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# Clinical predictive factors of improvement in Parkinson's disease patients treated by bilateral deep brain stimulation in subthalamic nuclei

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**THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1**  
*sous le sceau de l'Université Bretagne Loire*

Thèse en vue du

**DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE**

présentée par

**Jules Surgé**

Né le 8 octobre 1986 à HOUSTON (USA)

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**Facteurs cliniques  
prédictifs de  
l'amélioration des  
patients  
parkinsoniens traités  
par stimulation  
cérébrale profonde  
bilatérale des noyaux  
subthalamiques**

**Thèse soutenue à RENNES  
Thèse soutenue à RENNES  
le 19 octobre 2016**

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## **Introduction :**

Among treatment for the Parkinson disease (PD), the deep brain stimulation (DBS) is used with efficiency for several years for patients with an advanced forms<sup>1,2</sup> and which present fluctuations and complications of their motor symptoms (with ON/OFF periods). The drugs (L-DOPA, agonists...) are no longer sufficient to stabilize the pathology and the physical impairment, but the patients keep dopa sensitivity. This procedure is safe<sup>3</sup>, but do not preserve against axial and non-levodopa-responsive symptoms<sup>4</sup>. Its superiority on medical therapy was demonstrated with early motor complication<sup>5,6</sup>. The primary target of the stimulation is the sub-thalamic nucleus (STN), for its better results in the control of motor fluctuations<sup>7</sup>. The patients are carefully selected, because the secondary effects of the chirurgical intervention and the deep brain stimulation particularly<sup>8</sup>. They make the evaluation of the benefit of this treatment, by themselves, but especially by the improvement of the health related quality of life (HRQoL), which can be measured<sup>9-14</sup>. Some studies tried to find predictive factors<sup>8,15,16</sup>. With this statement, we wanted, in the context of a personalized medicine, to know if there were predictive factors, in particular clinical, having a significant role on the evolution of quality of life, to assess the benefit and the interest of the stimulation, even before the surgical intervention.

## **Material & method:**

In this monocentric, retrospective and descriptive study, we have followed 100 patients (men and women), from the neurology department of the RENNES hospital center, between the early 2000's and 2016. The protocol for deep brain stimulation was exclusively executed in the hospital. The patients had an idiopathic Parkinson disease, with every differential diagnosis eliminated, and featured symptoms of motor fluctuations. The various drugs (L-dopa, dopaminergic agonists, etc....) did not allow a satisfactory control of the impairment. Some of them had tested or refused to test Apomorphine pump. They were all volunteers participants, and they had taken their

decision after complete and clear information about the treatment that had been given to them. The various data collected about their pathology and the follow up of the treatment, respected the recommendations of the ethics committee.

Regarding the method, the patients potentially includable for the treatment, took part at least at two medical checkups before the intervention. A multidisciplinary team decided, or not, to launch the intervention. After the implementation of the device, a follow up was organized immediately and for the following months and years. The data were collected at each step. The data selected for this study, were at the last checkup before the surgery and one year after the latter. The general data about the population were also collected (sex, age, treatment and DBS settings). The surgical intervention is well described in the literature and the medical and surgical teams respected the practices. Concerning the analyzed data, the primary outcome studied, defining the primary endpoint, was the feeling of quality of life according to the PDQ 39 survey, which is adapted for the PD<sup>17</sup>. The patients were separated into two groups, in term of improvement of their HRQoL between before and after the surgery. The threshold was a decrease in score of more than five<sup>18</sup>. The explanatory variables were exclusively clinical. No information from additional tests was used. The three main variables were the motor, psychic and cognitive/associative fields, corresponding to the three main functions of the subthalamic nucleus. These explanatory variables were in line with the scientific recommendations. For the motor variables, UPDRS<sup>19</sup> (Unified Parkinson's Disease Rating Scale) from III to VI, was used. For the psychological variables, MADRS<sup>20</sup> (Montgomery-Åsberg depression rating scale), AES<sup>21</sup> (Apathy Evaluation Scale), AMDP-AT<sup>22</sup> (Association for Methodology and Documentation in Psychiatry) and RFE<sup>23</sup> (recognition of facial emotion) were used, and for the associative variables, UPDRS I and II, TMT<sup>24</sup> (trail making test), MDRS<sup>25</sup> (Mattis Dementia Rating Scale), STROOP<sup>26</sup> (Stroop task), WCST<sup>27</sup> (Wisconsin Card Sorting Test) and the verbal fluency evaluation<sup>28</sup> were used.

