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Abstract

To determine the clinical and demographic correlates of persistent, remitting, and new-onset impulse control behaviors (ICBs) before and after subthalamic deep brain stimulation (STN-DBS) in Parkinson's disease (PD). We compared the pre- and post-surgical prevalence of ICBs, classified as impulse control disorders (ICD), dopamine dysregulation syndrome (DDS), and punding in 150 consecutive PD STN-DBS-treated patients and determined the association with motor, cognitive, neuropsychological, and neuropsychiatric endpoints. At baseline (before STN-DBS), ICBs were associated with younger age ($p = 0.045$) and male gender (85 %; $p = 0.001$). Over an average follow-up of 4.3 ± 2.1 years of chronic STN-DBS there was an overall trend for reduction in ICBs (from 17.3 to 12.7 %; $p = 0.095$) with significant improvement in hypersexuality (12–8.0 %; $p = 0.047$), gambling (10.7–5.3 %; $p = 0.033$), and DDS (4.7–0 %; $p < 0.001$). ICB remitted in 18/26 patients (69 %) and persisted in 8/26 (31 %); the latter group was characterized by higher levodopa equivalent daily dose. Patients who developed a new-onset ICB during follow-up ($n = 11/150$) were characterized by younger age ($p = 0.042$), lower dyskinesia improvement ($p \leq 0.035$), and a gender distribution with higher prevalence of women ($p = 0.018$). In addition, new-onset ICB was more common among patients with borderline, schizoid, and/or schizotypal traits of personality disorders; persistent ICB in those with obsessive–compulsive traits. PD-related ICBs exhibit a complex outcome after STN-DBS, with a tendency for overall reduction but with age, gender, dopaminergic therapy, and neuropsychiatric features exerting independent effects.

Keywords

Parkinson's disease; Neurosurgery; Electrical stimulation; Impulse control behaviors; Personality

Introduction

Impulse control behaviors (ICBs) is a class of psychiatric disorders characterized by failure to resist an impulse even if harmful to oneself or others, including three disorders: dopamine dysregulation syndrome (DDS) [1]; impulse control disorder (ICD) [2, 3]; and punding [4]. This complex syndrome has a prevalence of 13.6 % in Parkinson's disease (PD) compared to 1 % in the general population [5], and may be thought of as the neuropsychiatric equivalent of levodopa-induced dyskinesia [6–8]. The risk of ICBs in PD is higher in males with younger age at disease onset, and in the context of dopamine agonists use [5, 9], pathological personality traits [10, 11], depression [12], and history of addictive behaviors [13, 14], as well as those with selected single nucleotide polymorphisms related to dopamine metabolism [15, 16] or parkin mutation [17]. Therapeutic strategies against ICB may be based on discontinuing dopamine agonists, with or without down titration of other dopaminergic therapies [18]. The role of subthalamic nucleus deep brain stimulation (STN-DBS) has been conflicting. Some studies reported improvement or resolution of ICB after STN-DBS [19–23] whereas others yielded mixed results, with some patients improving, worsening, or even developing de-novo ICB after surgery [24–28]. The data currently available are insufficient to ascertain whether ICB changes after STN-DBS are related to beneficial effects related to post-surgical decrease in dopaminergic treatment, to modulation of basal ganglia oscillatory patterns, or a combination thereof [29].

In this follow-up study, we sought to compare the rate of remission, persistence, and new appearance of ICBs after STN-DBS, as related to clinical/demographic features, dopaminergic therapies, stimulation parameters, mood, anxiety, apathy, and neuropsychological data.

Methods

Patients and clinical evaluations

Data from 172 consecutive PD patients treated with STN-DBS at the Department of Neuroscience, University of Turin, from June 2004 and June 2015 were retrospectively analyzed, comparing the pre-surgical and post-surgical prevalence of ICBs, specified as ICD (hypersexuality, gambling, pathological shopping, or a combination thereof [multiple ICD]), DDS (defined as an addictive pattern of dopaminergic drug use, with doses in excess of those required to control motor symptoms), and punding (defined as compulsive fascination with and prolonged performance of repetitive mechanical tasks). The presence/absence of ICBs was assessed by means of a clinical diagnostic interview based on specific diagnostic

