 | 0.05 ± 0.2 | 0.48 | 0.91 | 0.40 |
| Dopaminergic addiction | 0.11 ± 0.4 | 0.15 ± 0.5 | 0.11 ± 0.4 | 0.07 ± 0.3 | 0.88 | 0.19 | 0.42 |
| Excess motivation | 0.15 ± 0.4 | 0.15 ± 0.4 | 0.17 ± 0.4 | 0.07 ± 0.2 * | 0.66 | 0.13 | 0.174 |
| ICD | 0.6 ± 1.1 | 0.33 ± 0.8 * | 0.7 ± 1.0 | 0.5 ± 0.8 | 0.33 | 0.36 | 0.9 |

Abbreviations: ASBPD = Ardouin Scale of Behavior in Parkinson's Disease, ICD = impulse control disorders. ASBPD range from 0 to 84, with higher scores indicating worse functioning.
 *: p < 0.05 for within group comparison of absolute values between baseline and 12 months after DBS-STN
 P: between group comparisons of absolute values at baseline
 p[†]: between group comparisons of absolute values 12 months after DBS-STN
 p[‡]: between-group comparisons of variation between baseline and 12 months after DBS-STN

Baseline



12 months after STN-DBS

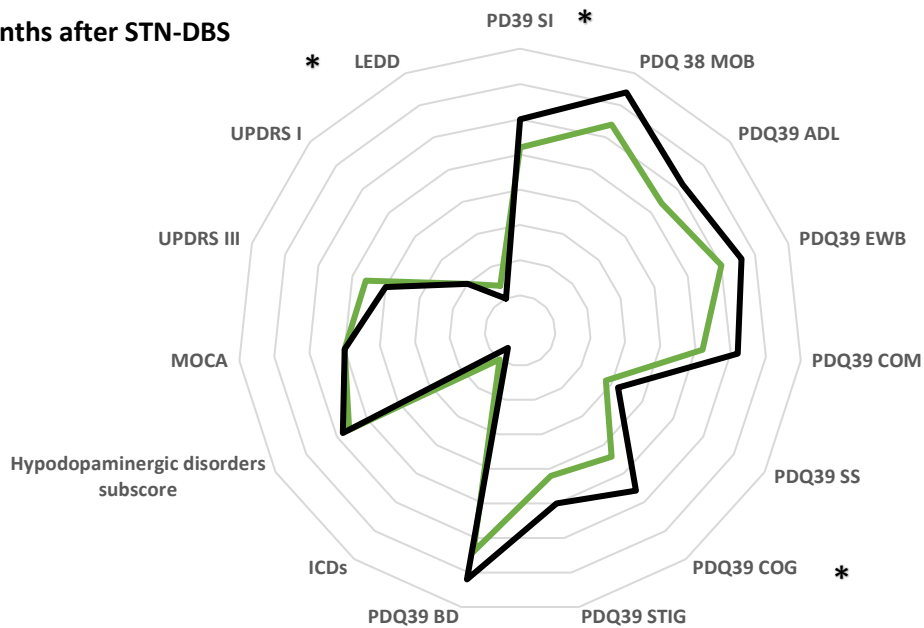
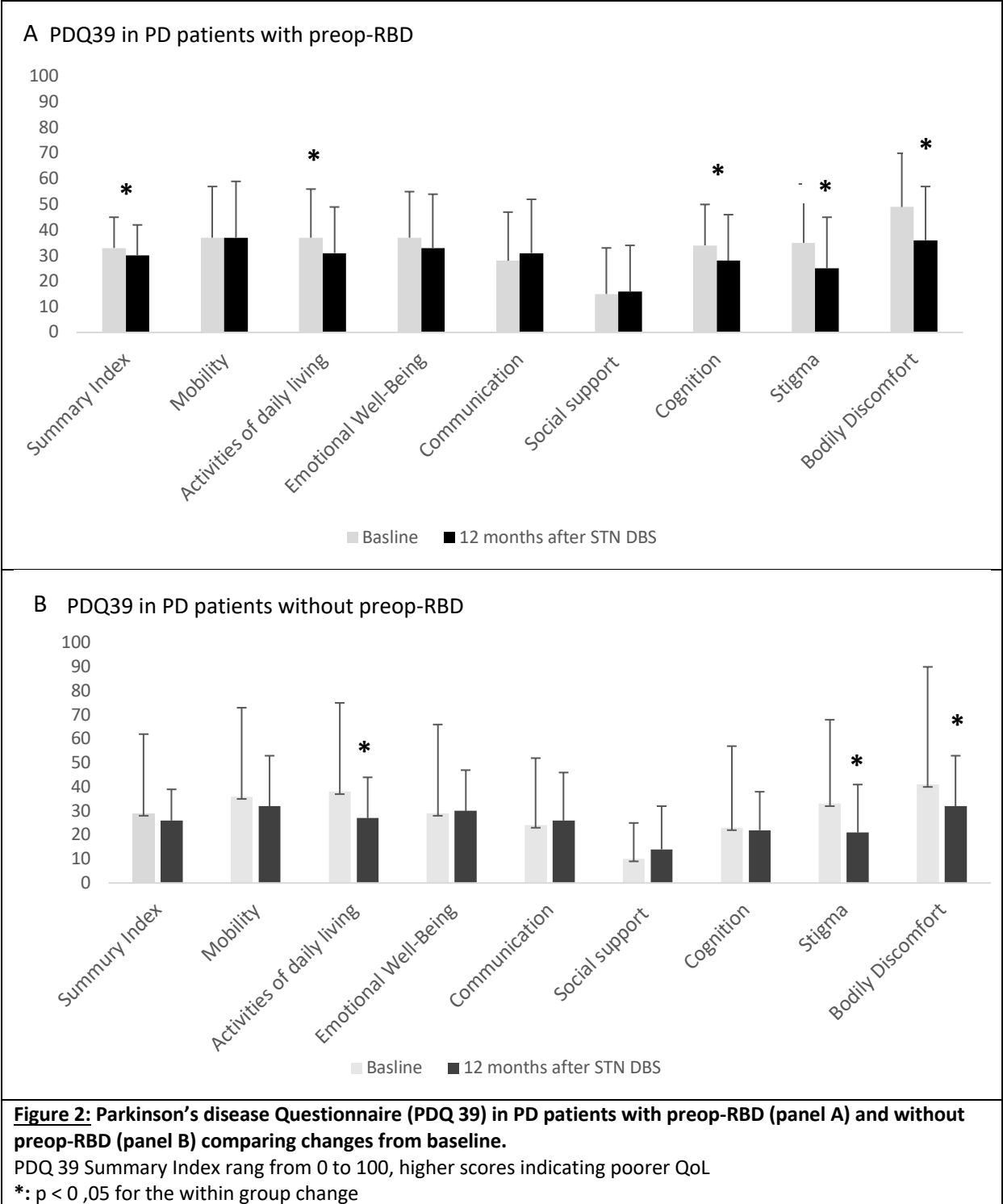


