



Personality dimensions of patients can change during the course of parkinson's disease

Mathilde Boussac, Christophe Arbus, Julia Dupouy, Estelle Harroch, Vanessa Rousseau, Aurélie Croiset, Fabienne Ory-Magne, Olivier J. Rascol, Caroline Moreau, Anne-Sophie Rolland, et al.

► To cite this version:

Mathilde Boussac, Christophe Arbus, Julia Dupouy, Estelle Harroch, Vanessa Rousseau, et al.. Personality dimensions of patients can change during the course of parkinson's disease. PLoS ONE, 2021, 16 (1), 10.1371/journal.pone.0245142 . hal-03128733

HAL Id: hal-03128733

<https://hal.science/hal-03128733>

Submitted on 2 Feb 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

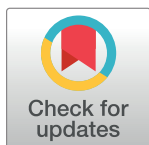


Distributed under a Creative Commons Attribution 4.0 International License

RESEARCH ARTICLE

Personality dimensions of patients can change during the course of Parkinson's disease

Mathilde Boussac^{1*}, Christophe Arbus², Julia Dupouy³, Estelle Harroch⁴, Vanessa Rousseau⁴, Aurélie Croiset⁵, Fabienne Ory-Magne^{1,4}, Olivier Rascol^{1,4}, Caroline Moreau⁶, Anne-Sophie Rolland⁶, David Maltête^{7,8}, Tiphaine Rouaud⁹, Mylène Meyer¹⁰, Sophie Drapier^{11,12}, Bruno Giordana¹³, Mathieu Anheim^{14,15,16}, Elodie Hainque¹⁷, Béchir Jarraya^{18,19}, Isabelle Benatru²⁰, Nicolas Auzou²¹, Lhaouas Belamri²², Mélissa Tir²³, Ana-Raquel Marques²⁴, Stephane Thobois^{25,26,27}, Alexandre Eusebio²⁸, Jean Christophe Corvol¹⁷, David Devos⁶, Christine Brefel-Courbon^{1,4}, on behalf of the PREDI-STIM study group[†]



OPEN ACCESS

Citation: Boussac M, Arbus C, Dupouy J, Harroch E, Rousseau V, Croiset A, et al. (2021) Personality dimensions of patients can change during the course of Parkinson's disease. PLoS ONE 16(1): e0245142. <https://doi.org/10.1371/journal.pone.0245142>

Editor: C. Robert Cloninger, Washington University, St. Louis, UNITED STATES

Received: October 20, 2020

Accepted: December 22, 2020

Published: January 7, 2021

Copyright: © 2021 Boussac et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The data underlying the results presented in the study are available from the University Hospital of Lille. It comes from the cohort of a multicentric study. This study is an ancillary analysis using data collected from the PREDISTIM cohort. PREDISTIM is an ongoing observational and 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/FCrin), approved from the CPP Nord Ouest-IV Ethical Committee and registered in

1 Toulouse NeuroImaging Center, University of Toulouse, Inserm, UPS, Toulouse, France, 2 Psychiatry Department of the University Hospital of Toulouse, CHU Purpan, Toulouse, France, 3 Department of Neurology, Hospital of Avignon, Avignon, France, 4 Department of Clinical Pharmacology and Neurosciences, Parkinson Expert Center, Centre d'Investigation Clinique CIC1436, University Hospital of Toulouse, NeuroToul COEN Center, NS-PARK/FCRIN Network, Toulouse, France, 5 CERPPS—Study and Research Center in Psychopathology and Health Psychology, University of Toulouse II Jean-Jaurès, Toulouse, France, 6 Department of Medical Pharmacology, Neurology and Movement Disorders Department, Referent Center of Parkinson's disease, CHU of Lille, Univ. Lille Neuroscience & Cognition, Inserm, UMR-S1172, Licend, NS-PARK/FCRIN Network, Lille, France, 7 Department of Neurology, Rouen University Hospital and University of Rouen, Rouen, France, 8 Laboratory of Neuronal and Neuroendocrine Differentiation and Communication, INSERM U1239, NS-PARK/FCRIN Network, Mont-Saint-Aignan, France, 9 Clinique Neurologique, Hôpital Guillaume et René Laennec, NS-PARK/FCRIN Network, Boulevard Jacques Monod, Nantes, France, 10 Neurology Department, Nancy University Hospital, Nancy, France, 11 Behavior and Basal Ganglia Research Unit (EA 4712), University of Rennes 1, Rennes, France, 12 Department of Neurology, Rennes University Hospital, NS-PARK/FCRIN Network, Rennes, France, 13 Service Universitaire de Psychiatrie, Hôpital Pasteur 1, CHU de Nice, Nice, France, 14 Service de Neurologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, 15 Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), INSERM-U964/CNRS-UMR7104/Université de Strasbourg, Illkirch, France, 16 Fédération de Médecine Translationnelle de Strasbourg (FMTS), Université de Strasbourg, NS-PARK/FCRIN Network, Strasbourg, France, 17 Département de Neurologie, Hôpital Pitié-Salpêtrière, AP-HP, Faculté de Médecine de Sorbonne Université, UMR S 1127, Inserm U 1127, and CNRS UMR 7225, and Institut du Cerveau et de la Moëlle épinière, NS-PARK/FCRIN Network, Paris, France, 18 Pôle Neurosciences, Foch Hospital, Suresnes, France, 19 Université de Versailles Paris-Saclay, INSERM U992, CEA Neurospin, France, 20 Service de Neurologie, Centre Expert Parkinson, CIC-INSERM 1402, CHU Poitiers, NS-PARK/FCRIN Network, Poitiers, France, 21 CHU de Bordeaux, Centre Expert Parkinson, Institut des maladies neuro-dégénératives, Bordeaux, France, 22 Hôpital Fondation A de Rothschild, Service de recherche clinique, Paris, France, 23 Department of Neurology, Department of Neurosurgery, Expert Centre for Parkinson's disease, Amiens University Hospital, EA 4559 Laboratoire de Neurosciences Fonctionnelles et Pathologie (LNFP) Université de Picardie Jules Verne, University of Picardie Jules Verne (UPJV), NS-PARK/FCRIN Network, Amiens, France, 24 Neurology Department, Université Clermont Auvergne, EA7280, Clermont-Ferrand University Hospital, NS-PARK/FCRIN Network, Clermont-Ferrand, France, 25 Univ Lyon, Université Claude Bernard Lyon 1, Faculté de Médecine Lyon Sud Charles Mérieux, Lyon, France, 26 CNRS, Institut des Sciences Cognitives, UMR 5229, Bron, France, 27 Centre Expert Parkinson, Hôpital Neurologique "Pierre Wertheimer", Hospices Civils de Lyon, NS-PARK/FCRIN Network, Lyon, France, 28 Aix Marseille Université, AP-HM, Hôpital de La Timone, Service de Neurologie et Pathologie du Mouvement, and UMR CNRS 7289, Institut de Neuroscience de La Timone, NS-PARK/FCRIN Network, Marseille, France