The main objective was to identify the clinical factors, measurable in pre-surgical period, associated with improvement of HRQoL.

The secondary objective was to identify the modifications of the explanatory variables (motor, associative and psychic) between before and after the surgery, associated with improvement of HRQoL.

For the statistical analysis and the comparison between groups, diverse tests were selected, depending on the data type. Thus, Pearson's chi-squared test (\*\*\*) for qualitative variables; Student's t-test (\*) and Mann–Whitney U test (\*\*), for quantitative variables; Wilcoxon signed-rank test and Student's t test (\* for paired data); were used.

## **Results:**

For the general distribution of ours population, there was slightly a greater number of man (63%). A medium age of disease onset at 45,5 years and of surgery at 57,7 years. The mean duration of disease before surgery was 12,2 years (table I).

**Table I: population characteristics (n=100).**

Characteristics	Category	Results
<b>Sex</b>	Women	37 (37%)
	Men	63 (63%)
<b>Age of disease onset</b>		45,5 (8,0)
		46,0 (39,0-52,0)
		17,0-60,0
<b>Age at surgery</b>		57,7 (8,5)
		60,0 (50,0-64,0)
		36,0-75,0
<b>Duration of disease before surgery</b>		12,2 (4,4)
		12,0 (9,0-15,0)
		5,0-24,0

**Mean (SD), Median (25-75th percentiles), minimum-maximum**

Overall, the patients had a significant QOL improvement, with an average of 6,8 point of decrease. We found in particular, an improvement of the PDQ 39 domains of mobility, daily life activities, shame, and bodily discomfort (Table II).

**Table II: Comparison of pre and post-surgical PDQ39 score domains**

Domains	Mean (SD): pre-surgical	Mean (SD): post-surgical	Mean differences (SD)	p-value
<b>Mobility*</b>	48,3 (21,1)	35,9 (21,4)	<b>-12,48 (17,88)</b>	<b>&lt;0,001</b>
<b>Activities of Daily Living *</b>	43,8 (18,8)	28,7 (18,7)	<b>-15,13 (17,95)</b>	<b>&lt;0,001</b>
<b>Emotional Well Being*</b>	34,4 (16,6)	31,0 (20,4)	-3,46 (18,76)	0.056
<b>Stigma*</b>	35,3 (22,3)	24,1 (21,9)	<b>-11,19 (20,67)</b>	<b>&lt;0,001</b>
<b>Social support*</b>	15,2 (19,7)	15,1 (17,3)	-0,08 (16,81)	0.902
<b>Cognition*</b>	27,8 (17,1)	25,6 (17,3)	-2,19 (17,19)	0.204
<b>Communication*</b>	30,7 (19,4)	32,9 (21,7)	2,25 (20,03)	0.261
<b>Bodily discomfort*</b>	47,6 (20,0)	35,1 (21,6)	<b>-12,50 (19,62)</b>	<b>&lt;0,001</b>
<b>PDQ 39 SI**</b>	35,1 (12,7)	28,2 (13,8)	<b>-6,85 (11,28)</b>	<b>&lt;0,001</b>

The mean voltages were 2,8V at the right stimulator and 2,6V at the left one. To both side, the main period was of 60 microseconds, and the mean frequency was 138Hz. The mean decrease of LEDD was of 367mg  $\pm$  454,4.

For responder and non-responder group the mean difference in PDQ-39 score was -14,83  $\pm$  7.36 points and +3,32  $\pm$  5,88, respectively. The evolution of the domains is detailed in the table III.

**Table III: Description of post-surgery improvement of the PDQ 39 domains, between responder and non-responder groups.**

Domains	Improvement PDQ39=no	Improvement PDQ39=yes
<b>Delta Mobility</b>	-1,7 (15,9) -2,5 (-11,3/6,3) -42,5/42,5	-21,0 (14,5) -17,5 (-32,5/ -8,8) -67,5/0,0
<b>Delta Activities of</b>	-4,4 (15,7)	-21,1 (24,8)