Figure 1 : Difference in motor symptoms, non-motor symptoms and quality of life at baseline and 12 months after bilateral subthalamic nucleus deep brain stimulation (SNT-DBS) in PD patients with and without preop-RBD.

Abbreviations: UPDRS= Unified Parkinson's disease Rating Scale; ICD = impulse control disorders; MoCA = Montreal Cognitive Assessment; LEDD = Levodopa Equivalent Daily Dose. PDQ39 SI = Parkinsons disease Questionnaire 39, MOB = Mobility, ADL = Activities of daily living, EWB = Emotional well-being, COM = communication, SS = social support, COG = Cognition, STIG = Stigma, BD = Bodily discomfort.

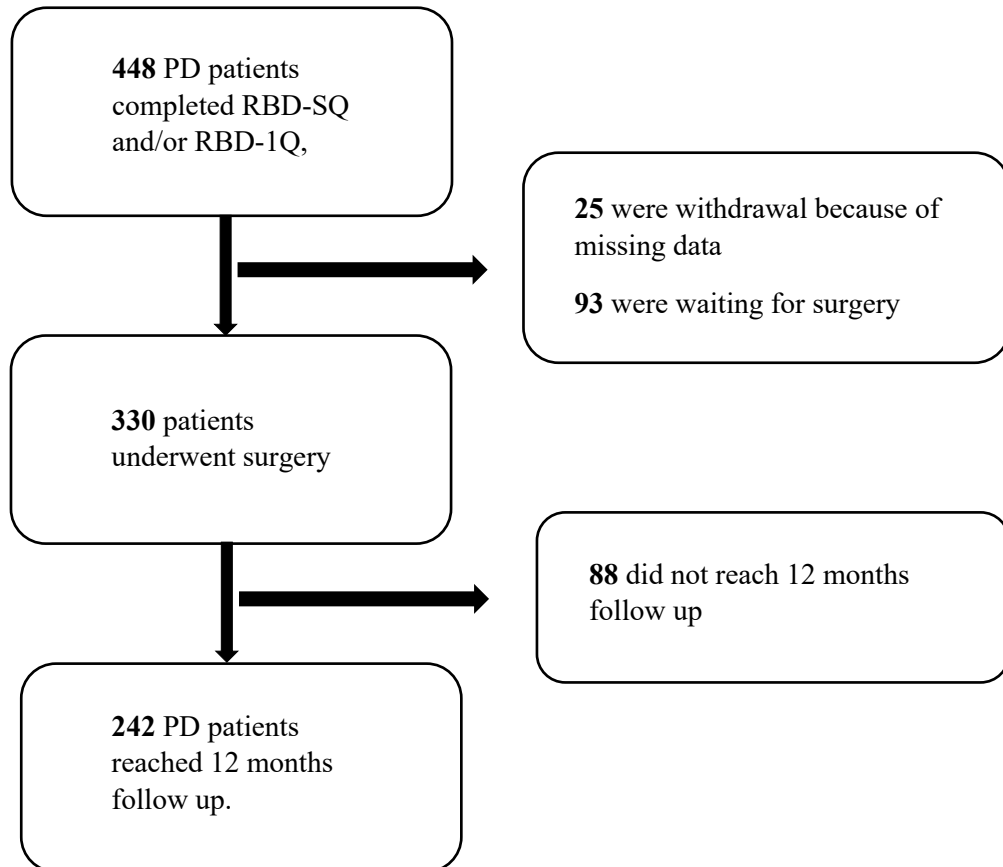
Higher scores for each item indicating worse functioning

*: $p < 0,05$ for between group comparisons of absolute values 12 months after DBS-STN.



Supplemental data

Flow Chart



Suppl. Table 4: Variation of cognitive functions 12 months after Bilateral Stimulation of the Subthalamic Nucleus compared to baseline in PD patients without and with RBD preoperatively.

| | pRBD+ | pRBD- | p‡: |
|---|-------------------------|-------------------------|------|
| | % changes from baseline | % changes from baseline | |
| Attention | | | |
| SDMT | -11 [-22; 1] | -13 [-22; -2] | 0.50 |
| Memory | | | |
| Digit Span Forward and Backward | | | |
| ▪ Digit Span Forward | -8 [-17; 11] | 0 [-17; 12] | 0.61 |
| ▪ Digit Span Backward | 0 [-20; 14] | -11 [-24; 14] | 0.63 |
| Subtests 16-item Free/Cued Recall Test | | | |
| ▪ First, second and third free recall trial | 0 [-6; 0] | 0 [-7; 0] | 0.24 |
| ▪ Total free recall score | -2 [-6; 2] | 0 [-8; 0] | 0.51 |
| ▪ Delayed free recall trial | 0 [-39; 34] | 0 [-40; 50] | 0.58 |
| 10/36 Spatial Recall Test | | | |
| ▪ Free recall score | 0 [-38; 34] | 0 [-40; 50] | 0.58 |
| ▪ Delayed recall score | 0 [-23; 29] | 0 [-33; 27] | 0.21 |
| Executive function | | | |
| D-KEFS Color–Word Interference Test | | | |
| ▪ inhibition | -2 [-48; 86] | -2,5 [-40; 86] | 0.78 |
| ▪ inhibition/switching | 4,6 [-55; 93] | 6,8 [-45 ; 73] | 0,74 |
| Oral Letter–Number Sequencing task | | | |
| ▪ base ligne | 0 [-14; 27] | 12,5 [-9; 33] | 0.11 |
| ▪ alternating task (s.) | 8,8 [-10; 37] | 8,8 [-9; 33] | 0,77 |
| ▪ errors (nb) | -55 [-100; 33] | -66.6 [-100; 0] | 0,77 |
| ▪ Switching cost | 10,1 [-15; 45] | 0,75 [-37; 25] | 0.22 |
| Langague | | | |
| Animal fluency test | -13 | -13.3 [-30; 2] | 0,6 |
| Boston Naming test | 0 [-7; 8] | 0 [-13; 7] | 0.17 |
| Visuospatial function | | | |
| CLOX clock-drawing | | | |
| ▪ Draw | 0% [-8; 8] | 0% [-7; 8] | 0,9 |
| ▪ Copy | 0 [-7; 0] | 0% [-7; 8] | 0,16 |
| Benton Judgement of Line Orientation test | 0% [-8; 15] | 0% [-15; 8] | 0.05 |
| Abbreviation: SDMT = Symbol Digit Modalities Test. | | | |
| p‡: between-group comparisons of variation between baseline and 12 months after DBS-STN | | | |