[†] Membership of the PREDI-STIM study group is provided in the Acknowledgments. The lead author is David Devos: david.devos@chru-lille.fr.

* mathilde.boussac@inserm.fr

the ClinicalTrials.gov website (NCT02360683). The authors of this study received complete access to the data because they are part of this multicentric study and specifically of this ancillary study. Hence, the promoter gave us the raw data. The data is available to researchers who meet the criteria for access to confidential data from the Research and Innovation unit of Lille University Hospital Center; contact Morgane COEFFET (clinical research associate): morgane.coeffet@chru-lille.fr.

Funding: The study was funded by the France Parkinson charity and French Ministry of Health (PHRC national 2012). This is an ancillary study to Protocol ID: 2013-A00193-42; ClinicalTrials.gov: NCT02360683. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Background

Studies assessing personality dimensions by the “Temperament and Character Inventory” (TCI) have previously found an association between Parkinson’s disease (PD) and lower Novelty Seeking and higher Harm Avoidance scores. Here, we aimed to describe personality dimensions of PD patients with motor fluctuations and compare them to a normative population and other PD populations.

Methods

All PD patients awaiting Deep Brain Stimulation (DBS) answered the TCI before neurosurgery. Their results were compared to those of historical cohorts (a French normative population, a de novo PD population, and a PD population with motor fluctuations).

Results

Most personality dimensions of our 333 included PD patients with motor fluctuations who are candidates for DBS were different from those of the normative population and some were also different from those of the De Novo PD population, whereas they were similar to those of another population of PD patients with motor fluctuations.

Conclusions

During the course of PD, personality dimensions can change in parallel with the development of motor fluctuations, either due to the evolution of the disease and/or dopaminergic treatments.

Introduction

Initial studies characterized PD patients as rigid, introverted, obsessional, and depressive. The “Temperament and Character Inventory” (TCI) was subsequently used to examine several PD populations to better assess their personality dimensions. The most recent review of the literature in PD shows that certain specific personality dimensions (lower Novelty Seeking and higher Harm Avoidance scores) differ from those of healthy subjects, based on the TCI and its derivatives (Tridimensional Personality Questionnaire, etc.) [1]. These results reflect the relatively anxious, reflective, and reserved temperament of PD patients. Nevertheless, most studies have been based on small PD samples with a heterogeneous duration of disease (mainly patients in early stages of PD with mild symptoms).

Our main objective was thus to better characterize personality of PD patients. It is why we decided to evaluate personality dimensions in a large cohort of PD patients with motor fluctuations awaiting deep brain stimulation of the sub-thalamic nucleus (DBS-STN) and compare them to those of three historical cohorts (a normative population and two PD populations). This objective was part of a bigger study of which the first part evaluated the association between personality dimensions and quality of life before DBS-STN [2].

Materials and methods

This is a secondary analysis of our PSYCHO-STIM [2] study, for which the objective was to identify personality dimensions associated with quality of life in PD patients awaiting DBS-STN.

The study population consisted of PD patients who participated in the PREDI-STIM study (<https://clinicaltrials.gov/ct2/show/NCT02360683>). All patients gave their informed written consent and the PREDI-STIM study was approved by the CPP Nord-Ouest IV Ethical Committee (N° IDRCB: 2013 A0019342).

The TCI assesses the patients' personality based on seven independent personality dimension scores: four temperament domains (Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), and Persistence (P), which is supposed to depend on the cerebral level of dopamine, serotonin, noradrenalin, and glutamate, respectively, according to the original model of C. Robert Cloninger) and three developmental character traits (Self-Directedness (SD), Cooperativeness (C), and Self-Transcendence (ST), which rely on the level of individual, social, and spiritual maturity, respectively).

We selected historical cohorts by first searching for a French normative population in PubMed using the keywords "TCI" and "French population", to avoid cultural differences in TCI scores, and found only one [3]. We then searched the primary studies with an additional PubMed search using the search terms "Parkinson", "TCI", "Novelty Seeking", "Harm Avoidance", "Reward Dependence", "Persistence", "Self-Directedness", "Cooperativeness", and "Self-Transcendence". After finding only one French PD study [4], we expanded our search to the international level. After removing all meta-analyses or reviews and retaining only studies using the full TCI, nine studies of historical PD cohorts remained. From them, we selected two PD cohorts [4, 5]: a French PD population with motor fluctuations and an early-stage PD population (*de novo*). The selection criteria of the PD cohorts are presented in "Table 1". Each historical cohort was selecting only if they had a sufficient number of subjects and if the selected population was well-described.