<b>Daily Living</b>	-2,1 (-12,5/4,2) -41,7/25,0	-20,8 (-37,5/ -12,5) -54,2/125,0
<b>Delta Emotional Well Being</b>	9,5 (15,3) 8,3 (-4,2/20,8) -20,8/45,8	-13,5 (14,5) -12,5 (-20,8/ -4,2) -50,0/16,7
<b>Delta Stigma</b>	0,1 (20,3) 0,0 (-9,4/9,4) -43,8/50,0	-20,1 (16,2) -18,8 (-25,0/ -12,5) -75,0/12,5
<b>Delta Social support</b>	6,8 (15,0) 0,0 (0,0/16,7) -33,3/50,0	-5,5 (16,3) 0,0 (-12,5/0,0) -58,3/41,7
<b>Delta Cognition</b>	7,7 (13,9) 6,3 (0,0/12,5) -25,0/43,8	-9,9 (15,5) -6,3 (-18,8/0,0) -50,0/25,0
<b>Delta Communication</b>	10,8 (17,8) 8,3 (0,0/16,7) -25,0/50,0	-4,5 (19,2) 0,0 (-16,7/8,3) -58,3/41,7
<b>Delta Bodily discomfort</b>	-2,1 (15,00) 0,00(-8,3/8,3) -41,7/33,3	-20,7 (18,40) -25,0 (-33,3/-12,5) -58,3/33,3
<b>Delta PDQ39 SI</b>	+3,32 (5,88) 2,19 (-0,44 / 5,47) -4,37 / 26,75	-14,83 (7,36) -12,75 (-19,37/-9,12) -34,37 / -5,13

**Mean (SD), Median (25<sup>th</sup> 75<sup>th</sup> percentiles), minimum/maximum**

For information, the post surgical PDQ 39 SI, for responder and non-responder groups was, respectively,  $24 \pm 13$  and  $33,6 \pm 13$  points (table IV).

**Table IV: post-surgical PDQ39 domains, according to the PDQ 39 improvement.**

Domains (post surgical)	Improvement PDQ39=no	Improvement PDQ39=yes
<b>Mobility</b>	41,4 (23,0) 46,3 (22,5-57,5) 0,0-85,0	31,5 (19,2) 27,5 (17,5-58,8) 0,0-85,0
<b>Activities of Daily Living</b>	33,2 (19,4) 33,3 (16,7-45,8) 0,0-75,0	25,2 (17,6) 20,8 (12,5-35,4) 0,0-66,7
<b>Emotional Well Being</b>	39,9 (20,3) 41,7 (31,3-52,1) 0,0-75,0	24,0 (17,7) 22,9 (6,25-37,5) 0,0-75,0
<b>Stigma</b>	29,7 (24,3) 28,1 (6,25-43,8) 0,0-93,8	19,8 (18,8) 18,8 (0,0-37,5) 0,0-75,0
<b>Social support</b>	17,8 (15,9) 16,7 (0,0-29,2) 0,0-50,0	13,0 (18,1) 0,0 (0,0-25,0) 0,0-58,3
<b>Cognition</b>	32,4 (17,0) 34,4 (18,8-43,8)	20,3 (15,8) 18,8 (6,3-31,3)



	0,0-62,5	0,0-62,5
<b>Communication</b>	33,3 (21,6)	32,6 (21,9)
	33,3 (16,7-50,0)	33,3 (12,5-50,0)
	0,0-83,3	0,0-75,0
<b>Bodily discomfort</b>	43,9 (19,7)	28,1 (20,6)
	41,7 (29,2-58,3)	25,0 (16,7-41,7)
	0,0-83,3	0,0-91,7
<b>PDQ39 SI*</b>	33,6 (13,0)	24,0 (13,0)
	34,0 (23,7-42,9)	23,8 (12,4-33,5)
	7,6-63,0	3,3-51,1
<b>Mean (SD), Median (25<sup>th</sup> 75<sup>th</sup> percentiles), minimum/maximum</b>		

On the main objective of this study, the pre-surgical clinical factors, affecting the improvement of HRQoL were: the UPDRS II Dopa OFF status (17.61 vs 21.51; p 0.012), the UPDRS III Dopa OFF total status (33.36 vs 39.73; p 0.037) and UPDRS IV fluctuations domain (3.03 vs 3.62; p 0.047). But also the pre-surgical PDQ 39 score itself: whether, the PDQ SI (30,3 vs 38,8, p<0,001); or its domains: ADL (37,6 vs 48,7, p 0,001), emotional well-being (30,4 vs 37,6, p 0,04) and communication (22,5 vs 37,1, p<0,001). Every time, the responder group (with significant improvement of QoI), had a worst score than the other group (tables V, VI, VII, VIII).

