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## Research Report

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# Personality Related to Quality-of-Life Improvement After Deep Brain Stimulation in Parkinson's Disease (PSYCHO-STIM II)

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## Abstract.

**Background:** Deep brain stimulation of the sub-thalamic nucleus (DBS-STN) reduces symptoms in Parkinson's disease (PD) patients with motor fluctuations. However, some patients may not feel ameliorated afterwards, despite an objective motor improvement. It is thus important to find new predictors of patients' quality of life (QoL) amelioration after DBS-STN. We hypothesized that personality dimensions might affect QoL after DBS-STN.

**Objective:** To evaluate associations between personality dimensions and QoL improvement one year after DBS-STN.

**Methods:** DBS-STN-PD patients ( $n=303$ ) having answered the "Temperament and Character Inventory" (TCI) before surgery and the PDQ-39 before and one year after surgery were included, from the cohort study PREDI-STIM. Linear regression models were used to evaluate associations between TCI dimensions and change in PDQ-39 scores after DBS-STN.

**Results:** Novelty Seeking and Cooperativeness scores before surgery were positively associated with PDQ-39 scores improvement after DBS-STN (FDR-adjusted  $p<0.01$ ). Moreover, paradoxically unimproved patients with deterioration of their PDQ-39 scores after DBS-STN despite improvement of their MDS-UPDRS-IV scores had lower Cooperativeness scores, while paradoxically improved patients with amelioration of their PDQ-39 scores despite deterioration of their MDS-UPDRS-IV scores had higher Reward Dependence scores.

**Conclusion:** Some presurgical personality dimensions were significantly associated with QoL amelioration and discrepancy between motor state and QoL changes after DBS-STN in PD. Educational programs before DBS-STN should take in account patient personality dimensions to better deal with their expectations.

Keywords: Cooperativeness, DBS-STN, novelty seeking, Parkinson's disease, quality of life

## INTRODUCTION

Deep brain stimulation of the sub-thalamic nucleus (DBS-STN) is proposed to Parkinson's disease (PD) patients with motor fluctuations and generally leads to a great improvement of their quality of life (QoL) [1–4]. Nonetheless, some patients do not feel DBS benefits despite objective motor improvement [5, 6]. That is why it seems crucial to find some individual predictive factors of QoL improvement after DBS-STN in order to assure at best patients' amelioration after this invasive therapy.

QoL improvement is an important outcome when evaluating treatment efficiency. It depends on both

objective and subjective factors such as physical and psychological health, as well as personal feeling of well-being and happiness experienced [7, 8].

Because personality is a very individual characteristic and describes how people think, behave and manage their life [9], it seems a factor of interest to predict QoL. To assess personality, several questionnaires have been developed, based on different concepts. From them, the Temperament and Character Inventory (TCI) evaluates personality through seven dimensions [10]. It is derived from the neurobiological and psychological concept of personality made by Cloninger [9]. The TCI was already used in several studies assessing PD personality [11] and was

validated by its stability [9, 12–15]. Moreover, our preceding study on PD patients with motor fluctuations has shown the adequacy of the TCI personality questionnaire on predicting QoL in this population before DBS-STN [16].

Our first objective was thus to identify associations between presurgical personality dimensions and QoL improvement one year after DBS-STN. Our second objective was to seek for characteristics of PD patients experiencing discrepancy between motor complications and QoL changes after DBS.

## MATERIALS AND METHODS

This study is an ancillary analysis using data collected from the PREDISTIM cohort which principal objective is to define the predictive factors of the therapeutic response to DBS-STN on the long-term QoL in PD. 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 clinical research network in France (NS-Park/F-Crin), approved from the CPP Nord Ouest-IV Ethical Committee and registered in the ClinicalTrials.gov website (NCT02360683).

### Patients

Briefly, patients undergoing DBS-STN in one of the participating centers were consecutive included into the study between 11/2013 and 09/2019. Inclusion criteria are a diagnosis of PD according to the UKPDSBB, disease duration  $\geq 5$  years, age between 18 and 75 and indication of DBS-STN. Exclusion criteria are atypical parkinsonism, severe cognitive impairment (Montreal Cognitive Assessment (MoCA) score  $< 23$ ), severe psychiatric disorders (following psychiatric evaluation by a psychiatrist), levodopa motor response  $< 30\%$  and contra-indications to surgery.

Patients gave written informed consent, the study was conducted according to the good clinical practice, local regulations and data collection was compliant with GDPR rules.

### Study design and clinical measures

For PREDISTIM, clinical data was collected at baseline, and then at 1-, 3-, and 5-years post-surgery. Clinical assessments at each visit included collection of demographic data, medical and treatment

history, MDS-UPDRS part I-IV [17], part-III being performed in OFF and ON state during a standardized acute levodopa challenge, neuropsychological testing, patient and caregivers' questionnaires. Along our ancillary study, only one personality questionnaire was added to evaluation at baseline: the TCI. Here, only patients evaluated before (V0) and after one year of DBS-STN (V1) were used in this study.