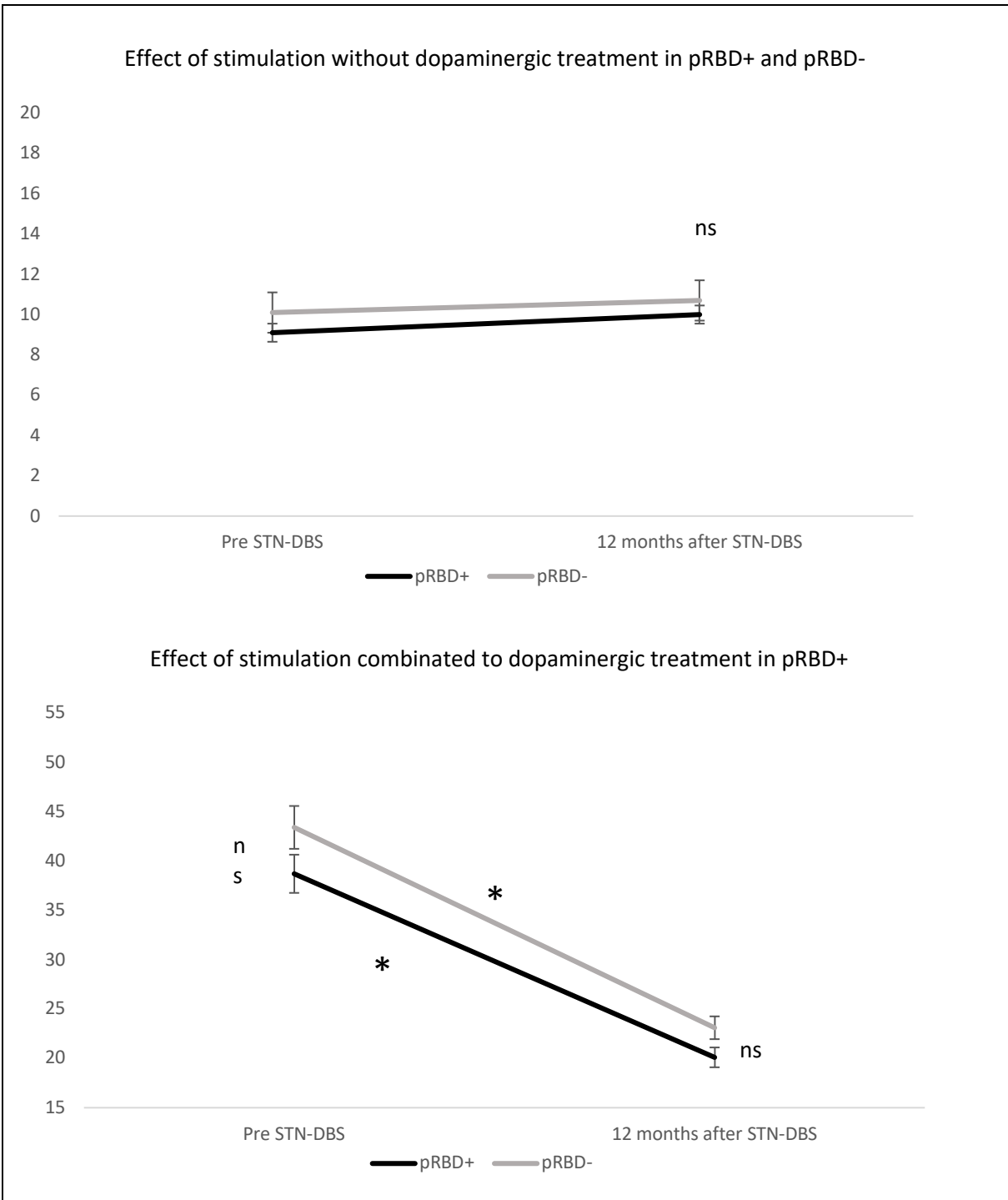
Suppl. Table 5: PDQ-39 outcomes at baseline and after bilateral subthalamic nucleus deep brain stimulation in PD patients with and without RBD preoperatively.