Statistical analyses

A descriptive analysis was performed on the study population, and missing responses in the TCI, were imputed [2].

First, one-sample Wilcoxon tests were used for each TCI dimension for comparisons of the study population with the two historical cohorts [3, 5], without full data available, using the mean scores of the TCI dimensions of the two cohorts. Two-sample Mann-Whitney tests were used for each TCI dimension for comparison with our previous study [4], for which full data were available. Then, the 95% confidence interval (CI95) was calculated for each population to check for statistical significance: a non-overlap between the CI95 represents a true difference between populations.

Then, multivariate linear regression models were generated to explain the variability of the TCI dimension scores using the TCI dimensions as response variables and three explanatory variables: the LED (levodopa equivalent dose), the presence versus absence of dopaminergic agonists, and the sex of the patient. Seven models were generated (one for each TCI dimension).

Tests were two-sided and the alpha level was set to 0.05. For comparisons with the historical cohorts, only results with a $p\text{-value} < 0.05$ and non-overlapping CI95 were considered significant. All analyses were performed using R Studio Software Version 1.1.456.

Results

Our PD population [2], included 333 PD patients (113 women and 220 men), with a mean age of 61.1 ± 7.2 and a mean duration of PD of 10.2 ± 4.1 years. All patients were under antiparkinsonian treatment at the time of study, with a mean LED of $1.181.6 \pm 789.4$ mg/day.

Table 1. Selection criteria of studies on personality in PD population.

Studies	Population	Exclusion criteria	Inclusion criteria
Kaasinen V , Nurmi E, Bergman J, et al. Personality traits and brain dopaminergic function in Parkinson's disease. In: Proceedings of the National Academy of Sciences of the United States of America. Vol 98.; 2001:13272–13277	• never-medicated PD patients (n = 61)	/	<ul style="list-style-type: none"> • never-medicated PD • age matched our population (62.1 y. o.) • all TCI dimensions scores available
McNamara P, Durso R, Harris E. "Machiavellianism" and frontal dysfunction: evidence from Parkinson's disease. <i>Cognit Neuropsychiatry</i> . 2007;12(4):285–300	• medicated PD patients (n = 35)	<ul style="list-style-type: none"> • stage of the PD not known • older than our population (70.4 y.o.) 	/
Bodi N, Keri S, Nagy H, et al. Reward-learning and the novelty-seeking personality: a between-and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. <i>Brain</i> . 2009;132(9):2385–2395	<ul style="list-style-type: none"> • never-medicated PD patients (n = 26) • recently medicated PD patients (n = 22) 	• only temperaments scores available (characters scores missing)	/
Fassino S, Abbate Daga G, Gramaglia C, et al. Novelty-seeking in Parkinson's disease after deep brain stimulation of the subthalamic nucleus: a case-control study. <i>Psychosomatics</i> . 2010;51(1):62–67. doi: 10.1176/appi.psy.51.1.62	<ul style="list-style-type: none"> • PD patients treated by DBS-STN (n = 22) • PD patients treated by drugs (n = 22) 	<ul style="list-style-type: none"> • only NS, C and ST dimensions scores available • non-matching DBS-STN surgery criteria and older than our population (68,1 y.o.) 	/
Dupouy J . Personnalité Et Maladie De Parkinson Idiopathique: À Propos D'Une Revue De La Littérature Et De Deux Études Expérimentales. Published online 2014.	• PD patients awaiting DBS-STN (n = 30)	/	<ul style="list-style-type: none"> • PD patients with motor fluctuations awaiting DBS-STN with matching demographic features as our population • all TCI dimensions scores available
Díaz-Santos M, Cao B, Yazdanbakhsh A, Norton DJ, Neargarder S, Cronin-Golomb A. Perceptual, cognitive, and personality rigidity in Parkinson's disease. <i>Neuropsychologia</i> . 2015;69:183–193. doi: 10.1016/j.neuropsychologia.2015.01.044	• medicated PD patients (n = 28)	<ul style="list-style-type: none"> • TCI dimensions scores non-available • TCI version expanded to 240 items 	/
Harris E, McNamara P, Durso R. Novelty seeking in patients with right- versus left-onset Parkinson disease. <i>Cogn Behav Neurol</i> . 2015;28(1):11–16. doi: 10.1097/WNN.0000000000000047	• medicated PD patients (2 PD groups: left-onset, n = 17; right-onset, n = 18)	• TCI version expanded to 240 items	/
Ishii T, Sawamoto N, Tabu H, et al. Altered striatal circuits underlie characteristic personality traits in Parkinson's disease. <i>J Neurol</i> . 2016;263(9):1828–1839	• un-medicated and medicated PD patients (n = 16)	• only temperaments scores available (characters scores missing)	/
Luca A, Nicoletti A, Mostile G, et al. Temperament traits and executive functions in Parkinson's disease. <i>Neurosci Lett</i> . 2018;684:25–28. doi: 10.1016/j.neulet.2018.06.040	• medicated PD patients (n = 50)	<ul style="list-style-type: none"> • only NS, HA and RD dimensions scores available • TCI version expanded to 240 items 	/

PD = Parkinson's disease; DBS-STN = Deep Brain Stimulation of the Sub-Thalamic Nucleus; y.o. = years old; NS = Novelty Seeking; HA = Harm Avoidance; RD = Reward Dependence; C = Cooperativeness; ST = Self-Transcendence; TCI = Temperament and Character Inventory.

<https://doi.org/10.1371/journal.pone.0245142.t001>

From the French normative population [3], we selected data of the “old group” (256 subjects aged from 50 to 88) for matching with our PD patients. The PD patients presented significantly higher scores for the NS, RD, P, SD, and C dimensions and significantly lower scores for the ST dimension than the “old group” of normative subjects (“Table 2”). Only the HA was similar between the two populations.