The MDS-UPDRS-III was evaluated for two conditions at V0: OFF and ON medication; and for four conditions at V1: ON stimulation ON medication (stimON-medON), ON stimulation OFF medication (stimON-medOFF), OFF stimulation ON medication (stimOFF-medON) and OFF stimulation OFF medication (stimOFF-medOFF).

The total Levodopa Equivalent Dose (LED) was calculated [18].

The Parkinson's Disease Questionnaire 39-items (PDQ-39) is a self-questionnaire evaluating specifically QoL of PD patients [19] and was assessed at V0 and V1. Its eight sub-scales can be divided into a Physical Component Score ("Mobility", "Activities of Daily Living" and "Bodily Discomfort" sub-scores) and a Mental Component Score ("Emotional Well-Being", "Stigma", "Social Support", "Cognition" and "Communication" sub-scores) of QoL.

The TCI was measured only at V0 in order to serve as predictive factor of QoL improvement after DBS-STN. It is a self-questionnaire of 226 binary questions used to assess patients' personality through seven dimensions [10]. It includes four temperaments (which are supposed to be genetically determined personality traits [9]): Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), and Persistence (P); and three characters (which are developmental personality traits evolving through time and life history [9]): Self-Directedness (SD), Cooperativeness (C), and Self-Transcendence (ST). Each of these seven personality dimensions are measured by an independent score: higher is the score, higher the individual will present the personality characteristic associated. NS corresponds to impulsive and curious temperament; HA to anxious and pessimist traits; RD to socially attached and sensitive individuals; P to hardworking and perseverant personality; and the three characters are associated to levels of maturity: SD to individual maturity, C to social maturity, and ST to spiritual maturity. Except the P, each of these seven dimensions is subdivided into sub-dimensions: NS and HA are formed by 4 sub-dimensions, RD and ST by 3, and SD and C by 5. Each of these twenty-four sub-dimensions represents

161 a specific aspect of the global dimension, also ranging  
162 in a spectrum of scores.

### 163 *Statistical analyses*

164 Descriptive analyses were performed. Moreover,  
165 Kruskal-Wallis tests or ANOVA (according to nor-  
166 mality of our data) followed by *post-hoc* analysis  
167 were done to control for homogeneity across centers  
168 for several variables (age, disease duration, LED at  
169 V0, percentage of PDQ-39 total score and sub-scores  
170 changes at V1, and TCI dimensions).

### 171 *Impact of DBS-STN at V1*

172 After DBS-STN, changes between V0 and V1 in  
173 LED, MDS-UPDRS, PDQ-39, Hamilton Depression  
174 Rating Scale (HAMD), Hamilton Anxiety Rating  
175 Scale (HAMA), Lille Apathy Rating Scale (LARS),  
176 and MoCA were checked (Wilcoxon Signed Rank  
177 Test for Paired Samples).

### 178 *Associations between TCI dimensions and* 179 *PDQ-39 scores at V0*

180 Linear regression models were performed to test  
181 the association between the different PDQ-39 sub-  
182 scores and total score at V0 and the seven TCI  
183 dimensions. Models were univariate with only one  
184 explanatory variable (each TCI dimensions) by mod-  
185 els, resulting in seven models per response variable  
186 (each PDQ-39 scores) which were adjusted by age,  
187 sex, disease duration and LED at V0. A False Dis-  
188 covery Rate (FDR) correction was applied for 31  
189 comparisons with calculation of q values (corre-  
190 sponding to FDR adjusted *p* values). We have chosen  
191 univariate models to study if some TCI personal-  
192 ity dimensions were separately associated with QoL.  
193 Moreover, because studying TCI sub-dimensions as  
194 well as main dimensions seemed of interest, multi-  
195 variate analysis seemed inappropriate since too many  
196 explanatory variables would be used (that is 31 vari-  
197 ables – 7 dimensions plus 24 sub-dimensions) which  
198 can be too much in view of the parsimony rule.

### 199 *Associations between MDS-UPDRS and* 200 *PDQ-39 scores at V1*

201 These associations were tested using linear regres-  
202 sion models adjusted by age, sex, disease duration,  
203 and LED at V1. The PDQ-39 scores at V1 served  
204 as response variables (the total and eight PDQ-39  
205 sub-scores) and the MDS-UPDRS (part-I, part-II  
206 stimON-medON, part-III stimON-medON and part-  
207 IV) scores at V1 as explanatory variables. Models

were univariate with only one explanatory variable  
by models, resulting in four models per response  
variable. An FDR correction was applied for 4 com-  
parisons.

### *Associations between TCI dimensions at V0 and* *PDQ-39 changes at V1*

Percentages of changes from V0 to V1 were  
calculated from the PDQ-39 total and sub-scores.  
Linear regression models were performed. The  
response variables corresponded to each calculated  
percentages of PDQ-39 change. The explanatory  
variables corresponded to each TCI dimensions and  
sub-dimensions. As explained above, models were  
univariate with only one explanatory variable by  
models, resulting in thirty-one models per response  
variable, adjusted by age, sex, disease duration and  
LED at V0, to account for any potential center effect.  
The same FDR correction was applied with q values  
calculation for 31 comparisons.