criteria [30], comparing their prevalence at baseline vs. post-surgical follow-up (regular evaluations were performed every 3–6 months collecting information from patients and caregivers), and classifying patients as follows: no ICB (before and after STN-DBS), remitting ICB; persistent ICB, and new-onset ICB after STN-DBS. Pre- and post-surgical ICBs prevalence was compared with demographic features (age and gender) and clinical, cognitive and pharmacological endpoints. Motor severity was assessed by means of the Unified Parkinson's Disease Rating Scale (UPDRS), evaluating the ON (maximal dopaminergic efficacy) and OFF conditions (reemergence of parkinsonian features, after at least 12 h since the last levodopa dose) in the preoperative assessment, and the MED-ON/STIM-ON (maximal dopaminergic efficacy/Stimulator ON) and MED-OFF/STIM-OFF conditions (at least 12 h since the last levodopa dose/Stimulator OFF) in the post-operative assessment.
Before surgery all patients received a comprehensive neuropsychiatric assessment aiming at assessing reasoning (Raven's Colored Progressive Matrices), memory (Digit Span, Bi-syllabic Words Repetition Test (Verbal Span), Corsi's Block Tapping Test (Spatial Span), and Paired Associative Learning), frontal executive function (Digit Cancellation Test, Trail Making Test part A and B, Nelson Modified Card Sorting Test, Frontal Assessment Battery and Phonemic Verbal Fluency) and language (Category Verbal Fluency). In addition, at the pre-surgical assessment patients were screened for personality disorders by means of the "Structured Clinical Interview and Questionnaire for DSM-IV Personality Disorders (SCID-II)" [31]. Subjects with personality disorders were excluded from DBS, while those with "personality disorder traits" were carefully selected for DBS according to a case-by-case discussion with the psychiatrist and neuropsychologist. Mood and anxiety were evaluated by means of the Beck Depression Inventory (BDI) [32], State-Trait Anxiety Inventory (STAI)-X1 (reaction to episodic stress conditions) and STAI-X2 (predisposition to experiencing persistent anxiety) [33]. Apathy was evaluated using the Marin Apathy Scale (MAS).
Finally, medications were logged as levodopa equivalent daily doses (LEDD) for all dopaminergic medications and for dopamine agonists; stimulation parameters as total electrical energy delivered (TEED = voltage2 × pulse width × frequency/impedance [34]).

Statistical analyses

Continuous variables were reported as average ± standard deviation (range). Cramer's V, Mann–Whitney and Kruskal–Wallis tests were used for inter-group comparisons, Wilcoxon test and repeated-measures ANOVA for longitudinal comparisons between groups. All tests were performed using SPSS 21.0, considering two-tailed p values with 0.05 as the statistical threshold. Bonferroni correction was used for multiple comparisons in post hoc analyses. The ethical committee

approved the study (CS/855; Prot. no. 475/2016) and patients provided written informed consent.

Results

Complete clinical and neuropsychological data were available for 150/172 patients (15 patients were followed-up in other Centers and 7 had incomplete data). The cohort consisted of 86 men and 64 women with PD treated with STN-DBS at the age of 59.1 ± 7.2 years (range 37–70 years), after 12.9 ± 1.5 years from symptom onset (range 7–25 years). At baseline, all patients (*n* = 150) were receiving L-dopa; 81.3 % (*n* = 122) were treated with dopamine agonists; 37.3 % (*n* = 56) with COMT inhibitors; and 16.0 % (*n* = 24) with MAO-B inhibitors.

Pre- vs. post-surgical ICBs

The pre-surgical prevalence of ICBs was 17.3 % (*n* = 26) (Table 1). Multiple ICDs were identified in 6.0 % of patients (*n* = 9), single ICD in 5.3 % (*n* = 8), multiple ICD + DDS in 3.3 % (n = 5), single ICD + punding in 1.3 % (*n* = 2), single ICD + DDS (*n* = 1) and single ICD + DDS + punding (*n* = 1) in 0.7 % each. Post-surgical data showed a trend for ICBs prevalence reduction in STN-DBS treated patients (mean follow-up of 4.3 ± 2.1 years), from 17.3 to 12.7 % (*p* = 0.095): 69.2 % (*n* = 18/26) remitted after 22.1 ± 15.3 months (range 8–60) and 30.8 % (*n* = 8/26) had persistent ICB after 41.4 ± 22.1 months of follow-up (range 11–82) (Table 2). During the entire follow-up period, 7.3 % of patients (*n* = 11/150) developed a new-onset ICB, after a mean follow-up of 40.6 ± 25.9 months (range 6–84). Among new-onset ICB, 45.4 % (*n* = 5/11) developed multiple ICDs (gambling + compulsive shopping in 3 patients and hypersexuality + compulsive shopping in 2 patients); 27.3 % (*n* = 3/11) single ICD (hypersexuality in 2 and compulsive shopping in 1); 18.2 % (*n* = 2/11) single ICD + punding (hypersexuality and compulsive shopping in 1 patient each); and 9.1 % (*n* = 1/11) punding alone.