In the linear models, sex was significantly associated with the HA, RD, C, and ST scores in our PD population (women having higher scores in these dimensions). Quantitative LED and the use of dopaminergic agonists were not associated with any TCI dimensions.

Discussion

This study shows that PD patients with motor fluctuations awaiting DBS may have a characteristic personality that changes during the course of the disease and the introduction of dopaminergic treatments.

Table 2. Comparisons with historical cohorts.

PD patients, PREDI-STIM (<i>n</i> = 333)			French general population, Pelissolo et al. (2000) [3] (<i>n</i> = 256)				De novo PD patients, Kaasinen et al. (2001) [5] (<i>n</i> = 61)				PD patients with motor fluctuations, Dupouy (2014) [4] (<i>n</i> = 30)			
	Mean	CI	Mean	CI		p.value	Mean	CI		p.value	Mean	CI		p.value
NS	16.8	16.3–17.3	14.5	13.9–15.1	N-O	7.4x10 ⁻¹⁵ *	13.1	11.6–14.6	N-O	3.0x10 ⁻²⁸ *	17.8	15.1–20.5		0.46
HA	17.5	16.8–18.2	16.6	15.8–17.4		4.7x10 ⁻² *	18.8	17.1–20.5		1.1x10 ⁻³ *	19.4	16.7–22.2		0.10
RD	15.4	15.1–15.8	14	13.5–14.5	N-O	3.6x10 ⁻¹² *	14.1	13.2–15.0	N-O	8.1x10 ⁻¹⁰ *	15.5	14.2–16.7		1.00
P	5.4	5.2–5.6	4.6	4.4–4.8	N-O	9.8x10 ⁻¹² *	3.51	3.0–4.0	N-O	5.8x10 ⁻³⁹ *	6.2	4.3–8.1		0.98
SD	34.2	33.5–34.9	32.7	32.0–33.4	N-O	2.4x10 ⁻⁷ *	31.4	29.8–33.0	N-O	4.1x10 ⁻¹⁷ *	31.1	28.3–33.9		0.04 *
C	33.6	33.2–34.1	32.3	31.7–32.9	N-O	1.6x10 ⁻¹¹ *	32.2	30.9–33.5		1.6x10 ⁻¹¹ *	33.4	31.8–35.0		0.78
ST	12.2	11.6–12.8	14.6	13.9–15.3	N-O	1.0x10 ⁻¹⁵ *	12.7	10.9–14.5		3.4x10 ⁻³ *	15.2	13.0–17.5	N-O	8.9x10 ⁻³ *

One-sample (for Pelissolo and Kaasinen studies) and two-sample (for Dupouy study) Wilcoxon tests: * p.value < 0.05 –CI = Confidence Interval at a confidence level of 95%–N-O = Non-overlapping CI95%–PD = Parkinson's disease; NS = Novelty Seeking; HA = Harm Avoidance; RD = Reward Dependence; P = Persistence; SD = Self-Directedness; C = Cooperativeness; ST = Self-Transcendence.

Our PD patients also presented significantly higher scores for the NS, RD, P, and SD dimensions than the de novo PD patients (never-medicated) [5] and significantly lower scores in the ST dimension than the other population of PD patients with motor fluctuations [4] (Table 2).

<https://doi.org/10.1371/journal.pone.0245142.t002>

PD patients with motor fluctuations who are candidates for DBS had significantly higher scores for Novelty Seeking, Reward Dependence, Persistence, Self-Directedness, and Cooperativeness and lower scores for Self-Transcendence than the age-matched French normative subjects [3], confirming that this group of PD patients have a specific personality. Nonetheless, our results diverge from the literature which has generally reported lower Novelty Seeking and higher Harm Avoidance scores in PD patients compared to controls [1]. The use of a general population (including subjects with depression, which may mask the higher Harm Avoidance scores of our PD population, as depression is also linked to higher Harm Avoidance scores [6]) as a control group instead of healthy volunteers may explain this divergence in Harm Avoidance scores. Plus, the sex ratio difference between our PD population (women = 33.9%) and the normative population (women = 56.3%) probably explains the higher Self-Transcendence score in the population of Pelissolo, because women generally have higher Self-Transcendence scores than men [3], as confirmed in our population. Finally, the unexpectedly higher Novelty Seeking, Reward Dependence, Persistence, Self-Directedness, and Cooperativeness scores in our PD population appear to be specific to the stage of motor fluctuations and/or dopaminergic treatments, as opposed to the earlier stage of PD populations in the literature [1]. Indeed, De Novo PD patients [5] presented significantly lower personality dimension scores (Novelty Seeking, Reward Dependence, Persistence, and Self-Directedness) than our PD patients with motor fluctuations. The appearance of these differences during the evolution of PD would be unusual, because in Cloninger's model, temperaments (Novelty Seeking, Reward Dependence, and Persistence) should not change over time in the general population [6], whereas the character (Self-Directedness) may evolve. We propose thus four hypotheses: differences in personality dimensions may i) result from the evolution of PD, with the presence of motor fluctuations, ii) be induced by dopaminergic treatments [7], iii) be linked to decision-making processes concerning surgery, or iv) be related to the stress of awaiting DBS-STN [8].

