Open Access Library Journal
2026, Volume 13, e14986
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Neurological, Neuropsychological, and Neuropsychiatric Assessment of Patients with Parkinson's Disease for Subthalamic Nucleus Deep Brain Stimulation Surgery

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How to cite this paper: Dillon, C., Driollet Laspiur, S., Bellotto, M., Romano, M., Vázquez, G.H., Barisic, M., Cupito, A., De Jauregui, M., Castro, D., Pérez Leguizamon, P., Viaggio, M.B. and Peralta, C.M. (2026) Neurological, Neuropsychological, and Neuropsychiatric Assessment of Patients with Parkinson's Disease for Subthalamic Nucleus Deep Brain Stimulation Surgery. *Open Access Library Journal*, **13**: e14986.
https://doi.org/10.4236/oalib.1114986

Received: February 4, 2026
Accepted: March 7, 2026
Published: March 10, 2026

Abstract

Introduction: Subthalamic nucleus Deep brain stimulation surgery (STN-DBS) is a treatment used for patients in the fluctuating and advanced stages of PD. For this, patients must meet specific inclusion and exclusion criteria. The objectives of this work were to evaluate the current neurological, neuropsychiatric status, and cognitive status of patients with PD for STN-DBS. **Methods**: A complete semi-structured neurological and neuropsychiatric interview, validated neurological and neuropsychiatric scales, brain MRI, and Levodopa tests, and a complete neuropsychological battery were administered according to CAPSYT recommendations. **Results**: 48 patients with PD were evaluated; the mean age and schooling were 65.70 years (±8.06), years of illness 15.67 (±7.3), and 12.27 years (±4.28), respectively. Seventeen of these patients were excluded as candidates for neurosurgery. Five patients were excluded due to advanced PD and long disease duration, four patients were excluded due to atypical Parkinsonism, and three patients were excluded due to dementia of multiple domains with a subcortical profile and impairment in daily life activities. Five of these patients were diagnosed with Severe Major Depression Episodes and exhibited more than two of the following conditions: 1) High scores on the Beck Depression Scale; 2) High Okasha suicidality score; 3) High total

score on Barrat impulsivity scale; and/or 4) The presence of psychotic symptoms. **Conclusions**: Our study highlights the relevance of a detailed and complete neurological, neuropsychological, and neuropsychiatric evaluation of PD patients to ensure they are suitable candidates for STN-DBS. The understanding of neurological, neuropsychological symptoms and the evaluation of psychiatric risk factors using validated scales are critical to managing patients before surgery and to guiding post-surgical care.

Subject Areas

Neuroscience

Keywords

Subthalamic Nucleus Deep Brain Stimulation Surgery, Parkinson's Disease, Neurological Symptoms, Neuropsychiatric Symptoms, Neuropsychological Symptoms

1. Introduction

In Parkinson's disease (PD), both motor and neuropsychiatric complications unfold as a consequence of both incremental striatal dopaminergic denervation and intensifying long-term dopaminergic treatment [1]. Together, this leads to dopaminergic sensitization, steadily increasing motor and behavioral responses to dopaminergic medication that result in the detrimental sequelae of long-term dopaminergic treatment [1]. Dopaminergic sensitization in PD affects the motor, cognitive, and limbic domains [1], leading to neuropsychiatric fluctuations, which are frequent and often inevitable consequences [2]-[5]. Paralleling motor fluctuations, [6] neuropsychiatric fluctuations occur as off-drug- and on-drug-related symptoms, with changes in mood and cognition depending on the dopamine level and the degree of sensitization.

Deep brain stimulation surgery (DBS) is a treatment used for patients with fluctuating and advanced stages of PD by stimulating the subthalamic nucleus or Globus pallidus nuclei [1]. Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) by itself has amphetamine-like psychotropic effects on off-period neuropsychiatric symptoms by enhancing well-being and attention and by lowering fatigue, anxiety, and inner restlessness when switching on stimulation in the off-drug condition [7]. These beneficial effects are also found with chronic STN-DBS, together with marked improvement in neuropsychiatric fluctuations [7]-[9].

For success in STN-DBS, careful patient selection must be performed. In 1999, within the framework of the Network for European Central Nervous System Transplantation and Restoration (NECTAR), a dedicated program entitled "Neurosurgical Interventions in Parkinson's Disease was funded to develop a new Core Assessment Program for Surgical Interventional Therapies in PD (CAPSIT-PD) [10]. The Committee proposed several inclusion and exclusion criteria to develop

DBS Surgery. The CAPSIT-PD evaluation [10] requires a multidisciplinary team that includes neurology with a sub-specialization in movement disorders, functional neurosurgery, neuropsychology, and psychiatry. According to CAPSIT-PD recommendations, good candidates for DBS must meet certain inclusion criteria, such as: more than 5 years of PD duration, patients over 40 years of age, patients in the fluctuating phase where medication adjustments are unable to effectively manage symptoms, and patients with problematic tremor that interferes with their quality of life. As exclusion criteria, patients must not have a diagnosis of dementia or suffer from uncontrolled major depression or non-stabilized psychiatric manifestations such as acute psychotic symptoms (hallucinations or delusions). Other exclusion criteria are patients with atypical Parkinsonism, patients with structural lesions observed in brain MRI scans, or patients over 80 years of age [10].

According to Weiss D *et al.* [1], it is important to consider STN-DBS early enough to prevent potentially irreversible psychosocial consequences of dopaminergic complications, but importantly not immediately before a patient shows the first clinical signs of dopaminergic complications. Weiss *et al.* [1] proposes to consider neuropsychiatric dopaminergic complications as a new inclusion criterion in addition to established motor criteria, but this concept will require validation in future clinical trials.

STN-DBS in PD patients is associated with personality changes of increased impulsivity [10]. The increased rate of impulsivity [11] and its possible psychiatric consequences (possible increased suicidal risk in patients with major depression) in patients who underwent STN-DBS underlines the need for a careful and accurate preoperative psychiatric evaluation for a more rigorous selection of patients. The aim of this work is, therefore, to comprehensively assess the current psychiatric and potential risk status and cognitive status of PD patient's candidates for STN-DBS. Overall, this study proposes to evaluate the current neurological, neuropsychiatric and cognitive status of patients with PD to determine inclusion and exclusion criteria for STN-DBS according to CAPSYT-PD recommendations. To achieve this goal, standardized neurological, neuropsychiatric, and cognitive assessment protocols were implemented to obtain a comprehensive picture of the patient's physical and mental condition.

2. Materials and Methods

Type of study: Descriptive observational cross-sectional study.

2.1. Participating Institutions

The study was performed by Neurologists, Neuropsychiatrists, and Neuropsychologists from the CEMIC University Hospital Department of Medicine Neurology Section. Also, Neurosurgeons from CEMIC University Hospital, Department of Medicine, Neurosurgery Section participated in this work.