PD population was also divided into two groups  
according to the Minimal Clinically Important Dif-  
ference (MCID) of PDQ-39 total score change [20]:  
an “improvement” (difference of PDQ-39 total score  
between V1 and V0 < -4.72) and a “no improvement”  
group (difference of PDQ-39 total score between  
V1 and V0 ≥ -4.72). TCI dimensions and sub-  
dimensions scores were compared in these groups  
(two-sample Mann-Whitney tests with FDR correc-  
tion for 31 comparisons).

### *Differences between groups of responding* *patients*

As supplementary exploratory analysis, we have  
chosen to study discrepancy between motor compli-  
cations (MDS-UPDRS-IV) and QoL (PDQ-39 total)  
evolution. From the two PDQ-39 groups above and  
two similar MDS-UPDRS-IV groups (an “improve-  
ment” group based on MCID [21] (difference of  
MDS-UPDRS-IV score between V1 and V0 < -0.9)  
and a “no improvement” group (difference of MDS-  
UPDRS-IV score between V1 and V0 ≥ -0.9)), PD  
patients were divided into three final groups of  
responding patients: a “paradoxically unimproved”  
group (MDS-UPDRS “improvement” group and  
PDQ-39 “no improvement” group), a “realistic”  
group (MDS-UPDRS and PDQ-39 “improvement”  
groups or MDS-UPDRS and PDQ-39 “no improve-  
ment” groups) and a “paradoxically improved”  
group (MDS-UPDRS “no improvement” group and  
PDQ-39 “improvement” group). Each group were  
compared two by two in terms of TCI dimensions and

Table 1  
Description of TCI dimensions and clinical characteristics at V0 and V1

	V0 (mean $\pm$ SD)	V1 (mean $\pm$ SD)	<i>p</i>	CI of the difference
Age	60.0 $\pm$ 7.4	/	/	/
Disease duration	10.1 $\pm$ 3.9	/	/	/
Novelty Seeking	16.7 $\pm$ 5.0	/	/	/
Harm Avoidance	17.4 $\pm$ 6.5	/	/	/
Reward Dependence	15.4 $\pm$ 3.5	/	/	/
Persistence	5.4 $\pm$ 1.7	/	/	/
Self-Directedness	34.4 $\pm$ 6.0	/	/	/
Cooperativeness	33.8 $\pm$ 4.7	/	/	/
Self-Transcendence	12.3 $\pm$ 5.8	/	/	/
LED	1348.6 $\pm$ 740.2	689.6 $\pm$ 480.3	$9 \times 10^{-33**}$	535.7; 674.0
HAMD	5.2 $\pm$ 4.1	4.6 $\pm$ 4.1	$4 \times 10^{-02*}$	0.0; 1.5
HAMA	5.9 $\pm$ 5.1	4.7 $\pm$ 4.2	$2 \times 10^{-03**}$	0.5; 2.0
LARS	-27.9 $\pm$ 5.7	-25.2 $\pm$ 8.3	$1 \times 10^{-06**}$	-3.0; -1.0
MoCA	27.1 $\pm$ 2.2	25.9 $\pm$ 2.8	$1 \times 10^{-11**}$	1.0; 1.5
MDS-UPDRS I	10.9 $\pm$ 5	9.3 $\pm$ 5.2	$5 \times 10^{-06**}$	1.0; 2.5
MDS-UPDRS II OFF <sup>†</sup>	18.7 $\pm$ 7.6	15.1 $\pm$ 8.5	$9 \times 10^{-12**}$	3.5; 5.5
MDS-UPDRS II ON <sup>‡</sup>	6.5 $\pm$ 5.9	8.1 $\pm$ 5.8	$8 \times 10^{-05**}$	-2.5; -1.0
MDS-UPDRS III OFF <sup>†</sup>	43 $\pm$ 16.2	21.8 $\pm$ 12.9	$3 \times 10^{-46**}$	19.0; 22.5
MDS-UPDRS III ON <sup>‡</sup>	12.5 $\pm$ 7.8	10.8 $\pm$ 7.9	$3 \times 10^{-02*}$	0.0; 2.5
MDS-UPDRS IV	8.8 $\pm$ 3.3	4.1 $\pm$ 3.7	$3 \times 10^{-33**}$	4.5; 5.5
PDQ-39 Total	31.3 $\pm$ 11.4	26.8 $\pm$ 13.5	$3 \times 10^{-11**}$	3.4; 6.0
PDQ-39 Mobility	36.7 $\pm$ 20.4	32.6 $\pm$ 22.7	$2 \times 10^{-03**}$	1.3; 6.3
PDQ-39 ADL	37.7 $\pm$ 18.1	29.2 $\pm$ 20	$5 \times 10^{-13**}$	8.3; 12.5
PDQ-39 Emotional Well-being	32 $\pm$ 17.7	31.1 $\pm$ 19.2	0.30	-0.00004; 4.2
PDQ-39 Stigma	33.2 $\pm$ 22.3	23.1 $\pm$ 20.3	$5 \times 10^{-15**}$	9.4; 15.6
PDQ-39 Social support	11.7 $\pm$ 15.9	14 $\pm$ 18	$1 \times 10^{-02*}$	-8.3; 0.0
PDQ-39 Cognition	28.3 $\pm$ 17.1	24 $\pm$ 17.2	$6 \times 10^{-05**}$	3.1; 6.3
PDQ-39 Communication	24.9 $\pm$ 17.9	28.1 $\pm$ 21	$3 \times 10^{-03**}$	-8.3; 0.0
PDQ-39 Bodily discomfort	46.3 $\pm$ 21.1	32.5 $\pm$ 21.4	$9 \times 10^{-19**}$	12.5; 20.8