**Tableau V: pre-surgical PDQ39 domains, according to the PDQ 39 improvement.**

Domains	Improvement PDQ39=no	Improvement PDQ39=yes	p-value
<b>Mobility</b>	43,1 (22,2)	52,5 (19,3)	<b>0,032</b>
	47,5 (25,0-62,5)	55,0 (36,3-67,5)	
	5,0-90,0	10,0-92,5	
<b>Activities of Daily Living</b>	37,6 (19,6)	48,7 (16,8)	<b>0,001</b>
	39,6 (22,9-50,0)	50,0 (37,5-58,3)	
	4,2-83,3	4,2-79,2	
<b>Emotional Well Being</b>	30,4 (14,9)	37,6 (17,3)	<b>0,040</b>
	33,3 (20,8-37,5)	37,5 (25,0-50,0)	
	0,0-62,5	4,2-75,0	
<b>Stigma</b>	29,6 (21,3)	39,8 (22,3)	<b>0,021</b>
	25,0 (12,5-43,8)	37,5 (25,0-56,3)	
	0,0-81,3	0,0-93,8	
<b>Social Support</b>	11,0 (16,4)	18,5 (21,6)	0,077
	0,0 (0,0-16,7)	8,3 (0,0-29,2)	
	0,0-66,7	0,0-75,0	
<b>Cognition</b>	24,7 (16,5)	30,3 (17,3)	0,129
	25,0 (12,5-37,5)	31,3 (18,8-43,8)	

	0,0-56,3	0,0-68,8	
<b>Communication</b>	<b>22,5 (15,8)</b> <b>25,0 (8,3-33,3)</b> <b>0,0-58,3</b>	<b>37,1 (19,8)</b> <b>37,5 (25,0-50,0)</b> <b>0,0-75,0</b>	<b>&lt;0,001</b>
<b>Bodily Discomfort</b>	46,0 (20,6) 50,0 (33,3-58,3) 0,0-91,7	48,8 (19,6) 50,0 (33,3-62,5) 0,0-83,3	0,412
<b>PDQ39 SI*</b>	<b>30,3 (11,4)</b> <b>31,8 (22,5-39,5)</b> <b>10,0-55,8</b>	<b>38,8 (12,4)</b> <b>40,1 (33,8-47,8)</b> <b>11,8-61,1</b>	<b>&lt;0,001</b>

Mean (SD), Median (25-75th percentiles), minimum maximum

**Table VI: Analysis of PDQ39 score improvement according pre-surgical psychological tests.**

Score	Missing values	PDQ39 improvement		p-value
		No	Yes	
<b>AES*</b>	30	31,58 (6,90)	34,05 (7,33)	0,155
<b>MADRS**</b>	29	4,58 (4,74)	6,15 (5,25)	0,186
<b>AMDPAT**</b>	31	7,57 (6,10)	11,13 (9,93)	0,271

Mean (SD)

**Table VII: Analysis of PDQ39 score improvement according pre-surgical cognitive tests.**

Score	Missing values	PDQ39 improvement		p-value
		No	Yes	
<b>MDRS**</b>	22	140,20 (3,11)	140,16 (3,00)	0,984
<b>TMT**</b>	6	86,98 (75,41)	76,70 (58,49)	0,703
<b>STROOP interference*</b>	3	-0,12 (7,78)	1,40 (7,45)	0,330
<i>Criterion</i> **	5	5,52 (0,83)	5,45 (1,03)	0,890
<i>Mistakes</i> **	5	5,95 (5,31)	6,40 (6,85)	0,964
<i>Perseverations</i> **	5	1,90 (2,24)	2,17 (3,25)	0,825
<b>RFE *</b>	43	82,16 (11,23)	84,02 (9,96)	0,528
<b>Fluency</b>				
<i>Categorical</i>	12	26,45	27,24	0,936

**		(9,02)	(11,23)	
<i>Lexical</i>	13	19,37	18,33	0,590
*		(8,66)	(9,10)	
<i>Action Verbal</i>	46	10,68	12,69	0,403
**		(7,75)	(6,96)	