Researchers from CONICET and the Faculty of Social Sciences of Palermo University (UP), Argentina, collaborated in the development of this paper, and from

Queen's University. School of Medicine. Department of Psychiatry and Center for Neuroscience Studies, Canada.

2.2. Study Population

We evaluated 48 patients of both sexes with a diagnosis of PD, over 40 years of age, who were candidates for DBS.

The study was conducted from 2017 to 2024 at the CEMIC University Hospital. The study was approved by the CEMIC ethics committee and the central ethics committee of the GCBA. All patients signed an informed consent.

Inclusion criteria [10]:

- Patient with more than 5 years of PD evolution.
- Patients over 40 years of age.
- Patients with fluctuating phase* PD that PD medication adjustments could not manage.
- Patients with tremors that interfere with their quality of life.
- Levodopa test, which confirms the dopaminergic responsiveness of patients.

*A fluctuating phase refers to patients with end-of-dose deterioration, off-resistant periods, and problematic dyskinesias.

Exclusion criteria [10]:

- Patients with atypical Parkinsonism.
- Patients with structural lesions observed in brain MRI scans.
- Patients are over 80 years of age.
- Patients with major depressive disorder.
- Patients with Dementia.
- Non-stabilized Psychiatric manifestations, such as acute psychotic symptoms.

2.3. Methodology

The selection process for patients who qualify for STN-DBS neurosurgery consists of two distinct stages (**Figure 1**).

In the first stage, patients were selected and evaluated by a neurology team specializing in PD. They completed the Unified Parkinson's Disease Rating Scale (UPDRS) [12] for motor symptoms, and a brain MRI was performed. The dopaminergic responsiveness has been evaluated through a pharmacological test, the Levodopa Challenge Test. The test had to induce at least a 33% decrease in the Unified Parkinson's Disease Rating Scale (UPDRS) part III score, according to the Capsit PD program. The timed tests were performed for the motor evaluation: Arm movement between two points 30 cm apart, and a walking test with the patient walking as fast as possible 7 m back and forth, including turning. These tests were performed during the drug challenge in the "defined-off" and "defined-on conditions, according to the Capsit PD program. After this initial evaluation, patients were referred to the neurosurgery team, which determined their eligibility for neurosurgical intervention. The objective of this first stage was to determine whether the patients met the inclusion criteria.

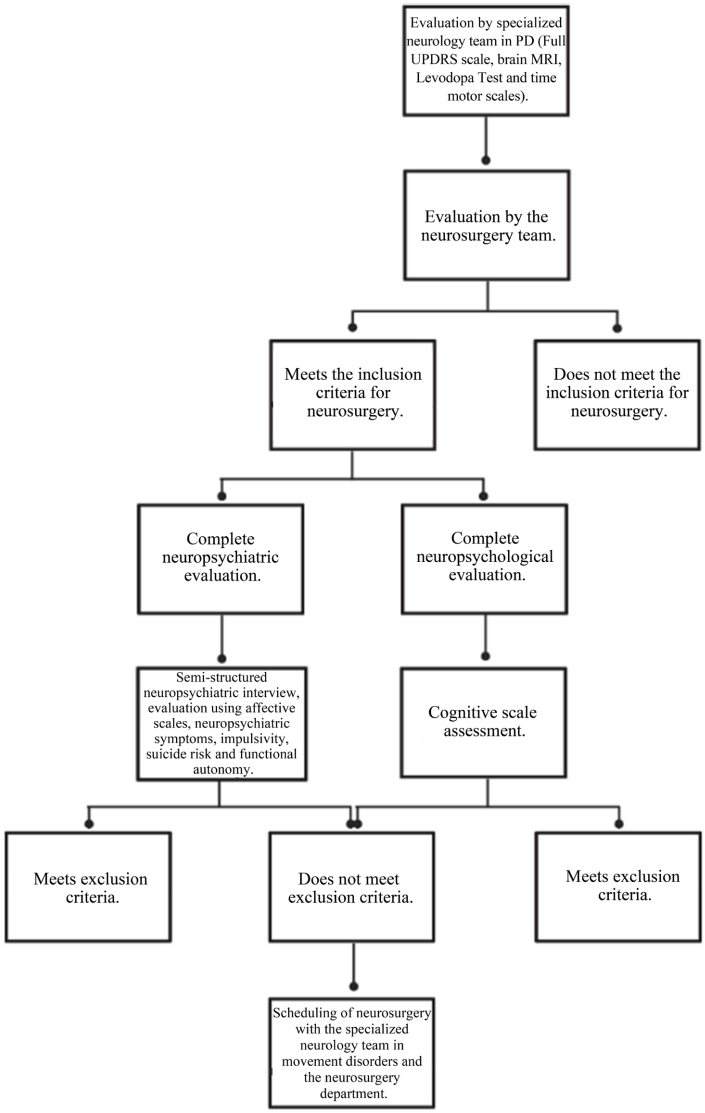

Figure 1. Flow chart of the neurosurgical evaluation protocol.

In the second stage, the patients underwent a comprehensive neuropsychiatric and neuropsychological evaluation. They participated in a semi-structured neuropsychiatric interview, which included a structured assessment of their mood, neuropsychiatric symptoms, impulsivity, risk of suicide, and functional autonomy. Additionally, a complete neuropsychological evaluation was conducted using validated and standardized cognitive scales. The objective of this second stage was to evaluate whether the patient presented exclusion criteria.

After completing both stages of evaluation, the patient returned for further consultation with Neurosurgery and Neurology consultation to make a decision prior to DBS surgery.

Clinical classifications and operational criteria for "advanced PD": the term APD remains poorly defined and a robust definition remains an unmet need in spite of consensus opinion. In this paper, advanced PD was defined as PD patients with a disease duration longer than 15 years who were experiencing a combination

of motor (wheelchair-bound in the ON state) and non-motor symptoms, particularly dementia, that precluded consideration for device-aided therapies such as DBS [13].

Atypical Parkinsonism: the term was used to refer to those patients with neurodegenerative parkinsonian features who differed from idiopathic PD in their clinical course, clinical criteria and response to treatment, who also met diagnostic criteria for Multiple System Atrophy, Progressive Supranuclear Palsy or Corticobasal Degeneration.

Dementia: The Movement Disorder Society (MDS) defines Parkinson's disease dementia (PDD) as a chronic cognitive decline in more than one cognitive domain—specifically affecting attention, executive function, visuospatial skills, and memory—that is severe enough to impair daily life (functional independence) and persists for at least 6 months [14].

Long disease duration: 5 patients were excluded for long disease duration (more than 15 years). These patients had also other motor and non motor limitations, such as being wheelchair-bound even in the ON state or having dementia.

2.4. Neuropsychiatric and Neuropsychological Evaluation Protocol

1) Semi-Structured Neuropsychiatric Interview: This interview was performed by a neuropsychiatrist who evaluated the results of the complete psychiatric assessment and made the final diagnosis according to DSM V criteria.