Mann-Whitney tests: \* $p < 0.05$ ; \*\* $p \leq 0.01$ ; CI, confidence interval of the difference in means at 95% confidence level; V0, baseline; V1, one year after DBS-STN; <sup>†</sup>MDS-UPDRS medOFF (V0) vs. stimON-medOFF (V1); <sup>‡</sup>MDS-UPDRS medON (V0) vs. stimON-medON (V1); ADL, Activities of Daily Living.

cognitive and behavioral (HAMD, HAMA, LARS, and MoCA) changes after DBS-STN (two-sample Mann-Whitney tests). FDR adjusted  $p$  values (q values) were calculated for 7 comparisons for the TCI dimensions analysis and for 4 comparisons for the cognitive and behavioral changes analysis.

All analyses were conducted on R Studio Software Version 1.1.456 and a threshold of bilateral statistical significance of 0.05 was used. As explained above, FDR corrections were applied and interpretations were made carefully according to strength of the results.

## RESULTS

Three hundred and three PD patients were enrolled in this study (204 men (67.3%) and 99 women (32.7%)) (Table 1). Statistical testing did not show relevant significant differences across centers: only age and disease duration shown significant

differences between centers in the Kruskal-Wallis testing ( $p = 0.003$  and  $p = 0.03$ , respectively) which no more reached significance during the *post-hoc* analysis; LED at V0, percentage of PDQ-39 changes at V1 and TCI dimensions were not different between centers ( $p > 0.05$ ). In any case, age, disease duration, sex and LED were used as adjustment variables in the linear regression models to control for any potential center effect.

### Impact of DBS-STN at V1 (Table 1)

One year after DBS-STN, PD patients had a significant decrease in their dopaminergic treatments (LED). HAMD, HAMA, and MoCA scores significantly decreased after DBS, while LARS scores slightly increased.

All parts of the MDS-UPDRS scores improved significantly after DBS-STN except the part-II-ON which worsened.

Table 2  
Significant associations between TCI dimensions at V0 and percentages of PDQ-39 change at V1 (n = 303)

Percentage of PDQ-39 evolution	TCI dimensions	coefficients	P	q	R2	CI
% PDQ-39 Total	NS	-1.02	0.04*	0.46	0.07	-2.01; -0.03
	HA4	-2.41	0.03*	0.46	0.07	-4.62; -0.21
	C3	-4.48	0.03*	0.46	0.07	-8.47; -0.49
% PDQ-39 Mobility	NS1	-9.42	0.0006**	<b>0.02</b> *	0.05	-14.75; -4.08
	NS4	-7.34	0.047*	0.29	0.02	-14.55; -0.13
	C	-3.11	0.01**	0.12	0.03	-5.60; -0.62
	C1	-13.17	0.004**	<b>0.04</b> *	0.04	-22.15; -4.19
	C4	-9.30	0.004**	<b>0.04</b> *	0.04	-15.65; -2.96
% PDQ-39 ADL	C3	-10.24	0.047*	0.978	0.02	-20.30; -0.18
% PDQ-39 Emotional Well-Being	HA	-2.30	0.02*	0.37	0.04	-4.29; -0.32
	HA4	-7.54	0.01**	0.35	0.05	-13.34; -1.74
	P	8.18	0.04*	0.40	0.04	0.46; 14.89
% PDQ-39 Stigma	RD	-2.39	0.03*	0.40	0.01	-4.53; -0.24
	RD3	-5.84	0.04*	0.40	0.01	-11.41; -0.28
	ST3	4.20	0.03*	0.40	0.01	0.40; 8.01
	ST	1.80	0.02*	0.31	0.02	0.29; 3.31
% PDQ-39 Social Support	ST3	5.30	0.02*	0.31	0.02	0.92; 9.68
	NS	-2.56	0.009**	0.262	0.03	-4.45; -0.66
	SD	1.63	0.04*	0.26	0.02	0.07; 3.19
% PDQ-39 Cognition	SD1	6.84	0.02*	0.26	0.02	0.98; 12.70
	C1	7.72	0.04*	0.26	0.02	0.30; 15.13
	C2	6.56	0.04*	0.26	0.02	0.27; 12.85
	HA4	-5.55	0.04*	0.70	0.00	-10.95; -0.15
% PDQ-39 Communication	NS	-1.90	0.01**	0.34	0.02	-3.37; -0.43
% PDQ-39 Bodily Discomfort	NS1	-3.78	0.03*	0.34	0.02	-7.20; -0.35
	C3	-6.50	0.03*	0.34	0.02	-12.45; -0.56

Adjusted linear regression models: \* $p < 0.05$ ; \*\* $p \leq 0.01$ ; q, FDR adjusted q value; significant  $p$  value in bold; CI, confidence interval at 95% confidence level; NS, Novelty Seeking; HA4, Fatigability; C3, Helpfulness; NS1, Exploratory excitability; NS4, Disorderliness; C, Cooperativeness; C1, Social acceptance; C4, Compassion; HA, Harm Avoidance; P, Persistence; RD, Reward Dependence; RD3, Dependence; ST3, Spiritual acceptance; ST, Self-Transcendence; SD, Self-Directedness; SD1, Responsibility; C2, Empathy.