- i. During the course of PD, dopaminergic deafferentation extends from the olfactory nucleus to the limbic system [9]. Such brain alterations consequently participate in the emergence of non-motor fluctuations, psychopathologies and impulse-control disorders [10]. Thus, such increasing dopaminergic deafferentation may also affect the personality of PD patients at

later stages of the disease. Indeed, the supposed link between TCI temperament dimensions and neurotransmitters [6] appears to be congruent with degeneration of the dopaminergic, serotonergic, and noradrenergic system in PD [10]. In this supposed link between temperament dimensions and neurotransmitters, Novelty Seeking is associated with dopamine levels in the brain, Harm Avoidance with serotonin, Reward Dependence with noradrenalin, and Persistence with glutamate. These links mainly came from biological and genetic studies [11–18]. Nonetheless, these classical assumptions are not as straightforward. Temperament dimensions seem to be much more complex and to rely on more than a single neurotransmitter. Harm Avoidance scores, for example, were found to be correlated with a dopamine uptake in the right caudate nucleus; whereas the Novelty Seeking scores were not [5]. Finally, it seems that maybe temperament dimensions are not simply linked to neurotransmitters levels but rather to cerebral networks activity. Indeed, Novelty Seeking and Harm Avoidance scores may both be correlated with connectivity between the striatum, hippocampus and amygdala [19]. Striatum connectivity with limbic areas seems therefore to impact personality dimensions [19]. All of this supports the idea that each TCI temperament dimension is a complex concept influenced by different neurotransmitters and/or brain areas, probably explaining why the specific dopaminergic deafferentation of PD impacts several TCI dimensions.

- ii. Dopaminergic treatments may induce changes in personality dimensions, such as an increase in Novelty Seeking scores in PD patients [7], and it seems that only the presence of dopaminergic treatment affects personality dimensions and not the dose nor pharmacological class of the treatment, as seen by the absence of significant association between LED or agonist treatments and personality dimensions. To confirm this result, it would have been interesting to be able to use the complete data from the de novo PD population of Kaasinen and collaborators, which unfortunately was not available. In any case, even if our population was on relatively high dose of LED, it presented a relatively good range of LED (SD = 789.4 mg/day) which should have been enough variability to show an impact of dose of treatment on TCI dimensions. Thus, changes in neurotransmitters levels induced by drugs may modulate some temperament scores [20]. Indeed, many studies have shown that dopaminergic treatments in PD could lead to impulsivity, addiction and risk-taking behaviors, which might be associated with personality dimensions, since personality, behaviors and mood are closed concepts. In fact, PD patients developing pathological gambling generally score higher on novelty-seeking tests [21]. Also, the cerebral pathway implicated in addictive syndromes in PD seems to be mainly the mesocorticolimbic pathway also implied in reward and reinforcement process [22], involved in personality expression. Concerning specifically the dopamine agonists, recently medicated PD patients had higher Novelty Seeking scores compared to controls, whereas never-medicated PD patients had lower Novelty Seeking scores compared to controls [7]. This difference was attributed to a direct effect of dopaminergic agonist [7], even if the reason of these changes was not clearly checked. It could also have appeared with levodopa treatment, as our result does not suggest a class effect of dopaminergic treatment on PD patients personality. Nonetheless, because there is good evidence that dopamine agonists are in part responsible of Impulse Control Disorders development in PD patients [23, 24], a direct causal implication of this class of treatment on personality dimensions cannot be ruled out, even if dopamine agonists are not the only treatment impacting behavioral disorders in PD population. Indeed, Dopamine Dysregulation Syndrome seems to be mainly associated with levodopa uptake [25], and has also been showed to lead to mood changes in PD patients as well as self-injury behaviors [26]. It

could thus also probably lead to personality changes. Finally, both levodopa and dopamine agonists could be associated with personality dimensions changes.

- iii. Not all PD patients accept and choose DBS. Thus, PD patients' personality may influence their choice of a second-generation treatment (DBS versus infusion therapies, for example).
- iv. Certain TCI personality dimensions have been shown to be predictive of a better response to stress (resilience) such as higher Persistence and Self-Directedness [8]. Moreover, resilience is the result of a positive adaptation in the face of adversity, depending on neurobiological mechanisms [27]. It is opposed to vulnerability to stress and depends to the strategy used in response to stress [27]. Thus, the higher scores for the Persistence and Self-Directedness dimensions in our PD population awaiting a stressful event (DBS-STN) relative to those of the *de novo* PD population may be linked to higher resilience to overcome the stressful event. Moreover, this relation of cause-consequence could be in both ways: either Persistence and Self-Directedness scores increase in order to improve PD patients resilience to deal with the stress of DBS; or only PD patients having enough basal resilience (partly shown by high Persistence and Self-Directedness scores) would choose DBS. In that respect, this second idea would be linked with our preceding hypothesis of DBS choice: maybe, only PD patients that are able to control their stress and demonstrate resilience, are the one accepting DBS.

These observations suggest that the personality dimensions of PD patients may change during the course of the disease. We even make the hypothesis that PD patients personality may not be much different from those of the healthy population at the beginning of the disease. Other factors (pharmacological treatments, evolution of PD, etc.) may be responsible for the observed personality differences. Indeed, in most of the studies that reported differences in the Novelty Seeking and Harm Avoidance scores between PD patients and controls, the PD patients were already being treated with dopaminergic drugs [1]. Even if Harm Avoidance was found increased in a *de novo* PD population [5], it could only be due to depression, not assessed in this study, and not to the disease itself; which could explain why we did not found any difference in Harm Avoidance scores between our population and the *de novo* one, depression being present at each stage of the disease.

Comparison of the two PD populations with motor fluctuations awaiting DBS [4], with an equivalent LED, showed similar TCI scores, supporting our four hypotheses. Thus, PD patients with motor fluctuations who are candidates for DBS have a specific personality, the sole small difference in Self-Transcendence likely being related to demographic differences, as Self-Transcendence is the most culturally variable dimension [28].

In conclusion, the personality of PD patients appears to depend on the stage of the disease, with differences due to either the evolution of PD itself, dopaminergic treatments, or psychological factors (the choice of DBS or the stress engendered by it).