The Semi-Structured Neuropsychiatric interview included demographic data, personal history, and family history, as well as a clinical neurological examination.

A complete psychiatric assessment was performed evaluating:

- The patient's orientation: in time and space and person.
- Affectivity: hyperthymia, hypothymia, dysthymia, affective flattening, apathy.
- Will: normal, increased, decreased.
- Thought, evaluating its course: normal, accelerated, slowed, disintegrated, weakened; its content: the presence of depressive ideas, suicidal ideas, delusional ideas.
- Judgment: weakened, impaired, deviant, normal.
- Sensory perception to evaluate the presence or absence of hallucinations: visual, auditory, sensory-perceptual, olfactory, gustatory.

2) For the assessment of neuropsychiatric symptoms, the following scales are completed:

- **Beck Depression Inventory** is 21 self-administered items that determine the severity of depression (mild: score 10 to 15, moderate: 16 to 24, and severe: 25 to 63) [15].
- **Patient Health Questionnaire (PHQ 9).** The PHQ-9 is a nine-item self-report measure that assesses the presence of depressive symptoms based on the DSM-IV criteria for major depressive episodes [16] [17]. In this case, the Spanish version of the scale was used [16] [17]. The PHQ-9 was created as a screening tool, with recommended cut-off scores between 8 and 11 indicating a probable case of major depression. [16] [17].

- **Generalized Anxiety Disorder Scale (Generalized Anxiety Disorder GAD 7):** This instrument has been created to serve as a screening instrument for generalized anxiety disorder [18] [19]. There is no cut-off points established for the Spanish version [18]. In the original version, the authors propose a cut-off point of greater than or equal to 10 [19].
- **Okasha Suicidality Scale** [20]**.** Self-administered, Likert type, formed by four items, where the first three explore suicidal ideation, and the fourth one inquiry about suicide attempt: the answers of the suicidal ideation items are collected in a category frequency scale that is scored from 0 to 3 points for each item: never, rarely, sometimes, many times. The sum of these three items makes up the suicidal ideation sub score, which can range from 0 to 9 points. The cut-off points for suicidal ideation to determine the presence of a suicide attempt were 5 points, with a sensitivity of 90% and a specificity of 79% [21].
- **Apathy Scale**. This scale was developed by Marin RS *et al.* (1991) [22] to assess apathy symptoms in patients with depression. It was later validated in Spanish by Starkstein SE *et al.* 1992 for the detection of apathy symptoms in patients with PD [23].
- **Barratt Impulsivity Scale**: The Barratt Impulsivity Scale is one of the most widely used instruments for the assessment of impulsivity. It was designed by Barratt (1995) and in our setting, it has been adapted by Oquendo *et al.* (2001) [24] [25]. It is a self-administered instrument consisting of 30 questions, grouped into three subscales: Items Cognitive Impulsivity, Motor Impulsivity, Unplanned Impulsivity. The total score is the sum of all the items. The total score is more valuable than the subscales. There are no cut-off points, although the median of the distribution has been proposed [22] [23]. In the Spanish validation study, the median scores obtained in a sample of psychiatric patients were: Cognitive impulsivity: 9.5, Motor impulsivity: 9.5, Unplanned impulsivity: 14 Total score: 32.5 [24] [25].
- **Neuropsychiatric Inventory (NPI)** [26] is completed by the patient's family member regarding the frequency and severity of neuropsychiatric symptoms in the patient. It consists of 12 symptoms to be scored according to their severity, frequency of occurrence, and overload to the family member in charge. The symptoms are scored by multiplying the frequency by the severity [26].

For Neuropsychiatric evaluation, tests were self-completed by patients and their caregivers, and then they were checked during the consultation visit with the Neuropsychiatrist, who performed the semi structured interview and evaluated the diagnosis according to DSM-5 criteria. The time used by the patients and caregivers to complete the psychiatric scales was 20 to 30 minutes.

3) For the assessment of **cognitive symptoms**, a structured cognitive assessment battery was performed, consisting of different tests to evaluate each cognitive function:

- Tests to evaluate Semantic Memory: Rey's Auditory Verbal Learning Test [27] [28].
- Tests to assess language: Verbal Fluency [29], Boston Vocabulary Test [30] [31].
- Tests to assess Executive Function: Trail making test part B [32], Phonological Fluency [29], Frontal Assessment Battery Scale [29].
- Tests to assess visuospatial: Rey's complex figure (1997) [33].
- Tests to evaluate Attention: Trail making test part A [34], Digits Span [35].

2.5. Post Surgical Follow-Up

All PD patients who received DBS, underwent structured and team-based follow-up to optimize outcomes and monitor for complications.

Initial postoperative visits were held one week after hospital discharge and focused on wound assessment and detection of surgical complications.

Typically, a few weeks after surgery, between 3 weeks to one month, the device was turned on, and a contact test through a monopolar review was done to systematically evaluate each electrode contact and determine the optimal stimulation settings. Following this, the initial parameters were set.

Subsequent visits, usually every three weeks were organized, to perform a gradual adjustment of stimulation parameters to achieve maximal symptom control while minimizing side effects, along with modification of antiparkinsonian medications.

Long-term follow-up included regular neurological evaluation of motor and non-motor symptoms, cognitive and psychiatric monitoring, assessment of speech and gait, and periodic review of device function and battery status, done in close collaboration among neurology, neurosurgery, psychiatry, and rehabilitation teams.

2.6. Statistical Analysis

The results were entered into a computerized database, specifically prepared for this protocol, on a Microsoft Excel 2010 version program.

A descriptive analysis of the population was performed. For categorical variables, the frequency distribution was established, and the results were expressed as percentages. For continuous variables, the mean with its corresponding standard deviation was determined. When the distribution was nonparametric, the variable was described by the median and the 10th and 90th percentiles.

For the analysis of the neuropsychological tests, the Z score (z) was used, determined by the average value for the age and schooling of the patients evaluated using the following formula: Mean obtained from the score of the patients evaluated (x), Mean of the population for that age and schooling (μ) divided by the standard deviation (o).

$$z = \frac{x - \mu}{o}$$

Z score thresholds: z scores of −1.5; −2; −3, determine cognitive impairment in

that domain (for example: memory, attention, executive functions, language, *o* visuospatial abilities).

If several (more than 1) domains have these scores, the patient will be diagnosed with a multidomian cognitive impairment. If only one domain is affected, for example memory, cognitive impairment will be determined by this domain and will be named in this case as follow: Amnestic cognitive impairment.

There are two typical kinds of cognitive profiles. 1) The cortical cognitive impairment profile: this profile is characterized by impairment in memory, language and visuospatial abilities. 2) The subcortical cognitive impairment profile in this profile attention and executive domains are the most affected. Patients with multidomain cognitive impairment have both cortical and subcortical impairments.