| | pRBD+ | | | pRBD- | | | p | p† | p‡ |
|----------------------------------|-----------------------|------------------------|----------------|-----------------------|-----------------------|----------------|-------|------|------|
| | Baseline (n = 237) | 12 months (n = 109) | % | Baseline (n = 205) | 12 months (n = 77) | % | | | |
| Summary Index | 33±12 | 30±12* | -8% [-31; 13] | 29±12 | 26±13* | -16% [-50; 7] | 0.03 | 0.04 | 0.54 |
| Mobility | 37±20 | 37±22 | -4% [-32; 42] | 36±22 | 32±21 | -21% [-46; 33] | 0.53 | 0.12 | 0.18 |
| Activites of daily living | 37±19 | 31±18* | -20% [-42; 23] | 38±20 | 27±17* | -30% [-67; 10] | 0.60 | 0.20 | 0.16 |
| Emotional well-Being | 37±18 | 33±21 | -11% [-33;38] | 29±17 | 30±17 | 0% [-33; 37] | <0.01 | 0.28 | 0.14 |
| Communication | 28±19 | 31±21 | 0% [-40; 67] | 24±18 | 26±20 | 0% [-50; 50] | 0.02 | 0.15 | 0.65 |
| Social support | 15±18 | 16±18 | 0% [-100; 50] | 10±15 | 14±18 | -50% [-100;25] | <0.01 | 0.49 | 0.48 |
| Cognition | 34±16 | 28±18* | -13% [-57; 14] | 23±15 | 22±16 | -8% [-62; 50] | <0.01 | 0.01 | 0.06 |
| Stigma | 35±23 | 25±20* | -33% [-67; 0] | 33±23 | 21±20* | -37% [-89; 0] | 0.20 | 0.14 | 0.48 |
| Bodily Discomfort | 49±21 | 36±21* | -25% [-50; 0] | 41±20 | 32* | -25% [-60; 25] | <0.01 | 0.13 | 0.32 |

Abbreviations : PDQ-39 = Parkinson's disease Questionnaire 39
 *: p< 0.05 for within group comparison of absolute values between baseline and 12 months after DBS-STN
 P : between group comparisons of absolute values at baseline
 p† : between group comparisons of absolute values 12 months after DBS-STN
 p‡: between-group comparisons of variation between baseline and 12 months after DBS-STN

Suppl. Table 6 Multivariate analysis of between group comparison of variation between baseline and 12 months after STN-DBS adjusted on age, sex, LEDD and UPDRS III off scores

| | Coef. | P> z | [95% Conf. Interval] |
|---|--------|-------|----------------------|
| UPDRS I | -1.140 | 0.183 | [-2.819; 0.537] |
| UPDRS II off | -0.019 | 0.774 | [-2.945; 2.191] |
| UPDRS IV | -0.191 | 0.756 | [-1.393; 1.012] |
| MOCA | -0.345 | 0.387 | [-1.129; 0.438] |
| ASBPD total scores | -0.043 | 0.946 | [-1.299;1.211] |
| Hypodopaminergic disorders subscore | -0.679 | 0.056 | [-1.375; 0.016] |
| Neuropsychiatric fluctuations subscore | 0.109 | 0.598 | [-0.298; 0.518] |
| Hyperdopaminergic disorders subscore | -1.588 | 0.256 | [-2.272; 0.903] |
| ICD | 0.055 | 0.745 | [-0.279; 0.391] |



Suppl. Figure 3: Effect of stimulation on motor disability score in pRBD+ and pRBD-

Effect of stimulation without dopaminergic treatment is assessed comparing Unified Parkinson's disease Rating Scale part III in "Med Off" condition at baseline to "Med Off / Stim On" after bilateral subthalamic nucleus stimulation.

Effect of stimulation combined with dopaminergic treatment is assessed comparing UPDRS III in "Med On" condition at baseline to "Med On / Stim On" after STN-DBS.

Abbreviation : ns = non significant between groups.