Acknowledgments

We thank all participants for their cooperation, Déborah Meligne from ToNIC (Toulouse NeuroImaging Center–INSERM, University of Toulouse III) and psychologists Gaelle Bongeot and Alice Dhellemmes from the CERPPS (Study and Research Center in Psychopathology and Health Psychology–University of Toulouse Jean-Jaurès) for their reflection. The authors are also grateful for support from the French clinical research network NS-Park/F-Crin and the Fédération de la Recherche Clinique du CHU de Lille (with Anne-Sophie Rolland, Alain Duhamel, Maeva Kheng, Julien Labreuch, Dominique Deplanque, Edouard Millois, Nolwen

Dautrevaux, Victor Laugeais, Maxime Caillier, Aymen Aouni, Pauline Guyon, Francine Niset, Valérie Santraine, Marie Pleuvret, Julie Moutarde and Laetitia Thibault).

We also thank all the members of the PREDI-STIM study group: Dr Caroline Moreau, Pr Luc Defebvre, Dr Nicolas Carriere, Dr Guillaume Grolez, Dr Guillaume Baille, Dr Kreisler, Pr Jean-Pierre Pruvo, Pr Leclerc, Dr Renaud Lopes, Dr Romain Viard, Dr Gregory Kuchcinski, Mr Julien Dumont, Pr Kathy Dujardin, Mme M Delliaux, Mrs M Brion, Dr Gustavo Touzet, Pr Nicolas Reyns, Pr Arnaud Delval, Mrs Valerie Santraine, Mrs Marie Pleuvret, Mrs Nolwen Dautrevaux, Mr Victor Laugeais, Thavarak Ouk, Camille Potey, Celine Leclercq and Elise Gers (for Lille University Hospital); Jean-Christophe Corvol, Marie-Vidaillhet, Elodie Hainque, Marie-Laure Welter, Lucette Lacomblez, David Grabli, Emmanuel Roze, Yulia Worbe, Cécile Delorme, Hana You, Jonas Ihle, Raquel Guimeraes-Costa, Florence Cormier-Dequaire, Aurélie Méneret, Andréas Hartmann, Louise-Laure Mariani, Stéphane Lehericy, Virginie Czernecki, Fanny Pineau, Frédérique Bozon, Camille Huiban, Eve Benchetrit, Carine Karachi, Soledad Navarro, Philippe Cornu, Arlette Welaratne, Carole Dongmo-Kenfack, Lise Mantisi, Nathalie Jarry, Sophie Aix and Carine Lefort (for the AP-HP, Paris); Dr Tiphaine Rouaud, Pr Philippe Damier, Pr Pascal Derkinderen, Dr Anne-Gaelle Corbille, Dr Elisabeth Calvier-Auf-fray, Mrs Laetitia Rocher, Mrs Anne-Laure Deruet, Dr Raoul Sylvie, Dr Roualdes Vincent and Mrs Le Dily Séverine (for Nantes University Hospital); Dr Ana Marques, Dr Berangere Debilly, Pr Franck Durif, Dr Philippe Derost, Dr Charlotte Beal, Carine Chassain, Laure Delaby, Tiphaine Vidal, Pr Jean Jacques Lemaire, Isabelle Rieu and Elodie Durand (for Clermont-Ferrand University Hospital); Pr Alexandre Eusebio, Pr Jean-Philippe Azulay, Dr Tatiana Witjas, Dr Frédérique Fluchère, Dr Stephan Grimaldi, Pr Nadine Girard, Eve Benchetrit, Marie Delfini, Dr Romain Carron, Pr Jean Regis, Dr Giorgio Spatola and Camille Magnaudet (for the AP-HM, Marseille); Dr Ansquer Solène, Dr Benatru Isabelle, Dr Colin Olivier, Pr Houeto JL, Pr Guillevin Remy, Mrs Fradet Anne, Mrs Anziza Manssouri, Mrs Blondeau Sophie, Dr Richard Philippe, Dr Cam Philippe, Dr Page Philippe, Pr Bataille Benoit, Mrs Rabois Emilie and Mrs Guillemain Annie (for Poitiers University Hospital); Dr Drapier Sophie, Dr Frédérique Leh, Dr Alexandre Bonnet, Pr Marc Vérin, Dr Jean-Christophe Ferré, Mr Jean François Houvenaghel, Pr Claire Haegelen, Mrs Françoise Kestens and Mrs Solenn Ory (for Rennes University Hospital); Pr Pierre Burbau, Dr Nathalie Damon-Perriere, Pr Wassilios Meissner, Pr Francois Tison, Dr Stéphanie Bannier, Dr Elsa Krim, Pr Dominique Guehl, Sandrine Molinier-Blossier, Morgan Ollivier, Marion Lacoste, Nicolas Auzou, Marie Bonnet, Pr Emmanuel Cuny, Dr Julien Engelhardt, Olivier Branchard, Clotilde Huet and Julie Blanchard (for Bordeaux University Hospital); Pr Rascol Olivier, Dr Christine Brefel Courbon, Dr Fabienne Ory Magne, Dr Marion Simonetta Moreau, Pr Christophe Arbus, Pr Fabrice Bonneville, Dr Jean Albert Lotterrie, Marion Sarraill, Charlotte Scotto d'Apollonia, Pr Patrick Chaynes, Pr François Caire and Estelle Harroch (for Toulouse University Hospital); Pr David Maltete, Dr Romain Lefaucheur, Dr Damien Fetter, Dr Nicolas Magne, Mrs Sandrine Bioux, Mrs Maud Loubeyre, Mrs Evangéline Bliaux, Mrs Dorothée Pouliquen, Pr Stéphane Derrey, Mrs Linda Vernon and Dr Frédéric Ziegler (for Rouen University Hospital); Mathieu Anheim, Ouhaïd Lagha-Boukbiza, Christine Tranchant, Odile Gebus, Solveig Montaut, S Kremer, Nadine Longato, Clélie Phillips, Jimmy Voirin, Marie des Neiges Santin, Dominique Chauss-emy and Dr Amaury Mengin (for Strasbourg University Hospital); Dr Caroline Giordana, Dr Claire Marsé, Lydiane Mondot, Bruno Giordana, Robin Kardous, Bernadette Baillet, Héloïse Joly, Denys Fontaine, Dr Aurélie Leplus, Amélie Faustini and Vanessa Ferrier (for Nice University Hospital); Pr Pierre Krystkowiak, Dr Mélissa Tir, Pr Jean-Marc Constans, Sandrine Wannepain, Audrey Seling, Dr Michel Lefranc, Stéphanie Blin and Béatrice Schuler (for Amiens University Hospital); Pr Stéphane Thobois, Dr Teodor Danaila, Dr Chloe Laurencin, Pr Yves Berthezene, Dr Roxana Ameli, Helene Klinger, Dr Gustavo Polo, Patrick Mertens, A