A correlation study of the different variables was carried out using Pearson's test and Spearman's Rho test. Correlation analyses were only exploratory and unadjusted.

A statistical measure that evaluates the linear relationship between two continuous variables. It is used to determine whether a linear association exists between two sets of data. This coefficient is denoted by "r" and ranges from −1 to 1.

- If r = 1, it indicates a perfect positive correlation, which means that as one variable increases, the other also increases in constant proportion.
- If r = −1, it indicates a perfect negative correlation, which means that as one variable increases, the other decreases in constant proportion.
- If r = 0, it indicates that there is no linear correlation between the two variables.

Bilateral Significance

A statistical approach in which the probability of observing an outcome at least as extreme as the one observed in either a positive or a negative direction is evaluated. In other words, it seeks to determine whether there are significant differences in both directions, either an increase or a decrease in the values of interest.

The information was processed using the SSPS 25 advanced statistical software.

2.7. Good Clinical Practice Guidelines

All clinical work will be subject to the ICH Rules of Good Clinical Practice, the latest revisions of the Helsinki declarations (75th WMA General Assembly, Helsinki, Finland, October 2024), and the regulations of the Secretary of Health of the government of Buenos Aires city GCBA, according to Bill 3301.

3. Results

This work was developed based on previous research published in 2022 [36]. The present study's sample size was increased concerning our previous study.

3.1. Sociodemographic Data

Forty-eight patients with PD were evaluated. The mean age was 65.70 (SD 8.06), and the mean years of education was 12.27 (SD 4.285). Of the total number of

patients, 26 (43.3%) were female, and 34 (56.7%) were male (see Table 1).

Table 1. Demographic data.

Demographic data	Mean	SD
Age	65.70	8.06
Schooling	12.27	4.28

References: Values were expressed in Mean and SD: standard deviation.

3.2. Patients Flow

We evaluated 48 patients of both sexes with a diagnosis of PD, over 40 years of age, who were candidates for DBS. The selection process for patients who qualify for STN-DBS neurosurgery consists of two distinct stages.

In the first stage, patients were selected and evaluated by a neurology team specializing in PD. In this first stage, five patients were excluded due to advanced PD and long disease duration, four patients were excluded due to atypical Parkinsonism.

In the second stage, the patients underwent a comprehensive neuropsychiatric and neuropsychological evaluation, after this, three patients were excluded due to dementia of multiple domains with a subcortical profile and impairment in daily life activities. Five of these patients were diagnosed with Severe Major Depression Episodes and exhibited more than two of the following conditions: 1) High scores on the Beck Depression Scale, 2) High Okasha suicididability score, 3) High total score on Barrat impulsivity scale, and/or 4) The presence of psychotic symptoms.

In summary of the 48 selected patients, seventeen of these patients were excluded as candidates for neurosurgery.

3.3. Neurological Symptoms

Neurological symptoms described in Table 2 were the results of the Unified Parkinson's Disease Rating Scale depicted (UPDRS) [12].

After the Levodopa challenge test we observed an improvement in the UPDRS of 56.96% in Part 1, OF 49.16% in Part 2, and 49.37% in Part 3. Important inclusion criteria for the selection of patients for STN-DBS were an improvement of more than 33% of improvement in the results of UPDRS Part 3.

Neurological exclusion criteria are atypical Parkinsonism; four patients evaluated in our study were diagnosed as such and thus excluded for the STN-DBS surgery.

Patients had a mean of 15.67 (SD ± 7.3) years of illness. Five patients were excluded due to advanced PD and long disease duration.

The UPDRS [12] (Unified Parkinson's Disease Rating Scale) is divided into four main parts that cover different aspects of Parkinson's disease: Part I is for mentation, behavior, and mood; Part II is for activities of daily living (ADLs); Part III is the motor examination; and Part IV is for complications of therapy.

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Neurological exclusion criteria are atypical Parkinsonism, four patients evaluated in our study were diagnosed as such and thus excluded for the STN-DBS surgery.

Patients had a mean of 15.67 (SD ± 7.3) years of illness. Five patients were excluded due to advanced PD and long disease duration.

Medication context is important at the time of assessment. At baseline, all patients were receiving optimized medical therapy for PD and medication doses were recorded. Levodopa was prescribed in all patients, while approximately 30% of patients were also receiving dopamine agonists, 15% received MAOB inhibitors and 10% COMT inhibitors.

There were also patients receiving benzodiazepines, melatonin, antidepressants or quetiapine.

Adjustments to therapy were made postoperatively according to clinical response and DBS programming.

Generally neuropsychological and neuropsychiatric tests were performed with patients experiencing ON status.

Table 2. Unified Parkinson's Disease Rating Scale (UPDRS) results.

	Minimun	Maximun	Mean	SD
UPDRS Part 1	0	11	3.79	2.604
UPDRS Part 1 ON	0	8	2.15	1.719
Improvement UPRS Part 1	−2	5	1.60	1.567
% Improvement UPRS Part 1	0%	100%	56.96%	33.80%
UPDRS Part 2	12	42	23.02	6.384
UPDRS Part 2 ON	3	31	11.38	5.644
Improvement UPRS Part 2	0	25	11.16	5.524
% Improvement UPRS Part 2	20%	100%	49.16%	19.44%
UPDRS Part 3	28	76	44.65	10.505
UPDRS 3 Part ON	12	55	21.85	7.847
Improvement UPDRS Part 3	8	44	22.79	8.528
% Improvement UPDRS Part 3	21.82%	77.14%	49.37%	12.32%
UPDS Part 4	0	14	5.40	3.450

Reference: Values were presented in Minimum, Maximum, Mean, and SD: standard deviation. UPDRS Part 1 patients in OFF status. UPDRS Part 1 patients in ON status. UPDRS Part 2 patients in OFF status. UPDRS Part II ON patients in ON status. UPDRS Part 3 patients in OFF status. UPDRS Part III ON patients in ON status. UPDRS Part 4 patients in OFF status.

3.4. Neuropsychiatric Manifestations

In the scales assessing depressive symptoms (Beck Depression Inventory and PHQ-9), the average scores indicated a mild degree of depression. However, five

patients exhibited scores suggesting moderate to severe depression (see Table 2).

Regarding the Anxiety Scales (GAD and Beck Anxiety Scale), mild to moderate anxiety symptoms were noted (see Table 3).

Intellectual performance was significantly affected according to the anosognosia scale (see Table 3).

In the impulsivity scale, patients scored above the cut-off points, with notable results in the total score (see Table 3).

Several patients also exhibited high scores on the apathy scale (see Table 3).

Table 3. Neuropsychiatric scales.