294 Total PDQ-39 scores significantly improved after  
295 one year of DBS-STN as well as the “Mobility”,  
296 “Activities of Daily Living”, “Stigma”, “Cogni-  
297 tion”, and “Bodily Discomfort” sub-scores, whereas  
298 the “Emotional Well-Being” sub-score did not sig-  
299 nificantly change. The “Social Support” and “Com-  
300 munication” sub-scores significantly worsened after  
301 surgery.

#### 302 Associations between TCI dimensions and 303 PDQ-39 scores at V0

304 TCI dimensions were mainly associated with  
305 the Mental Component Score of the PDQ-39 at  
306 V0. Indeed, the linear regression models between  
307 TCI dimensions and PDQ-39 sub-scores at V0  
308 showed that HA and ST scores were significantly  
309 and positively associated with PDQ-39 total score  
310 ( $q = 1 \times 10^{-8}$ ,  $R^2 = 0.16$ ; and  $q = 9 \times 10^{-3}$ ,  $R^2 = 0.07$ ,  
311 respectively) whereas SD scores were significantly  
312 and negatively associated with PDQ-39 total score  
( $q = 2 \times 10^{-7}$ ,  $R^2 = 0.14$ )).

#### Associations between MDS-UPDRS and PDQ-39 scores at V1

315 At V1, the MDS-UPDRS part-I and part-II  
316 stimON-medON were positively associated with  
317 PDQ-39 total and 8 sub-scores ( $q < 0.01$ ). The  
318 MDS-UPDRS part-III stimON-medON and part-  
319 IV were positively associated with PDQ-39 total  
320 score ( $q < 10^{-4}$ ), most of the Physical Component  
321 Score (“Mobility” and “Activities of Daily Living”)  
322 ( $p < 10^{-3}$ ) and part of the Mental Component Score  
323 (“Emotional Well-Being”, “Stigma”, and “Com-  
324 munication”) ( $q < 0.05$ ). The “Bodily Discomfort”  
325 was associated only with the MDS-UPDRS part-IV  
326 ( $q < 10^{-3}$ ).

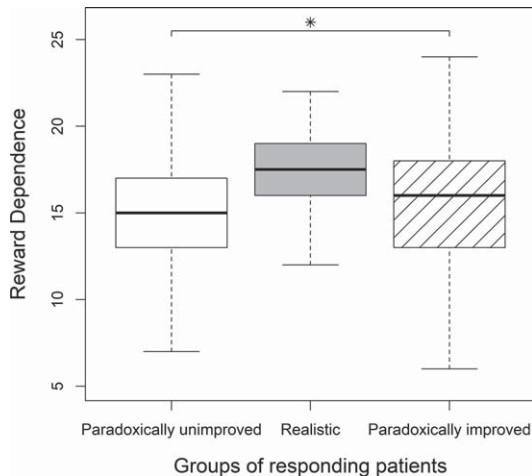
#### Associations between TCI dimensions at V0 and PDQ-39 changes at V1 (n = 303)

327 There were significant associations between TCI  
328 dimensions and PDQ-39 sub-scores change at V1  
329 (Table 2). We mainly considered TCI dimensions  
330  
331

Table 3  
Differences of TCI dimensions scores between PDQ-39 total improvement groups at V1 ( $n = 303$ )

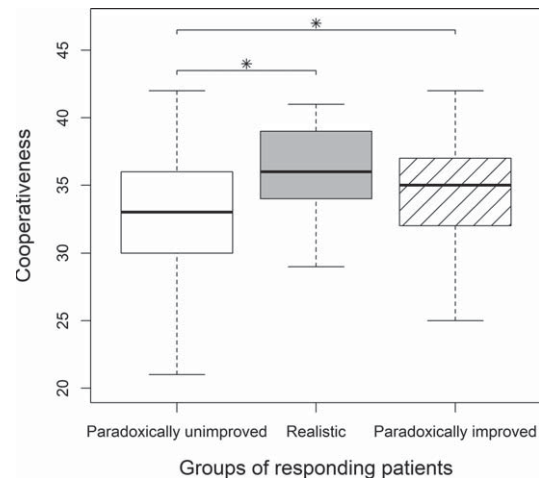
TCI dimensions	$p$	$q$	CI	Mean $\pm$ SD	
				PDQ-39 total "improvement" group ( $n = 150$ )	PDQ-39 total "no improvement" group ( $n = 153$ )
HA4	0.03*	0.29	0; 1.0	5.4 $\pm$ 2.0	4.7 $\pm$ 2.4
C	0.01*	0.47	0; 2.0	34.4 $\pm$ 4.5	33.2 $\pm$ 4.7
C3	0.006**	0.78	0, 0.9	6.6 $\pm$ 1.2	6.2 $\pm$ 1.3

Mann-Whitney tests: \* $p < 0.05$ ; \*\* $p \leq 0.01$ ;  $q$ , FDR adjusted  $p$  value; CI, confidence interval of the difference at 95% confidence level; HA4, Fatigability; C, Cooperativeness; C3, Helpfulness.