* : $p < 0,05$ pour variation between baseline and 12 months after surgery

3. CONCLUSION

Dans ce travail de thèse, qui est une étude ancillaire du Programme hospitalier de recherche clinique national PREDISTIM, nous avons montré que parmi les 448 patients atteints de la Maladie de Parkinson, 242 patients, soit 54%, présentaient des troubles du comportement en sommeil paradoxale (TCSP) probables avant la mise en place d'une stimulation des noyaux sous-thalamiques. En pré opératoire, les profils cliniques différaient surtout en raison d'un âge plus élevé, d'une symptomatologie extra pyramidale moins sévère, de troubles psycho-comportementaux tel que l'apathie, l'anxiété et la dépression, plus importants et d'une qualité de vie plus altérée chez les patients qui présentaient des TCSP en préopératoire comparativement aux patients qui n'en présentaient pas.

Il existait une amélioration significative des paramètres moteurs et non moteurs dans les deux groupes 12 mois après la chirurgie et le bénéfice de la stimulation était comparable entre les groupes.

Un an après la chirurgie, les profils cliniques étaient comparables pour les fonctions motrices, cognitives et psycho-comportementales tandis que la qualité de vie demeurait plus altérée chez les patients avec des TCSP en préopératoire.

En conclusion ce travail a montré que la présence de TCSP en préopératoire n'était pas associée à une évolution défavorable sur le plan moteur, cognitif ou psycho-comportemental comparativement aux patients sans TCSP un an après stimulation cérébrale profonde dans la Maladie de Parkinson.

4. SERMENT D'HIPPOCRATE

Conseil national de l'ordre des médecins

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

Rôle prédictif de la présence de troubles du comportement en sommeil paradoxal en préopératoire sur l'évolution motrice, cognitive, psycho-comportementale et sur la qualité de vie un an après stimulation cérébrale profonde dans la Maladie de Parkinson

CONTEXTE Les troubles du comportement en sommeil paradoxal (TCSP) peuvent être associés à une atteinte plus sévère sur le plan moteur et non moteur lorsqu'ils sont associés à la maladie de Parkinson. Nous avons cherché à savoir si leur présence était prédictive d'une mauvaise évolution un an après stimulation cérébrale profonde des noyaux sous thalamiques.

OBJECTIF : Comparer l'évolution motrice, psycho-comportementale, cognitive et la qualité de vie entre les patients parkinsoniens avec et sans TCSP en préopératoire (préop-TCSP) un an après stimulation cérébrale profonde des noyaux sous thalamiques.

METHODE Nous avons réalisé une étude, ancillaire de l'étude PREDISTIM qui est une étude prospective nationale multi centrique, visant à comparer l'évolution du syndrome parkinsonien, de l'atteinte cognitive, psycho-comportementale et de la qualité de vie un an après la chirurgie chez les patients parkinsoniens avec préop-TCSP probable (TCSP+) versus sans préop-TCSP probable (TCSP-), dépistés en préopératoire à l'aide des questionnaires RBD-1Q et RBDSQ.

RESULTATS Parmi les 448 patients 242 (54%) présentaient un trouble du comportement en sommeil paradoxal probable (TCSP). Les profils cliniques à l'inclusion différaient en raison d'un âge plus élevé ($p=0,02$), une symptomatologie motrice moins sévère ($p=0,003$) mais une moins bonne expérience non motrice de la vie quotidienne ($p<0,001$) avec plus de symptômes hypodopaminergiques à type d'anxiété ($p=0,01$), de dépression ($p=0,001$) et d'apathie ($p=0,02$) et une qualité de vie plus altérée ($p=0,03$) dans le groupe TCSP+. Un an après la chirurgie il existait une amélioration significative de l'ensemble des paramètres moteurs et non moteurs dans les deux groupes, excepté pour les fonctions cognitives, et le bénéfice de la stimulation était comparable entre les groupes et cohérent avec celui attendu conformément aux données acquises de la science. Un an après la chirurgie les profils cliniques étaient devenus comparables en ce qui concerne l'atteinte motrice, l'atteinte cognitive et psycho-comportementale. Bien qu'il existât une amélioration significative de la qualité de vie dans les deux groupes ($p<0,05$), celle-ci demeurait plus altérée chez les patients TCSP+ ($p=0,04$)

CONCLUSION Ce travail a montré que la présence de TCSP en préopératoire n'était pas associée à une évolution plus défavorable du syndrome parkinsonien, des fonctions cognitives, de l'atteinte psycho-comportementale et la qualité de vie, comparativement aux patients sans TCSP préopératoire un an après stimulation cérébrale profonde dans la Maladie de Parkinson.

Mots-clés :

- Maladie de Parkinson
- Troubles du comportement en sommeil paradoxal
- Stimulation cérébrale profonde