Neuropsychiatric Scales	Minimum	Maximum	Mean	SD
Depression				
Beck Depression total score	0	31	12.69	6.445
PHQ 9	1	31	13.21	7.337
Anxiety				
Beck Anxiety Total Score	2	58	23.22	15.664
GAD Scale 9	0	15	2.64	4.241
Suicidality				
Suicidality Scale total score	0	8	0.80	1.504
Impulsivity				
Cognitive Impulsivity (attention)	3	25	12.92	4.735
Motor Impulsivity	0	29	10.27	8.598
Barratt Impulsivity Scale total score	0	81	33.98	22.325
Apathy scale	0	20	9.44	7.020
Anosognosia scale cognitive performances patient	5	23	9.78	3.140
Anosognosia scale of patient behavioral performances	2	13	5.11	3.140
Anosognosia scale family cognitive performances	2	20	9.33	6.282
Anosognosia scale family behavioral performances	3	13	6.60	3.782

Reference: Values were presented in Minimum, Maximum, Mean, and SD: standard deviation.

3.5. Activities of Daily Living (ADL)

Patients generally did not report dependence in instrumental activities of daily living (mean 1.63), in contrast to family members (mean 3.8) who did report a greater degree of dependence on these activities [36].

According to the Neuropsychiatric Inventory completed by the caregivers, nocturnal behaviors were the most prominent symptoms reported (mean 0.86) (SD 0.9), followed by Depression (mean 0.59) (SD 0.9), Anxiety (mean 0.48) (SD 0.8) and disinhibition (mean 0.43) (SD 0.8) [36].

3.6. Neuropsychological Evaluation

The results of the complete neuropsychological evaluation showed a subcortical cognitive impairment pattern, with predominant executive dysfunction. The Frontal Assessment Battery (FAB) total score was significantly affected, with a *z* score of minus 2, showing a clear impairment in executive functions (see Table 4).

Table 4. Neuropsychological assessment.

Table 3. Neuropsychological assessment	Minimum	Maximum	Mean	SD	Score *z*
Verbal Memory					
Verbal Learning List A	12	62	37.28	11.43	−0.10
Verbal Learning List B	0	7	3.74	1.78	−0.76
Intrusions	0	4	0.50	0.86	
Free recall	0	14	6.70	2.97	−0.15
Deferred Recall	0	16	6.56	3.14	−0.10
Intrusions	0	2	0.38	0.64	
Recognition	0	15	12.22	2.69	0.75
Intrusions	0	8	2.22	2.16	
False Acknowledgments	0	7	1.34	1.76	
Language					
Designation	20	60	48.59	9.44	−0.76
Semantic Fluency	5	31	18.18	6.372	−0.24
Attention					
Direct Digits	3	8	5.82	1.335	−0.53
Attentional Errors	0	2	0.22	0.571	
Perseverative Errors	0	2	0.12	0.400	
Executive Functioning					
Indirect Digits	0	6	3.90	1.199	−0.55
Total FAB	6	18	14.90	3.105	−2.04
Conceptualization	2	3	2.68	0.48	
Verbal flexibility	2	3	2.77	0.43	
Motor programming	1	3	2.45	0.74	
Sensitivity to Interference	0	3	2.45	1.01	
Inhibitory Control	0	3	1.68	1.04	
Prehension behavior	3	3	3	0	
Phonological Fluency	3	25	13.94	5.83	−0.54
Visual construction					
Rey Complex Figure	5	36	27.120	8.866	−0.72

Reference: Values were presented in Minimum, Maximum, Mean, SD: standard deviation, and Score Z (zeta).

3.7. Correlations

Significant correlations ($p < 0.005$) were found between the suicidality scale and the Beck depression scale, and motor impulsivity scales (Table S1A). A direct relationship was also found between variables of the neuropsychiatric inventory (NPI) (such as apathy, euphoria, disinhibition, and depression) and the cognitive impulsivity scale (Table S1B). The Barratt impulsivity scale presented significant correlations ($p < 0.005$) between unplanned motor impulsivity and cognitive impulsivity, along with significant correlations with NPI variables: depression, nocturnal behaviors, and irritability (Table S1C).

Finally, the Beck Depression Scale, total FAB, and the Rey Complex Figure (ROCF) test were somewhat significant ($p < 0.05$) (Table S1D).

Correlations also indicated that with longer disease durations, there was a decrease in depression, disinhibition, nocturnal behaviors, and appetite scores (Table S1E).

Highly significant positive correlations ($p < 0.005$) were found between UPDRS part 1 (OFF) and Beck Depression Inventory and GAD 7 Anxiety scale, and positive significant ($p < 0.05$) correlations were found between UPDRS part 1 (OFF) and Suicidality scale (Table S1F).

Significant ($p < 0.05$) positive correlations were found between UPDRS part 1 (ON) and Beck Depression Inventory (Table S1F).

Significant ($p < 0.05$) positive correlations were found between UPDRS part 2 (OFF) and GAD 7 Anxiety scale, and between UPDRS part 3 (OFF) and GAD 7 Anxiety scale (Table S1F).

3.8. Excluded Patients

Out of all the patients evaluated, seventeen were excluded from DBS consideration.

Table 5. Excluded patients due to Neuropsychiatric symptoms.

Patient	Beck Depression Scale total score	Anxiety scale total score	Suicidality scale total score	Barratt Impulsivity Scale total score	Cognitive impulsivity (attention)	Motor Impulsivity	Unplanned impulsivity	Psychotic symptoms
1	25	25	6	51	17	19	15	YES
2	26	49	3	81	25	29	27	YES
3	31	29	6	51	17	19	15	NO
4	26	14	7	41	8	19	14	NO
5	43	20	8	37	16	19	2	NO

References: The raw total score of the Beck Depression Scale, Beck Anxiety Scale, Suicidality Scale, and Barratt Impulsivity Scale with its subitems (total score, cognitive impulsivity, motor impulsivity, unplanned impulsivity) is described. The presence (YES) or absence (NO) of psychotic symptoms is described.

Five of these patients were excluded due to psychiatric symptoms of severe de-

pression, as evaluated by the scales administered and in the semi-structured neuropsychiatric interview. Suicidal risk symptoms were also found through the Okasha suicidality scale. High levels of impulsivity and active psychotic symptoms (predominantly visual hallucinations and paranoid delusional ideation) were found in two patients (see Table 5).

Three patients were excluded due to dementia with multiple domains deficits and impairment of daily life activities (ADL score more than 2 points). The other 5 patients were excluded for long disease duration (more than 25 years). Four patients were excluded for an atypical Parkinsonism diagnosis.

3.9. Follow-Up

As per post-DBS follow-up, thirty-one patients were followed up in the medical care setting. These patients had an improvement in motor-related symptoms (such as tremors and stiffness, on-off symptoms), verified in clinical evaluations. As for Neuropsychiatric evolution, most of them presented an improvement in Depression, Anxiety, and Impulsivity symptoms. Of the 31 patients who underwent surgery, only two experienced neuropsychiatric complications within the first three months' post-surgery.