Mann-Whitney tests: \* $q < 0.05$  between the "paradoxically unimproved" and "paradoxically improved" groups

Fig. 1. Differences in Reward Dependence scores between groups of responding patients.



Mann-Whitney tests: \* $q < 0.05$  between the "paradoxically unimproved" and "paradoxically improved" or "realistic" groups

Fig. 2. Differences in Cooperativeness scores between groups of responding patients.

332 having the strongest association with PDQ-39 sub-  
333 scores (presenting only significant FDR adjusted  $p$   
334 value that is  $q \leq 0.05$ ) to avoid making assumption  
335 about lower associations.

336 The NS1 sub-dimension and some C sub-dimens-  
337 ions (C1 and C4) were significantly and negatively  
338 associated with the PDQ-39 "Mobility" sub-score  
339 change.

340 PD patients were separated into the PDQ-39 total  
341 "improvement" ( $n = 150$ ) and the "no improvement"  
342 ( $n = 153$ ) groups according to the MCID [20]. Among  
343 the "no improvement" group, 63% of patients had  
344 a no clinically relevant amelioration (that is a delta  
345 PDQ-39 total score between the MCID of  $-4.72$  and  
346 0) and 37% were not ameliorated (that is a delta  
347 PDQ-39 total score superior to 0). Uncorrected sig-  
348 nificant differences of HA4, C and C3 scores were  
349 found between the "improvement" group and the "no  
350 improvement" group which did not maintain signifi-  
cance with FDR correction (Table 3).

#### Differences between groups of responding patients ( $n = 264$ )

351 For this second exploratory objective, because of  
352 missing data in the MDS-UPDRS-IV, only 264/303  
353 PD patients were used to form the three groups of  
354 responding patients according to their PDQ-39 and  
355 MDS-UPDRS-IV changes: 97 patients were in the  
356 "paradoxically unimproved" group, 149 in the "real-  
357 istic" group, and 18 in the "paradoxically improved"  
358 group.

359 Reward Dependence scores were significantly  
360 higher in the "paradoxically improved" group com-  
361 pared to the "paradoxically unimproved" group  
362 ( $q = 0.04$  and  $CI = [1.0; 4.0]$ ) (Fig. 1). Cooperative-  
363 ness scores were significantly lower in the "paradoxi-  
364 cally unimproved" group compared to the "realistic"  
365 and "paradoxically improved" groups ( $q = 0.03$  and  
366  $CI = [1.0; 3.0]$ ;  $q = 0.04$  and  $CI = [1.0; 5.0]$ , respec-  
367 tively) (Fig. 2).  
368



369 Concerning the HAMA, HAMD, LARS, and  
370 MoCA changes, there were no significant differences  
371 between groups.

## 372 DISCUSSION

373 In this study, presurgical TCI personality dimen-  
374 sions such as higher Cooperativeness and Novelty  
375 Seeking sub-dimensions were associated with QoL  
376 improvement after one year of DBS-STN in PD  
377 population. This favorable outcome affected mainly  
378 the physical component of QoL (“Mobility” evolu-  
379 tion). Secondly, patients with lower Cooperativeness  
380 scores were more paradoxically unimproved after  
381 DBS-STN: their objective motor complications  
382 improvement was not translated into QoL improve-  
383 ment; while patients with higher Reward Dependence  
384 scores were more paradoxically improved after DBS-  
385 STN: they had QoL improvement despite the absence  
386 of motor complications reduction.

387 According to the literature [1–3, 22, 23], this  
388 study reported an improvement in MDS-UPDRS and  
389 PDQ-39 scores after one year of DBS-STN and a  
390 significant reduction of dopaminergic treatments. A  
391 slight amelioration of depression and anxiety was also  
392 shown after DBS, whereas apathy and global cog-  
393 nition slightly deteriorated while remaining below  
394 the threshold of apathy (LARS scale) and cogni-  
395 tive deficit (MoCA). Thus, DBS did not affect much  
396 behavior of our PD patients which globally did not  
397 develop either anxio-depressive state or apathy or  
398 cognitive decline.

399 First, we confirm the results of our previous study  
400 showing that personality dimensions are associated  
401 with different QoL sub-scores before DBS-STN in  
402 PD [16].