Overall, there was a reduction in the prevalence of hypersexuality (12–8.0 %; *p* = 0.047), gambling (10.7–5.3 %; *p* = 0.033), and DDS (4.7–0 %; *p* < 0.001). There were no changes in the prevalence of multiple ICD (9.3–6.7 %; *p* = 0.197), compulsive shopping (6.7–5.3 %; *p* = 0.617), and punding (2.0–3.3 %; *p* = 0.414) (Fig. 1).

Table 1
Demographic/clinical features (baseline)

	Baseline ICB (*n* = 26)	**Baseline no-ICB (*n* = 124)**	***P***
Gender (males/females)	23/3 (88.5 %)	63/61 (50.8 %)	0.001
Age at onset (years)	45.2 ± 7.2 (32–59)	46.6 ± 7.2 (24–62)	0.302
Disease duration (years)	12.9 ± 5.5 (8–25)	12.9 ± 4.3 (7–25)	0.468
UPDRS-I	1.5 ± 1.2 (0–4)	1.7 ± 1.5 (0–7)	0.827
UPDRS-II OFF	19.4 ± 7.3 (7.5–33)	20.8 ± 7.3 (0.5–37.5)	0.394
UPDRS-II ON	5.7 ± 5.3 (0–18.5)	7.2 ± 4.9 (0–22)	0.150
UPDRS-III OFF	42.1 ± 14.7 (17.5–78)	43.5 ± 15.1 (10–83)	0.726
UPDRS-III ON	14.2 ± 7.4 (4.5–38.5)	15.3 ± 7.5 (3–45.5)	0.361
UPDRS-IV	6.2 ± 3.9 (0–15)	7.7 ± 3.7 (0–16)	0.103
Dyskinesia duration	1.1 ± 1.08 (0–3)	1.3 ± 0.94 (0–3.5)	0.191
Dyskinesia severity	1.1 ± 1.01 (0–3)	1.3 ± 1.08 (0–4)	0.121
% Waking day in OFF	1.1 ± 0.81 (0–3)	1.3 ± 0.72 (0–3)	0.433
Schwab and England OFF (%)	53.8 ± 20.6 (20–90)	56.2 ± 21.5 (10–90)	0.622
Schwab and England ON (%)	94.1 ± 8.5 (70–100)	91.0 ± 11.8 (40–100)	0.305
Total LEDD (mg)	1362.4 ± 368.4 (700–2298)	1227.5 ± 401.9 (300–2180)	0.101
DA LEDD (mg)	297.8 ± 268.6 (0–1060)	300.5 ± 235.3 (0–1120)	0.703
DA use	21/5 (80.8 %)	101/23 (81.5 %)	0.872

Values are reported as average ± standard deviation; minimum and maximum values are reported in brackets

DA dopamine agonists, LEDD L-dopa equivalent daily dosage, UPDRS Unified Parkinson's Disease Rating Scale

P value Mann–Whitney and Cramer's V test

Table 2

Demographic/clinical features (baseline and follow-up)