Nunes and Elise Metereau (for Lyon University Hospital); Dr Lucie Hopes, Dr Solène Frismand, Dr Emmanuelle Schmitt, Mrs Mylène Meyer, Mrs Céline Dillier, Pr Sophie Colnat and Mrs Anne Chatelain (for Nancy University Hospital); Dr Jean-Philippe Brandel, Dr Cécile Hubsch, Dr Patte Karsenti, Dr Marie Lebouteux, Dr Marc Ziegler, Dr Christine Delmaire, Dr Julien Savatowky, Mrs Juliette Vrillac, Mrs Claire Nakache, Dr Vincent D'Hardemare and Mr Lhaouas Belamri (for the Rothschild foundation of Paris); Dr Philippe Graveleau, Dr Camille Decroq, Dr Frédéric Bourdain, Dr Vadim Afanassiev, Dr Anne Boulin, Mrs Elodie Dupuy, Dr Bérénice Gardel, Pr Béchir Jarraya, Mrs Delphine Lopez and Mr Christophe Fruit (for the Foch Hospital of Paris-Saclay University); David Gay, Robin Bonicel, Fouzia El Mountassir, Clara Fischer, Jean-François Mangin, Marie Chupin and Yann Cointepas (for CATI (MRI acquisition management, preprocessing and data management)); Bertrand Accart, Patrick Gelé, Florine Fievet, Matthieu Chabel, Virginie Derenaucourt, Loïc Facon, Yanick Tchantchou Njossé and Dominique Deplanque (for CRB of Lille (Center of Biological Resources)); and Alain Duhamel, Lynda Djemmane and Florence Duflot (for Data management of Lille).

Author Contributions

Conceptualization: Christine Brefel-Courbon.

Data curation: Anne-Sophie Rolland.

Formal analysis: Mathilde Boussac.

Funding acquisition: David Devos.

Investigation: Christine Brefel-Courbon.

Methodology: Mathilde Boussac, Vanessa Rousseau, Jean Christophe Corvol.

Software: Mathilde Boussac.

Supervision: Christophe Arbus, Christine Brefel-Courbon.

Validation: Estelle Harroch, Vanessa Rousseau, Aurélie Croiset, Christine Brefel-Courbon.

Writing – original draft: Mathilde Boussac.

Writing – review & editing: Mathilde Boussac, Christophe Arbus, Julia Dupouy, Estelle Harroch, Vanessa Rousseau, Aurélie Croiset, Fabienne Ory-Magne, Olivier Rascol, Caroline Moreau, Anne-Sophie Rolland, David Maltête, Tiphaine Rouaud, Mylène Meyer, Sophie Drapier, Bruno Giordana, Mathieu Anheim, Elodie Hainque, Béchir Jarraya, Isabelle Benatru, Nicolas Auzou, Lhaouas Belamri, Mélissa Tir, Ana-Raquel Marques, Stéphane Thobois, Alexandre Eusebio, Jean Christophe Corvol, David Devos, Christine Brefel-Courbon.

References

1. Santangelo G, Garramone F, Baiano C, D'Iorio A, Piscopo F, Raimo S, et al. Personality and Parkinson's disease: A meta-analysis. *Parkinsonism*. 2018.
2. Boussac M, Arbus C, Dupouy J, Harroch E, Rousseau V, Ory-Magne F, et al. Personality Dimensions Are Associated with Quality of Life in Fluctuating Parkinson's Disease Patients (PSYCHO-STIM). *J Park Dis*. 2020 Jan 1; 10(3):1057–66. <https://doi.org/10.3233/JPD-191903> PMID: 32444557
3. Pélissolo A, Lépine JP. Normative data and factor structure of the Temperament and Character Inventory (TCI) in the French version. *Psychiatry Res*. 2000 Apr 24; 94(1):67–76. [https://doi.org/10.1016/S0165-1781\(00\)00127-X](https://doi.org/10.1016/S0165-1781(00)00127-X) PMID: 10788679
4. Dupouy J. Personnalité Et Maladie De Parkinson Idiopathique: À Propos D'Une Revue De La Littérature Et De Deux Études Expérimentales. Toulouse; 2014.
5. Kaasinen V, Nurmi E, Bergman J, Eskola O, Solin O, Sonninen P, et al. Personality traits and brain dopaminergic function in Parkinson's disease. In: *Proceedings of the National Academy of Sciences of*