403 Second, we found associations between personal-  
404 ity dimensions and QoL improvement after one year  
405 of DBS-STN. Some Cooperativeness and Novelty  
406 Seeking sub-dimensions (C1 (Social Acceptance),  
407 C4 (Compassion), and NS1 (Exploratory Excitabil-  
408 ity)) were strongly related to the physical component  
409 of QoL (“Mobility”): PD patients with high Coop-  
410 erativeness and Novelty Seeking before DBS-STN  
411 had the best QoL improvement (physical component)  
412 after DBS-STN.

413 Cooperativeness is a character reflecting social  
414 maturity and described as a tendency to consider  
415 and accept others [24, 25]. PD patients with higher  
416 Cooperativeness probably better listen to their rel-  
417 atives and believe them, which can help them to

418 remember their past difficulties and to realize the  
419 strong motor improvement they benefit from DBS-  
420 STN. Indeed, it is usual that PD patients forget  
421 their past difficulties after DBS and need a reminder  
422 from their relatives or caregivers to become aware  
423 of their improvements [26]. In literature, low Coop-  
424 erativeness was associated with treatment-resistance  
425 in depressive patients [27], and high Cooperativeness  
426 was also linked with good QoL or life satisfaction in  
427 different populations [28–30]. Also, this hypothesis  
428 makes sense because Cooperativeness mostly impact  
429 physical QoL improvement after DBS, only part of  
430 QoL that can be assessed by patients’ relatives. There-  
431 fore, relatives probably have a more objective feeling  
432 on these improvements which may contrast with  
433 patients’ subjective one. Moreover, it is interesting  
434 to compare personality-QoL associations before and  
435 after DBS. Before, Self-Directedness (representing  
436 the individual maturity) was associated with better  
437 QoL [16]; whereas, after, Cooperativeness (social  
438 maturity) becomes associated with better QoL. This  
439 may reflect that, before surgery, PD patients were  
440 used to their disease and to their relatives’ comments  
441 because of adaptive process through chronic dis-  
442 ease; whereas, after DBS, PD patients are confronted  
443 to abrupt changes [31] and motor improvement are  
444 often obvious. Thus, their relatives can appreciate  
445 these improvements and inform the patients, helping  
446 them to become more aware of these changes. Hence,  
447 before surgery, in case of a slowly evolving chronic  
448 disease, PD patients may rely more on their personal  
449 resources (individual maturity) to adapt and have a  
450 better QoL [16]; whereas, after DBS, they focus more  
451 on the external comments (social maturity) to adapt  
452 to the abrupt changes. It would thus be interesting to  
453 see the impact of Cooperativeness on QoL after long-  
454 time of DBS, when PD patients would have become  
455 used to these changes, with the PREDISTIM 5-year  
456 QoL evaluation.

457 Novelty Seeking is a temperament representing a  
458 tendency to respond positively and with excitation  
459 to new stimuli [24, 25]. It reflects good adaptability  
460 to new situations and motivation facing change. PD  
461 patients with higher Novelty Seeking may thus better  
462 adapt to the abrupt changes caused by DBS-STN and  
463 so really feel the strong motor improvement they ben-  
464 efit from the stimulation. In literature, higher Novelty  
465 Seeking was also associated with better global QoL  
466 and physical health in patients with schizophrenia  
467 [32].

468 Interestingly, Novelty Seeking and/or Coopera-  
469 tiveness are two personality dimensions potentially  
470

470 implicated in placebo responses [33–35]. Therefore,  
471 these two personality dimensions may enhance the  
472 part of placebo effect induced by DBS-STN [36].  
473 For example, the sub-dimension C3 (Helpfulness)  
474 reflects solidarity and good level of team work which  
475 may enhance placebo effect [37].

476 Moreover, our study has shown good associa-  
477 tions between the more objective evaluation of PD  
478 symptoms (MDS-UPDRS) and the subjective eval-  
479 uation of PD QoL (PDQ-39). Mainly, the objective  
480 motor examination, MDS-UPDRS-III, as well as the  
481 motor complications assessed by the MDS-UPDRS-  
482 IV, were mostly associated with physical components  
483 of the PDQ-39 evaluation, assuring that both scales  
484 are reliable and evaluate PD patients in the same  
485 way [38]. Nonetheless, some PD patients (43.6%)  
486 had a feeling of evolution after DBS-STN that differs  
487 from the objective motor complications examina-  
488 tion (MDS-UPDRS-IV). Indeed, eighteen patients  
489 (6.8%) felt “paradoxically improved” after DBS: they  
490 felt improvement of their QoL, whereas the MDS-  
491 UPDRS-IV showed no improvement of their motor  
492 complications. Also, ninety-seven patients (36.7%)  
493 felt “paradoxically unimproved” after DBS: they did  
494 not feel any improvement of their QoL, whereas the  
495 MDS-UPDRS-IV showed an improvement of their  
496 motor complications. This dissociation between real-  
497 ity of PD symptoms improvement after DBS and PD  
498 patients’ feelings has already been shown in several  
499 studies [5, 6] and can be explained by differences  
500 between patients’ expectations and reality, difficul-  
501 ties of psychosocial adjustment, mood and behavioral  
502 changes [26, 31, 39, 40], etc. Moreover, we have  
503 decided to focus our analysis on discrepancy between  
504 QoL evolution and MDS-UPDRS-IV change since  
505 DBS preferentially improves motor complications.