One of them experienced a psychiatric complication (a self-harm episode), despite having mild depression on both the Beck Depression Inventory and PHQ-9 during the pre-surgical assessment. This patient also had a history of isolated self-harm episodes in younger years, though no risk was indicated on the Okasha Scale (3 points). This self-harm episode was without suicidal thoughts and did not recur in other follow-up evaluations. The second patient demonstrated an increase in impulsivity in clinical settings and received psychopharmacological treatment indicated by the neuropsychiatrist, showing then improvement of depression and anxiety symptoms and a decrease in the level of impulsivity.

4. Discussion

In the present study, 48 patients with PD were evaluated to determine inclusion and exclusion criteria for STN-DBS according to CAPSYT-PD recommendations.

As regards Neurological evaluation, the assessment with UPDRS was elemental to determine inclusion criteria for the selection of patients for STN-DBS. Patients with more than 33% improvement in the results of UPDRS Part 3 were selected for STN-DBS. After the Levodopa challenge test we observed an improvement in the UPDRS of 56.96% in Part 1, OF 49.16% in Part 2, and 49.37% in Part 3. Important inclusion criteria for the selection of patients for STN-DBS were an improvement of more than 33% of improvement in the results of UPDRS Part 3.

The UPDRS [12] (Unified Parkinson's Disease Rating Scale) is divided into four main parts that cover different aspects of Parkinson's disease: Part I is for mentation, behavior, and mood; Part II is for activities of daily living (ADLs); Part III is the motor examination; and Part IV is for complications of therapy.

Atypical Parkinsonism evaluated in brain MRI and clinical settings was another mandatory exclusion criterion. Four patients evaluated in our study were diag-

nosed as such and thus excluded for the STN-DBS surgery.

Years of illness also determined the selection of patients for STN-DBS. Long term disease duration was another exclusion criterion. Patients had a mean of 15.67 (SD ± 7.3) years of illness. Five patients were excluded due to advanced PD and long disease duration.

According to neuropsychiatric symptoms, mild depressive symptoms and mild to moderate anxiety symptoms were found. Impulsivity and nocturnal behaviors were frequent symptoms.

It is well known that one of the most prevalent psychiatric disorders in PD patients is depression, and severe depression is an exclusion criterion for DBS. Two well-known, efficient, and validated scales, such as the Beck Depression Inventory and PHQ9 were used for the screening of depressive symptoms and to determine the severity.

Dillon *et al.* investigated different subtypes of depressive syndromes that exist in late life and found that many of them have underlying cognitive impairment, which, sometimes, makes it difficult to differentiate from dementia [37]-[39]. In our previous research studies [37]-[39], the Beck Depression Inventory (BDI) and the Mini-Mental State Examination (MMSE) were significant variables that helped us to differentiate depressive groups in the elderly [37]-[39].

Regarding PHQ9, it has been widely used to investigate depressive features in PD [16] [40]. Chagas *et al.* [38], evaluated the validation and internal consistency of PHQ-9 for Major Depression in Patients with PD and found that maximal discrimination between depressed and non-depressed patients was reached with a cut-off score of 9 in the PHQ-9 (sensitivity of 100% and specificity of 83.1%). The internal consistency of the scale was 0.83 and when used as a diagnostic instrument, the PHQ-9 had a sensitivity of 52.6% and a specificity of 95.4% [40].

Concerning recommended screening tests for psychiatric disorders, the Minnesota Multiphasic Personality Inventory (MMPI) is psychology's most widely used clinical assessment tool [41]. The original MMPI was developed by Hathaway and McKinley and published in 1943 [41]. The MMPI-2 has 567 true-false questions and takes approximately 60 to 90 minutes to complete; the MMPI-2-RF has 338 true-false questions, taking 35 to 50 minutes to finish [42]. MMPI-3: The latest version of the instrument, MMPI-3, was released in 2020. The test takes 25 to 50 minutes to be administered [43]. In comparison to our neuropsychiatric validated screening tests, MMPI takes too much time to be performed.

Another recommended test for depression assessment is the Montgomery-Åsberg Depression Rating Scale (MADRS) [44]. This test has both advantages and disadvantages. The Advantages are that it is sensitive and specific and is designed to assess treatment changes. The disadvantage is that it may not include atypical depressive symptoms like hypersomnia and hyperphagia. It may not be accurate for individuals with dementia, especially Alzheimer's disease, and may not be reliable without a structured interview. Additionally, it may be challenging for people with cognitive impairments due to the complex wording of some subtests.

The other two important scales used in our study were the Barratt Impulsiveness Scale (BIS) and Okasha Suicidal Scale. The BIS is one of the most widely used self-report questionnaires for measuring impulsivity [27]-[45]. Among the various self-reports that target any of the four dimensions of decision-making deficits, the Barratt Impulsivity Scale (BIS) is one of the most frequently used instruments [45]. The BIS is arguably the most commonly administered self-report measure for the assessment of impulsiveness in both research and clinical settings [45]. Moreover, the Okasha Suicidality Scale [20] is a 4-item self-administered scale. The first three items explore suicidal ideation, and the fourth item asks about suicide attempts. It is a self-administered scale that takes a few minutes to perform and is easy to understand. This scale was validated in the Chilean adolescent population by Salvo *et al.* [21] who reported that the suicidality scale showed high internal consistency ($\alpha = 0.89$) and appropriate validity evidence (discriminant and concurrent). The internal consistency for this investigation was 0.87.

The scales used to assess mood disorders indicated that, on average, the patients exhibited mild depressive symptoms and mild to moderate anxiety symptoms. Additionally, they showed frequent impulsive behaviors and nocturnal activities.

In the neuropsychological assessment, subcortical cognitive impairment, predominantly executive dysfunction, was observed. Significant correlations were found between neuropsychiatric and neuropsychological scales.

Out of the 48 patients evaluated, seventeen were deemed ineligible for DBS and were excluded from the procedure. The reasons for their exclusion were their psychiatric symptoms (five patients), having long disease duration (five patients), diagnosis of atypical Parkinson's disease (4 patients), and having a diagnosis of dementia (3 patients).

Five patients were excluded due to neuropsychiatric symptoms, they exhibited more than two of the following conditions: 1) High scores on the Beck Depression Scale (more or equal to 25 total score which implies severe Depression symptoms), 2) High Okasha suicididability score (cut-off point 5 or more), 3) High total score in Barrat impulsivity scale (more than 32.5 points) and/or 4) The presence of psychotic symptoms. It is important to take into consideration that these tests were supervised and analyzed by a neuropsychiatrist who confirmed these results with an extensive neuropsychiatric semi structured interview and made a Psychiatric diagnosis according to DSM-5 criteria for Severe Major depressive episode with, or without, psychotic symptoms. Psychiatric treatment was indicated for these excluded patients.