- the United States of America. 2001. p. 13272–13277. <https://doi.org/10.1073/pnas.231313198> PMID: 11687621
6. Hansenne M. Le modèle biosocial de la personnalité de Cloninger. *Année Psychol.* 2001; 101(1):155–81.
 7. Bodi N, Keri S, Nagy H, Moustafa A, Myers CE, Daw N, et al. Reward-learning and the novelty-seeking personality: a between-and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. *Brain.* 2009; 132(9):2385–2395. <https://doi.org/10.1093/brain/awp094> PMID: 19416950
 8. Chae H, Park SH, Garcia D, Lee SJ. Cloninger's TCI associations with adaptive and maladaptive emotion regulation strategies. *PeerJ [Internet].* 2019 Oct 24 [cited 2019 Dec 13];7. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6815648/> <https://doi.org/10.7717/peerj.7958> PMID: 31660279
 9. Braak H, Del Tredici K, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging.* 2003 Apr; 24(2):197–211. [https://doi.org/10.1016/s0197-4580\(02\)00065-9](https://doi.org/10.1016/s0197-4580(02)00065-9) PMID: 12498954
 10. Castrioto A, Thobois S, Carnicella S, Maillet A, Krack P. Emotional manifestations of PD: Neurobiological basis. *Mov Disord.* 2016; 31(8):1103–13. <https://doi.org/10.1002/mds.26587> PMID: 27041545
 11. Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, et al. Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nat Genet.* 1996 Jan; 12(1):78. <https://doi.org/10.1038/ng0196-78> PMID: 8528256
 12. Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nat Genet.* 1996 Jan; 12(1):81. <https://doi.org/10.1038/ng0196-81> PMID: 8528258
 13. Noble EP, Ozkaragoz TZ, Ritchie TL, Zhang X, Belin TR, Sparkes RS. D2 and D4 dopamine receptor polymorphisms and personality. *Am J Med Genet.* 1998 May 8; 81(3):257–67. PMID: 9603615
 14. Hansenne M, Ansseau M. Harm avoidance and serotonin. *Biol Psychol.* 1999 Oct; 51(1):77–81. [https://doi.org/10.1016/s0301-0511\(99\)00018-6](https://doi.org/10.1016/s0301-0511(99)00018-6) PMID: 10579422
 15. Ricketts MH, Hamer RM, Sage JL, Manowitz P, Feng F, Menza MA. Association of a serotonin transporter gene promoter polymorphism with harm avoidance behaviour in an elderly population. *Psychiatr Genet.* 1998; 8(2):41–4. <https://doi.org/10.1097/00041444-199800820-00001> PMID: 9686420
 16. Curtin F, Walker JP, Peyrin L, Soulier V, Badan M, Schulz P. Reward dependence is positively related to urinary monoamines in normal men. *Biol Psychiatry.* 1997 Aug 15; 42(4):275–81. [https://doi.org/10.1016/S0006-3223\(96\)00364-2](https://doi.org/10.1016/S0006-3223(96)00364-2) PMID: 9270904
 17. Garvey MJ, Noyes R, Cook B, Blum N. Preliminary confirmation of the proposed link between reward-dependence traits and norepinephrine. *Psychiatry Res.* 1996 Nov 1; 65(1):61–4. [https://doi.org/10.1016/0165-1781\(96\)02954-x](https://doi.org/10.1016/0165-1781(96)02954-x) PMID: 8953662
 18. Ham B-J, Choi M-J, Lee H-J, Kang R-H, Lee M-S. Reward dependence is related to norepinephrine transporter T-182C gene polymorphism in a Korean population. *Psychiatr Genet.* 2005 Jun; 15(2):145–7. <https://doi.org/10.1097/00041444-200506000-00012> PMID: 15900230
 19. Ishii T, Sawamoto N, Tabu H, Kawashima H, Okada T, Togashi K, et al. Altered striatal circuits underlie characteristic personality traits in Parkinson's disease. *J Neurol.* 2016; 263(9):1828–1839. <https://doi.org/10.1007/s00415-016-8206-0> PMID: 27334907
 20. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. *Arch Gen Psychiatry.* 1993 Dec; 50(12):975–90. <https://doi.org/10.1001/archpsyc.1993.01820240059008> PMID: 8250684
 21. Heiden P, Heinz A, Romanczuk-Seifert N. Pathological gambling in Parkinson's disease: what are the risk factors and what is the role of impulsivity? *Eur J Neurosci.* 2017; 45(1):67–72. <https://doi.org/10.1111/ejn.13396> PMID: 27623191
 22. Ceravolo R, Frosini D, Rossi C, Bonuccelli U. Spectrum of addictions in Parkinson's disease: from dopamine dysregulation syndrome to impulse control disorders. *J Neurol.* 2010 Nov 1; 257(2):276–83. <https://doi.org/10.1007/s00415-010-5715-0> PMID: 21080189
 23. Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, et al. Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Arch Neurol.* 2006; 63(7):969–973. <https://doi.org/10.1001/archneur.63.7.969> PMID: 16831966
 24. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology.* 2009 May 26; 72(Issue 21, Supplement 4):S1–136. <https://doi.org/10.1212/WNL.0b013e3181a1d44c> PMID: 19470958
 25. Warren N, O'Gorman C, Lehn A, Siskind D. Dopamine dysregulation syndrome in Parkinson's disease: a systematic review of published cases. *J Neurol Neurosurg Psychiatry.* 2017; 88(12):1060–4. <https://doi.org/10.1136/jnnp-2017-315985> PMID: 29018160

26. Evans AH, Strafella AP, Weintraub D, Stacy M. Impulsive and compulsive behaviors in Parkinson's disease. *Mov Disord*. 2009; 24(11):1561–70. <https://doi.org/10.1002/mds.22505> PMID: 19526584
27. Wood SK, Bhatnagar S. Resilience to the effects of social stress: Evidence from clinical and preclinical studies on the role of coping strategies. *Neurobiol Stress*. 2015 Jan 1; 1:164–73. <https://doi.org/10.1016/j.ynstr.2014.11.002> PMID: 25580450
28. Garcia-Romeu A. Self-transcendence as a measurable transpersonal construct. *J Transpers Psychol*. 2010; 42(1):26–47.