**Mean (SD)**

**Table VIII: Analysis of PDQ39 score improvement according pre-surgical UPDRS scores.**

Score	Missing values	Classes	PDQ39 improvement		p-value
			No	Yes	
<b>UPDRS I</b>					
	15		1,50 (1,81)	1,70 (1,41)	0,214
<b>UPDRS II</b>					
dopa ON	15		3,91 (2,78)	5,89 (5,02)	0,139
**					
dopa OFF	15		<b>17,61 (6,29)</b>	<b>21,51 (7,54)</b>	<b>0,012†</b>
*					
<b>UPDRS III</b>					
<i>Total</i>					
dopa ON	0		9,60 (10,89)	10,20 (6,80)	0,249
**					
dopa OFF	1		<b>33,36 (14,31)</b>	<b>39,73 (15,12)</b>	<b>0,037†</b>
**					
<i>Axial Score</i>					
dopa ON	0		1,14 (1,15)	1,59 (1,79)	0,309
**					
dopa OFF	0		5,84 (4,20)	6,98 (4,20)	0,181
*					
<i>Speech</i>					
dopa ON	0	Score=0	32 (48,5)	34 (51,5)	0,208
***		Score=1 or 2	12 (35,3)	22 (64,7)	
dopa OFF	0	Score=0	14 (53,9)	12 (46,1)	0,111
***		Score=1	23 (47,9)	25 (52,1)	
		Score=2 or 3	7 (26,9)	19 (73,1)	
dopa ON	0	Score=0	43 (44,8)	53 (55,2)	0,435
***		Score=1	1 (25,0)	3 (75,0)	
dopa OFF	0	Score=0	23 (43,0)	27 (54,0)	0,531
***		Score=1 or 2	16 (47,1)	18 (52,9)	
		Score=3 or 4	5 (31,3)	11 (68,7)	
<i>Posture</i>					
dopa ON	0	Score=0	28 (42,4)	38 (57,6)	0,416
***		Score=1	14 (50,0)	14 (50,0)	
		Score=2 or 3	2 (33,3)	4 (66,7)	
dopa OFF	0	Score=0	12 (52,2)	11 (47,8)	0,764
***		Score=1	17 (39,5)	26 (60,5)	
		Score=2	9 (47,4)	10 (52,6)	

		Score=3 or 4	6 (40,0)	9 (60,0)	
<b>Stability</b>					
dopa ON	0	Score=0	37 (48,7)	39 (51,3)	0,093
***		Score=1 or 2	7 (29,2)	17 (70,8)	
dopa OFF	0	Score=0	11 (78,6)	3 (21,4)	<b>0,043†</b>
***		Score=1	16 (39,0)	25 (61,0)	
		Score=2	9 (34,6)	17 (65,4)	
		Score=3 or 4	8 (42,1)	11 (57,9)	
<b>Gait</b>					
dopa ON	0	Score=0	34 (45,3)	41 (54,7)	0,642
***		Score=1 or 2	10 (40,0)	15 (60,0)	
dopa OFF	0	Score=0	6 (46,2)	7 (53,8)	0,989
***		Score=1	18 (43,9)	23 (56,1)	
		Score=2	13 (41,9)	18 (58,1)	
		Score=3 or 4	7 (46,7)	8 (53,3)	
<b>UPDRS IV</b>					
<i>Total</i>	15		8,35	9,16	0,360
**			(3,25)	(3,55)	
<i>Dyskinesias</i>	15		4,23	4,67	0,441
**			(2,78)	(2,73)	
<i>Fluctuations</i>	15		<b>3,03</b>	<b>3,62</b>	<b>0,047†</b>
**			<b>(1,29)</b>	<b>(1,43)</b>	
<b>UPDRS V</b>					
dopa ON	13	Score=0	14 (53,9)	12 (43,1)	0,562
		Score=1 or 1,5	14 (40,0)	21 (60,0)	
		Score=2, 2,5 or 3	12 (46,2)	14 (53,8)	
dopa OFF		Score=1 or 1,5	9 (69,2)	4 (30,8)	0,103
		Score=2, 2,5 or 3	19 (37,3)	32 (62,7)	
		Score=4 or 5	12 (50,0)	12 (50,0)	
dopa ON	13		1,0	1,1	0,455
**			0,9	0,9	
dopa OFF			2,6	2,8	0,314
**			1,1	0,9	
<b>UPDRS VI</b>					
dopa ON	13		88,0	87,0	0,654
**			(9,92)	(9,76)	
dopa OFF			61,8	54,2	0,121
			(21,7)	(21,2)	

### Mean (SD)

None of the general characteristics of the population (sex, disease evolution, LEDD etc.), did have significant impact on HRQoL improvement. The two groups were rather homogeneous.

Concerning the secondary objective, on the variation of explanatory variables and their impact on improvement of HRQoL, (first value for non-responder group and the second for responder group), them were significant: the MADRS (1.39 vs -2.58; p 0.006), the AMDPAT (0.48 vs -4.61; p 0.03), RFE (2.40 vs -5.67; p 0.017), the verbal fluency (0.32 vs -2.79; p 0.049), the UPDRS I (1.11 vs -0.36; p 0.005), the UPDRS II ON (3.50 vs 0.11; p 0.034), OFF (-1.92 vs -8.55; p 0.001), the UPDRS III total OFF (-13.10 vs -20.74 ; p 0.03), Axial score OFF (-1.68 vs -3.35 ; p 0.044), Posture OFF (-0.34 vs -0.87 ; p 0.008), the UPDRS IV total (-2.84 vs -4.71 ; p 0.042), fluctuations (-0.46 vs -1.79 ; p 0.002). (Tables IX, X, XI).