506 Here, paradoxically unimproved PD patients had  
507 lower Cooperativeness scores than realistic and para-  
508 doxically improved ones. This result seems to be  
509 congruent with our previous observation that lower  
510 Cooperativeness scores before surgery lead to less  
511 improvement of QoL after DBS-STN. Moreover,  
512 paradoxically improved PD patients had higher  
513 Reward Dependence scores than the paradoxically  
514 unimproved ones. Reward Dependence temperament  
515 is associated with sensitive, dependent and social  
516 individuals [41]. It is a system facilitating condi-  
517 tioning to reward stimuli [25] and therefore may  
518 be associated with placebo effect. Indeed, some  
519 studies have found associations between higher  
520 Reward Dependence scores and better outcomes  
521 after interpersonal therapy [42] or antidepressants

522 [43]. Moreover, treatment adherence was shown to  
523 be related to higher Reward Dependence tempera-  
524 ment in a weight-loss therapy, probably thanks to  
525 better collaborative relationship with the clinicians  
526 [44]. Nonetheless, these differences between realis-  
527 tic, paradoxically improved or unimproved patients  
528 could not be explained by differences in cognitive or  
529 behavioral changes after DBS-STN.

530 This study has some limits. Being the first study on  
531 this subject, only analyses of associations between  
532 QoL outcomes and personality dimensions were  
533 done. Thus, our results are not predictive but rather  
534 suggestive. Hence, they should be used in order to  
535 prevent disappointment of PD patients after DBS-  
536 STN (not to select PD patients for DBS) acting in two  
537 ways: 1) by supporting them upstream and explain-  
538 ing them at best what they should expect of DBS, and  
539 2) by preparing and encouraging their relatives to be  
540 really present with the patients after the operation to  
541 enhance their cooperation (which seems to facilitate  
542 their positive outcomes). Additionally, our models  
543 explaining less than ten percent of the variance ( $R^2$ )  
544 of QoL improvement after DBS-STN, we are aware  
545 that personality dimensions are not enough to guar-  
546 anty PD patients’ QoL improvement after stimulation  
547 and that other variable are needed to explain at best  
548 QoL outcome after surgery. However, our focus being  
549 concentrated on personality dimensions’ evaluation,  
550 we did not look for other potential predictive variables  
551 as it will be the aim of the main PREDI-STIM study.  
552 Finally, only personality dimensions before DBS  
553 were evaluated (there was no re-evaluation of person-  
554 ality after stimulation), and it remains possible that  
555 some personality dimensions evolve after DBS. Even  
556 if temperaments are not supposed to change with  
557 time [9], personality in PD patients seems to evolve  
558 with the disease course particularly with the intro-  
559 duction of dopaminergic treatments [45]. DBS could  
560 also impact personality as shown by some studies  
561 [46–50]. In any case, our aim was to find “predic-  
562 tive” factors of QoL improvement after DBS. Thus,  
563 even if personality changes after stimulation, it is not  
564 supposed to affect our results. Lastly, our three groups  
565 of responding PD patients (“paradoxically unim-  
566 proved”, “realistic” and “paradoxically improved”) were  
567 done according to their motor complications  
568 improvement (reflected by MDS-UPDRS part-IV)  
569 since it is the main purpose of DBS-STN action.  
570 Nonetheless, improvements of non-motor symptoms  
571 (pain, fatigue etc.) were not accounted in these anal-  
572 yses, although non-motor symptoms can benefit of  
573 DBS-STN [51] and are best predictors of QoL in PD

[52], because we were interested in more objective assessments than MDS-UPDRS parts I and II. Moreover, we are aware that using MCIDs to classify into groups of “improvement” or “no improvement” may not precisely reflect the evolution of patients after DBS, mainly since at this stage of motor fluctuations a change of 0.9 points in the MDS-UPDRS part-IV may not be sufficient to be clinically significant. Nonetheless, the choice of this MCID was done accordingly with literature. Ultimately, we are aware that there are other models of personality that could have been explored in this study to depict a more complete exploration of personality associated with QoL. Nonetheless, the TCI being a long questionnaire, we thought that using a multilayer approach (through different personality investigations) would have been too complex in clinical practice and too tiring for the PD patients.

In conclusion, PD patients with higher Cooperativeness and Novelty Seeking scores at baseline seem to have the best QoL outcome after one year of DBS-STN in the physical component of QoL. A tendency of being more trustful towards relatives and more motivated by changes could explain the ability of these PD patients to feel a better QoL improvement following the abrupt changes after surgery. Moreover, PD patients with low Cooperativeness were more paradoxically unimproved after DBS, whereas PD patients with high Reward Dependence were more paradoxically improved after DBS. Therefore, systematic TCI examination could be proposed as standard evaluation before DBS. Subsequently, according to PD patients’ scores at the Novelty Seeking and Cooperativeness dimensions, specific educational programs should be proposed to patients with higher risk of QoL unimprovement after DBS to prepare them at best for the stimulation. For this, we are now looking for cut-off scores for these dimensions.

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