Non-motor symptoms are highly prevalent in PD patients. Non-motor symptoms are known to impact the patient's quality of life and their social, family, and work environment.

The causes for the high prevalence of anxiety and depression are not clearly understood [46]. Degeneration of neurotransmitter systems other than dopamine could play a specific role in the onset of these affective disorders [47]. While some authors associate depressive symptoms with depletion in dopamine and noradrenaline in the limbic system [47], others [48] relate them to serotonergic degen-

eration that occurs at the onset of PD.

Poletti and Bonuccelli [49] reviewed several studies regarding impaired impulse control and its association with PD. They found that previous personality and the intake of dopamine agonists could worsen these behaviors. The investigators further found preliminary empirical evidence suggesting the hypothesis that both personality (trait negative affect, high premorbid levels of impulsivity) and cognitive characteristics (poor executive functioning, especially inhibitory control) may represent risk factors for the development of impulse control deficits in medicated PD patients. This trait was found in our study along with impaired inhibitory control, mood disturbance, and nocturnal behaviors.

As for the neuropsychological battery of this study, unlike the previous study, we found a cognitive impairment with a subcortical profile, predominantly executive dysfunction, demonstrating severe alterations in the Frontal Assessment Battery (FAB). A greater impact was found in inhibitory control, sensitivity to interference, and motor programming. On the contrary, in comparison with the previous study [34], no significant alterations were found neither in the area of memory or visuospatial skills.

Three patients were excluded due to a dementia diagnosis that was observed in neuropsychological tests with cognitive impairment in multiple domains and a subcortical profile with impairment in daily life activities (ADL score of more than 2 points).Regarding the results at the cognitive level, Brandão *et al.* report that episodic memory impairment and inhibitory control failures are strong predictors of conversion to dementia, while other studies concluded that performance in executive functioning tasks, working memory, phonological verbal fluency, and language did not predict dementia in PD. Likewise, the presence of mild cognitive impairment in PD observed during the initial assessment predicted a 6-fold increased risk of dementia in five years [50].

In the present study, more significant correlations were found between the neuropsychiatric scales and between them and the neuropsychological scales than in the previous study. Positive significant correlations were found between the suicidality scale and the Beck depression and anxiety scales as well as with motor impulsivity, showing that the symptoms observed may be related to each other. Then, we can infer that there is a possible relation between higher levels of depressive symptoms with a correlative higher level of impulsivity which can be a risk factor for a higher level of suicidal symptoms or suicidal thoughts enactment.

On the other hand, significant correlations were found with the variables of the neuropsychiatric inventory (NPI): depression, nocturnal behaviors, and irritability. Other NPI variables, such as apathy, euphoria, disinhibition, and depression, were found to correlate with cognitive impulsivity.

Dag Arsland *et al.* found positive correlations between depressive symptoms, anxiety, and apathy in PD patients [51]. Another study showed that in univariate tests, higher Beck Depression Inventory (BDI) cognitive-affective item scores were associated with lower values of general cognition and also with worse scores on each of the individual cognitive tests, indicating an association between more

severe depressive symptoms and worse cognitive performance.

Surprisingly, negative correlations were seen between disease duration and psychiatric symptoms. These symptoms were observed in the NPI test, but not in the Beck or the PHQ 9 scales. NPI was completed by the caregivers. A possible explanation for this could be, as it occurs in the advanced stages of dementia, the behavioral and psychological symptoms of dementia (BPSD) tend to decrease and apathy tend to increase. In advanced PD patients, a similar pattern may occur. Degenerative diseases such as Dementia tend to have more neuropsychiatric symptoms in mild and moderate stages, decreasing their appearance in severe stages and trending to symptoms such as Apathy [52].

Screening for non-motor symptoms in patients with PD who were selected for STN-DBS neurosurgery using a standardized protocol enabled healthcare providers to objectively diagnose and identify patients with neuropsychiatric exclusion criteria. This step was crucial during the pre-surgical evaluation process to monitor the potential evolution of psychiatric conditions in the post-surgery period and to mitigate risks such as increased impulsivity. In five patients, the presence of severe depression, suicidal risk, high impulsivity, and associated psychotic symptoms indicated that they should be excluded from DBS. Instead, these patients were directed towards psychiatric treatment or a review of their existing psychiatric medications, if they were already receiving treatment.

This comprehensive approach will not only contribute to a more careful selection of candidates for DBS from the neuropsychiatric and neuropsychological point of view but will also provide a solid basis for the development of interventional strategies and postoperative psychological support. Furthermore, it will advance the understanding of the relationship between motor symptoms and psychiatric aspects of PD, leading to a more personalized and effective treatment.

5. Limitations

In this study, the patients chosen for STN-DBS surgery underwent a thorough evaluation. This study describes a multidisciplinary pre-surgical assessment protocol for STN-DBS candidacy in 48 patients with Parkinson's disease evaluated at a single centre (2017-2024). It is important to note that the results cannot be generalized to all patients diagnosed with Parkinson's disease (PD), as not all PD patients are suitable for STN-DBS. This sample examined was specifically selected for this research.

Another limitation is that in this paper there is not enough quantitative research data (neuropsychiatric and neuropsychological validated scales) to make statistical analyses and compare pre-surgical and post-surgical outcomes.

Moreover, other limitations in relation to the correlations are that these analyses were only exploratory and unadjusted.

6. Conclusions

From the present study, we can conclude some possible objective guidelines for

patient exclusion in cases of Diagnosis of Major Depression episode, such as patients exhibiting more than two of the following conditions: 1) High scores on the Beck depression Scale (more or equal to 25 total score which implies severe Depression symptoms); 2) High Okasha suicidality score (cut-off point 5 or more); 3) High total score in Barrat impulsivity scale (more than 32.5 points); and/or 4) The presence of psychotic symptoms.

Also, we suggest taking into consideration the years of illness (more than 20 or 25 years of diagnosis of Parkinson's disease) and the presence of cognitive symptoms of dementia using a complete neuropsychological battery associated with an evaluation of daily life activities.

Thus, it is important to evaluate these patients' neurological, neuropsychological and neuropsychiatric status before STN-DBS surgery. This evaluation helps determine their suitability for the surgery and provides baseline data that can be used to assess their recovery and progress after the procedure.

Author Contributions

For research articles with several authors, Conceptualization, Dillon C and Peralta C.; methodology, Dillon C and Peralta C.; software, Dillon C.; validation, Romano M; formal analysis, Dillon C. Peralta C; investigation, Dillon C, Peralta C, Driollet Laspiur S.; resources, Dillon C, Peralta C, Driollet Laspiur S, Perez Leguizamon P, Castro C and Viaggio MB, data curation, Dillon C.; writing—original draft preparation, Barisic, M, de Jauregui M, Cupito A, Belloto M and Carol Dillon; writing—review and editing, Bellotto M, Dillon C and Peralta C; visualization, Vazquez GH and Romano M. and Viaggio MB; supervision, Dillon C.; project administration, Dillon C. All authors have read and agreed to the published version of the manuscript.