**Table IX: Analysis of comparison between average of PDQ39 post-surgical improvement and the variation of psychological tests results.**

Score	Missing values	PDQ39 improvement		p-value (average)
		No	Yes	
<b>Delta AES*</b>	32	2,29 (5,52)	1,89 (7,63)	0,809
<b>Delta MADRS**</b>	31	<b>1,39</b> <b>(6,57)</b>	<b>-2,58</b> <b>(5,31)</b>	<b>0,006†</b>
<b>Delta AMDPAT**</b>	31	<b>0,48</b> <b>(7,72)</b>	<b>-4,61</b> <b>(9,03)</b>	<b>0,030†</b>
<b>Mean (SD)</b>				

**Table X: Analysis of comparison between average of PDQ39 post-surgical improvement and the variation of cognitive tests results.**

Score	Missing values	PDQ39 improvement		p-value
		No	Yes	
<b>Delta MDRS**</b>	21	-1,36 (3,96)	-1,47 (3,67)	0,726
<b>Delta TMT**</b>	7	36,88 (113,15)	-5,83 (55,71)	0,100
<b>Delta STROOP interference*</b>	3	1,65 (7,14)	1,17 (8,39)	0,767
<i>Criterion **</i>	8	-0,56 (1,47)	-0,11 (1,54)	0,143
<i>Mistakes **</i>	8	0,48 (5,84)	0,40 (7,56)	0,603
<i>Perseverations**</i>	8	0,26 (3,86)	-0,04 (3,75)	0,445
<b>Delta RFE *</b>	52	<b>2,40</b> <b>(8,65)</b>	<b>-5,67</b> <b>(13,01)</b>	<b>0,017†</b>
<i>Categorical**</i>	27	1,07 (6,31)	-1,45 (10,45)	0,258

<i>Lexical *</i>	28	-1,87 (7,91)	-0,45 (8,50)	0,476
<i>Action Verbal **</i>	54	<b>0,32</b> <b>(5,09)</b>	<b>-2,79</b> <b>(6,70)</b>	<b>0,049†</b>

**Mean (SD)**

**Table XI: Analysis of comparison between average of PDQ39 post-surgical improvement and the variation of UPDRS results.**

Score	Missing values	PDQ39 improvement		p-value
		No	Yes	
<b>UPDRS I</b>	20	<b>1,11</b> <b>(2,68)</b>	<b>-0,36</b> <b>(2,28)</b>	<b>0,005†</b>
<b>UPDRS II</b>				
dopa ON **	18	<b>3,50</b> <b>(6,24)</b>	<b>0,11</b> <b>(4,61)</b>	<b>0,034†</b>
dopa OFF *	21	<b>-1,92</b> <b>(8,89)</b>	<b>-8,55</b> <b>(8,33)</b>	<b>0,001†</b>
<b>UPDRS III</b>				
<i>Total</i>				
dopa ON **	4	-1,67 (12,77)	-2,03 (7,70)	0,359
dopa OFF **	3	<b>-13,10</b> <b>(15,62)</b>	<b>-20,74</b> <b>(16,52)</b>	<b>0,030†</b>
<i>Axial Score</i>				
dopa ON **	2	0,27 (2,80)	0,00 (1,78)	0,204
dopa OFF *	2	<b>-1,68</b> <b>(4,06)</b>	<b>-3,35</b> <b>(4,01)</b>	<b>0,044†</b>
<i>Speech</i>				
dopa ON **	2	0,20 (0,79)	0,09 (0,78)	0,549
dopa OFF **	2	0,02 (0,90)	-0,24 (0,93)	0,130
<i>Chair Lift</i>				
dopa ON **	2	-0,05 (0,65)	0,07 (0,47)	0,780
dopa OFF **	2	-0,27 (1,01)	-0,57 (1,54)	0,276
<i>Posture</i>				
dopa ON **	2	<b>-0,09</b> <b>(0,94)</b>	<b>-0,15</b> <b>(0,66)</b>	<b>0,491</b>
dopa OFF **	2	<b>-0,34</b> <b>(1,22)</b>	<b>-0,87</b> <b>(1,06)</b>	<b>0,008†</b>
<i>Stability</i>				
dopa ON **	2	0,12 (0,69)	0,00 (0,61)	0,197
dopa OFF	2	-0,5	-0,85	0,154

	**		(1,07)	(1,12)	
<i>Gait</i>					
dopa ON	**	2	0,09 (0,91)	-0,02 (0,60)	0,423
dopa OFF	*	2	-0,59 (1,13)	-0,81 (1,23)	0,355
<b>UPDRS IV</b>					
<i>Total</i>	**	20	<b>-2,84</b> <b>(3,52)</b>	<b>-4,71</b> <b>(3,88)</b>	<b>0,042†</b>
<i>Dyskinesia</i>	**	19	-2,51 (3,22)	-2,88 (2,57)	0,586
<i>Fluctuation</i>	**	19	<b>-0,46</b> <b>(1,76)</b>	<b>-1,79</b> <b>(1,92)</b>	<b>0,002†</b>
<b>UPDRS V</b>		16	0,00 (1,33)	-0,34 (1,07)	0,288
<b>UPDRS VI</b>	**	17	1,84 (11,82)	5,56 (11,79)	0,217

### Mean (SD)

Eventually, the improvement of the PDQ 39 score was correlated with improvement of the motor status (according to the UPDRS), the mood (MADRS), anxiety (AMDPAT), but also with degradation of the verbal fluency and the ability to recognize emotions.

To note that there was no statistical link with the variation of dopamine drug use (LEDD), or even with the personal evaluation of improvement (CGI).

## Discussion:

Our study suggests that the major clinical factors, affecting the improvement of HRQoL after the surgery, were, in the first place, the motor fluctuations and the OFF period motor symptoms of the patients. For those with preserved dopaminergic sensitivity, the patients with the most important discomfort in OFF period, were those who felt the most, the improvement of their situation, translated in a better HRQoL. In clinical translation, more the patient has a significant motor impairment, when his medical treatment no longer stabilize the disease, more he will felt the benefit of this stimulation.

This result seems logical: all the patients who are includible in the surgical protocol should normally well improve their motor state. And those with the most important signs felt better improvement.

Secondarily, and this was consistent with the first point, those who felt the greater the alteration of quality of life (according the PDQ39 score), before surgery, were those who felt better improvement.

Concerning the variations of the subthalamic nucleus dimensions with the DBS, and their impact on the modification of the HRQoL, we found that, for the psychic role of the STN, there was a link between improvement of the mood (MADRS) and the HRQoL in the responder group. This was not always confirmed in the literature<sup>29</sup>. We also found an improvement in anxiety in the responder group. It is very likely that these two parameters are correlated. On the other hand, there was no significant impact of apathy on the evolution of HRQoL, whatever the group, unlike some results published<sup>30</sup>.

On the other hand, the significant improvement of HRQoL (in the responder group), was associated with a degradation of some associative functions. Particularly with the alteration of verbal fluency and the ability to recognize facial emotions. This result is well known by specialized teams working on DBS<sup>31-35</sup>. It should be noted that the cognitive domain of UPDRS (I) was improved contrariwise.

For the motor symptoms (UPDRS III, IV), the improvement of HRQoL was linked with an upgrade of OFF symptoms and surprisingly, on axial symptoms (axial score), while stimulation is not intended to improve these symptoms. There was also an improvement of fluctuations in the responder group.

We point out on more time that no general feature distinguished the two groups. Although it was known for gender<sup>36</sup>, it was not sure for age of onset<sup>37</sup>.



In summary, the main clinical predictive factors of HRQoL improvement in patient with PD, treated by DBS of STN, were the physical ones, and in particular, their severity in OFF periods. The benefit after the surgical intervention was also mainly on motor symptoms, and it is well known<sup>38</sup>.

But the responder group had also a deterioration of some significant cognitive and psychological capacities (verbal fluency and RFE), compared to the non-responder group, without this having an impact on the HRQoL. These results were consistent with the known characteristics of the STN, and in particular, the motor, cognitive and psychological role of this nucleus<sup>39,40</sup>. But eventually, the improvement of motor impairment, it seems, up for the alterations of other functions of the STN.

Unlike previous studies that dealt with predictive factor of improvement after DBS<sup>15,16</sup>, the patients in our cohort who felt the best this improvement (in the responder group), had a worst HRQoL before the intervention. But on the other side, there was again a link between the improvement of motor symptoms and the HRQoL. The main difference with these two studies, was that we had precautionary selected the patients, taking into account of the dopa sensibility and the presence of axial symptoms.

On the limits of this study, there was the monocentric character of the research, with medical care made only on the RENNES's hospital. This was an epidemiological study, nonrandomized, and without comparison group (with L-DOPA or Apomorphine pump treated patients, for example).