Funding

This research was supported by CEMIC University Hospital and CEMIC University Institute.

Institutional Review Board Statement

The present research study was evaluated by the Ethical Research Committee from CEMIC University Hospital and the central ethics committee of the GCBA. Ethics Approval Code: 1333 and Date 5 October/2020.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Supporting reported results can be found: in the following link: https://doi.org/10.1016/j.neuarg.2022.06.001. (https://www.sciencedirect.com/science/article/pii/S1853002822000301)

Carol Dillon, Adriana Leis, Diego M. Castro, Virginia García, Cecilia Zegarra, Patricio Perez Leguizamón, Mónica Feldman, Santiago Driollet Laspiur, Maria Belen Viaggio, Cecilia Peralta. Estudio de síntomas neuropsiquiátricos y neuropsicológicos en pacientes con enfermedad de Parkinson seleccionados para la cirugía de estimulación cerebral profunda, Neurología Argentina, Volume 14, Issue 4, 2022, Pages 229-238, ISSN 1853-0028.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supplementary Materials

Supplementary Table 1. Scale correlations.

Table S1A. Correlations of Suicidality scale vs. other Neuropsychiatric scales.

		Beck-Anxiety	Beck-Depression	PHQ9-Depression	Motor impulsivity
Suicidality scale	Pearson correlation	0.464	0.729	0.532	0.344*
	Bilateral Significance (p)	0.003	0.000	0.004	0.011
	Spearman correlation	0.509**	0.517**	0.391*	0.391**
	Bilateral Significance (p)	0.001	0.0001	0.044	0.003

Reference: Relevant correlations associated with the Suicidality Scale.

Table S1B. Correlations of Cognitive Impulsivity (Barratt Impulsivity scale) vs. other Neuropsychiatric scales.

		Unplanned motor impulsivity	Hallucinations	Depression	Apathy	Euphoria	Disinhibition
Cognitive impulsivity	Pearson correlation	0.433	0.605**	0.662**	0.465*	0.564*	0.477*
	Bilateral Significance (p)	0.001	0.006	0.001	0.045	0.012	0.039
	Spearman correlation	0.387**	0.462	0.561	0.150	0.390	0.383
	Bilateral Significance (p)	0.004	0.046	0.008	0.540	0.099	0.106

References: Relevant correlates associated with cognitive impulsivity.

Table S1C. Correlations of Barratt Impulsivity scale (total score) vs. other Neuropsychiatric scales.

		Cognitive impulsivity	Suicidality scale	Nocturnal behaviors	Depression	Irritability	Unplanned motor impulsivity
Barratt's Impulsivity	Pearson correlation	0.655**	0.086	0.466*	0.448*	0.481*	0.829**
	Bilateral Significance (p)	0.000	0.527	0.033	0.032	0.027	0.000
	Spearman correlation	0.607	0.289*	0.366	0.347	0.454	0.797
	Bilateral Significance (p)	0.000	0.029	0.103	0.105	0.038	0.000

References: Relevant correlations associated with Baratt's Impulsivity.

Table S1D. Correlations of Beck Depression scale vs. other Neuropsychiatric scales and Neuropsychological tests.

		Beck-Anxiety	GAD 9-Anxiety	Scale of Suicidality	Total FAB	FCR
Beck-Depression	Pearson correlation	0.667**	0.794	0.729**	0.230	−0.242
	Bilateral Significance (p)	0.000	0.000	0.000	0.120	0.118
	Spearman correlation	0.620**	0.734**	0.517**	−0.303*	−0.352*
	Bilateral Significance (p)	0.000	0.000	0.000	0.038	0.021

References: Statistical correlations associated with the Beck Depression Scale.

Table S1E. Correlations of Years of illness vs. other Neuropsychiatric scales (sections of Barratt Impulsivity scale and NPI scale).

		Unplanned motor impulsivity	Depression/ Dysphoria	Disinhibition	Behavior-nocturnal	Appetite
Years of illness	Pearson correlation	0.299*	−0.455*	−0.477*	−0.439*	−0.498*
	Bilateral Significance (p)	0.029	0.029	0.029	0.047	0.022
	Spearman correlation	0.342	−0.413	−0.498	−0.408	−0.385
	Bilateral Significance (p)	0.012	0.050	0.022	0.067	0.085

References: Relevant correlations associated with Years of illness. In the present table you can observe the scales that were taken that presented significant correlations. The p is significant at level < 0.05. Significant values are expressed with "*" and highly significant values with "**". NS corresponds to non-significant values, *i.e.* p > 0.05.

Table S1F. Correlations of UPDRS scale vs. other Neuropsychiatric scales.

		Beck Depression Inventory	GAD 9-Anxiety	Scale of Suicidality	Cognitive Impulsivity	Motor Impulsivity	Unplanned Motor Impulsivity	Barret Impulsivity Total
UPDRS part 1	Pearson correlation	0.475**	0.411**	0.357*	0.038	−0.021	0.086	0.033
	Bilateral significance (p)	0.001	0.006	0.016	0.811	0.897	0.589	0.836
UPDRS part 1 ON	Pearson correlation	0.347*	0.214	0.268	−0.037	−0.051	0.107	0.062
	Bilateral significance (p)	0.021	0.169	0.075	0.815	0.747	0.499	0.695
UPDRS part 2	Pearson correlation	0.271	0.350*	0.135	0.036	0.092	0.036	−0.093
	Bilateral significance (p)	0.075	0.021	0.376	0.821	0.564	0.820	0.555
UPDRS part 2 ON	Pearson correlation	0.083	0.227	−0.088	0.076	0.118	0.061	0.110
	Bilateral significance (p)	0.591	0.144	0.563	0.633	0.458	0.701	0.484
UPDRS part 3	Pearson correlation	0.115	0.302*	−0.097	0.099	0.088	0.040	−0.049
	Bilateral significance (p)	0.451	0.046	0.521	0.526	0.576	0.800	0.751
UPDRS part 3 ON	Pearson correlation	0.005	−0.025	−0.021	0.028	−0.030	0.060	0.002
	Bilateral significance (p)	0.972	0.874	0.890	0.856	0.847	0.705	0.989
UPDRS part 4	Pearson correlation	0.079	−0.181	0.073	−0.137	−0.137	−0.058	−0.155
	Bilateral significance (p)	0.604	0.239	0.630	0.381	0.383	0.714	0.316

References: Correlation between UPDRS and Neuropsychiatric scales. In the present table you can observe the scales that were taken that presented significant correlations. The p is significant at level < 0.05. Significant values are expressed with "*" and highly significant values with "**". NS corresponds to non-significant values, *i.e.* p > 0.05.