For some explanatory variables, there was a significant lack of data (like for the RFE), and it was univariate analyzes that have been conducted. And we must specify that the collection of patient data be made over several years, with different team. And that this could explain the missing data, and could perhaps have an impact on results.

It should be noted that the HRQoL in PD is subject, like any chronic disease, to some extra medical factors<sup>41</sup>. And they are probably other factors<sup>42</sup> that have not been taken into account, like income, in the evolution of this PD's patients.

We can also specify, that despite its high specificity, the PDQ 39 may have limitations in clinical research<sup>43</sup>. And its use and interpretation must remain cautious<sup>44</sup>. This precaution must be applied to the other scales, whether physical, cognitive or psychological.

But these results could have an impact for potential therapeutic decision, through a personalized medicine. Indeed, the patients suffering of PD, presenting motor symptoms fluctuations could be offered an adapted treatment, according to the severity of their signs (mainly physical in OFF period), and the health profit that can be expected (through HRQoL), and the expected side effects.

Those, for which the benefit proved insufficient could benefit from therapeutic alternatives, like the Apomorphine pump.

And it seems that a cut off of 30 points at the PDQ 39 scale could be used, according to the results of this study.

For the patients eligible to the DBS, information on psychic and associative effects could be given to them. They would be well advised for the risk on their speech (action verbal fluency) and on their behavior and emotions (RFE), while specifying it will be linked to motor symptoms improvement.

The future therapeutic developments, in PD, knowing the variability of the clinical presentation of the disease, the brain compensation phenomena, which can mask the progression of this one, with the help of imaging (like the TEP-TDM), could allow a more appropriate management of the PD and its symptoms. It was already demonstrated for the PD<sup>18,45</sup>.

It is very likely that the clinical evaluation alone, via the HRQoL, is not enough to provide the best decision, when choosing treatment.

But for the moment, this seems to be a good indicator, and, furthermore, its use is easy and inexpensive.

### **Conclusion:**

To conclude, taking account the importance of the pre surgical medical check-up, having only clinical parameters, and thinking about a personalized medicine, this study show that PD patients could benefit of a STN DBS, really adapted to their conditions, their discomfort and their physical and psychological specificity, with the help mainly of motor and HRQoL assessment, with a cut off of 30 points for the latter.

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## FACULTE DE MEDECINE

NOM et Prénom : SURGÉ JULES

### TITRE DE LA THESE d'EXERCICE

(Ce document sera à insérer dans les thèses définitives)

Titre : FACTEURS CLINIQUES prédictifs de l'amélioration  
des patients parkinsoniens traités par stimulation  
cérébrale profonde bilatérale des noyaux sub-thalamiques

Rennes, le 14-9-2016  Le Directeur de thèse	Rennes, le 14-9-2016  Le Président de jury
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**SURGE, Jules.- Titre de la thèse : facteurs cliniques prédictifs de l'amélioration des patients parkinsoniens traités par stimulation cérébrale profonde bilatérale des noyaux subthalamiques.**

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**Résumé français**

La stimulation cérébrale profonde des noyaux subthalamiques (NST) est un des traitements de références pour la maladie de Parkinson idiopathique dopa-sensible, lors du stade des fluctuations motrices. Ce travail cherche à trouver des facteurs prédictifs cliniques, de l'amélioration des patients sous ce dispositif, évaluée par l'intermédiaire de la qualité de vie (score PDQ 39), avant l'implantation chirurgicale. Notre travail retrouve comme principaux facteurs prédictifs d'amélioration, la gravité des symptômes moteurs en période OFF, ainsi que la présence d'une altération plus marquée de la qualité de vie, en pré chirurgical. Les patients répondeurs présentaient une amélioration de leurs symptômes moteurs, de leur moral, de leur anxiété, mais également une dégradation des fluences verbales et les capacités à reconnaître les émotions. L'amélioration des éléments moteurs semblant être prépondérant au niveau de la qualité de vie, par rapport aux autres fonctions du NST. Ces résultats pourraient permettre aux médecins de mieux sélectionner les éventuels bénéficiaires de l'intervention, et les patients pourraient mieux appréhender et évaluer les avantages et inconvénient de la stimulation, avant qu'elle soit réalisée. Un cut-off autour de 30 points de PDQ 39 pré chirurgical pourrait être utilisé.

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Mots-clés : maladie de Parkinson idiopathique, qualité de vie, stimulation cérébrale profonde, noyaux sub-thalamiques

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