	No ICB (*n* = 113)	**Remitting ICB (*n* = 18)**	**Persistent ICB (*n* = 8)**	**New-onset ICB (*n* = 11)**	***P***
Gender (males/females)	60/53	15/3	8/0	3/8	0.001
Age at onset (years)	46.6 ± 7.3 (24–62)	43.8 ± 5.7 (32–53)	48.2 ± 9.4 (32–59)	45.7 ± 6.4 (30–54)	0.315
Disease duration (years)	13.1 ± 4.4 (7–25)	12.7 ± 4.3 (8–24)	13.4 ± 7.8 (8–25)	12.2 ± 2.6 (7–15)	0.570
Follow-up duration (months)	53.5 ± 39.2 (12–140)	54.2 ± 36.9 (12–139)	41.4 ± 22.1 (12–82)	49.4 ± 29.7 (12–94)	0.947
UPDRS-I					
Baseline	1.6 ± 1.6 (0–7)	1.5 ± 1.3 (0–4)	1.5 ± 1.0 (0–3)	2.1 ± 1.3 (1–4)	0.269
Follow-up	2.8 ± 2.2 (0–9)	3.2 ± 2.1 (0–6)	2.7 ± 1.9 (0–6)	2.9 ± 2.1 (0–6)	0.426
UPDRS-II OFF					
Baseline	21.5 ± 7.1 (4–37.5)	19.3 ± 6.2 (9–33)	19.8 ± 10.7 (7.5–31)	16.2 ± 6.8 (0.5–24)	0.102
Follow-up	18.9 ± 10.0 (4–46)	19.2 ± 7.6 (9.5–36)	17.8 ± 8.4 (3.5–35)	16.7 ± 7.4 (2–26)	0.458
UPDRS-II ON					
Baseline	7.4 ± 4.9	5.6 ± 5.6 (0–	6.2 ± 5.0	4.8 ± 3.9	0.20

	No ICB (n = 113)	Remitting ICB (n = 18)	Persistent ICB (n = 8)	New-onset ICB (n = 11)	*P*
	(0–22)	18.5)	(1–12)	(0–11)	6
Follow-up	13.9 ± 8.2 (1–35.5)	12.8 ± 6.5 (3–26.5)	9.3 ± 5.6 (3–16)	9.4 ± 5.5 (1.5–17)	0.386
UPDRS-III OFF					
Baseline	43.8 ± 15.1 (10–83)	42.1 ± 13.8(17.5–78)	42.1 ± 17.4 (22–68)	40.2 ± 15.1(17–65.5)	0.920
Follow-up	51.2 ± 13.5 (16–76)	54.2 ± 10.3 (37–74)	44.7 ± 14.8 (28–63)	46.7 ± 18.9 (18–75)	0.778
UPDRS-III ON					
Baseline	15.5 ± 7.8 (3–45.5)	14.1 ± 7.8 (4.5–38.5)	14.3 ± 6.7(6.5–26.5)	13.4 ± 4.2 (4–18)	0.767
Follow-up	19.2 ± 11.7 (3–62.5)	18.7 ± 11.4 (6–46.5)	16.5 ± 8.7 (6.5–22)	18.9 ± 10.1 (4–36)	0.983
UPDRS-IV					
Baseline	7.6 ± 3.7 (0–16)	6.7 ± 3.6 (0–15)	5.3 ± 2.1 (0–11)	7.8 ± 4.9 (2–15)	0.342
Follow-up	3.3 ± 2.4 (0–9)	3.9 ± 3.1 (0–9)	3.8 ± 2.6 (0–9)	5.9 ± 3.6 (1–13)	0.121
Dykinesia duration					
Baseline	1.4 ± 0.9 (0–3.5)	1.2 ± 1.2 (0–3)	0.9 ± 0.9 (0–2)	0.9 ± 0.6 (0–2)	0.103
Follow-up	0.6 ± 0.7 (0–3)	0.6 ± 0.9 (0–3)	0.6 ± 0.9 (0–2)	0.9 ± 0.6 (0–3)	0.631

	No ICB (n = 113)	Remitting ICB (n = 18)	Persistent ICB (n = 8)	New-onset ICB (n = 11)	*P*
Dykinesia severity					
Baseline	1.3 ± 1.1 (0–4)	0.9 ± 1.2 (0–3)	0.9 ± 1.3 (0–3)	1.3 ± 1.2 (0–3)	0.327
Follow-up	0.5 ± 0.8 (0–3)	0.5 ± 0.7 (0–2)	0.3 ± 0.5 (0–2)	1.2 ± 1.1 (0–3)	0.141
Total LEDD (mg)					
Baseline	1216.2 ± 403.0 (300–2180)	1267.4 ± 321.7 (700–1830)	1576.4 ± 397.6 (1050–2298)	1342.0 ± 390.0 (800–1934)	0.089
Follow-up	762.2 ± 311.2 (150–1670)	908.5 ± 357.0 (300–1548)	1245.4 ± 505.3 (557–1865)	944.5 ± 410.4 (475–2000)	0.021
DA LEDD (mg)					
Baseline	297.2 ± 235.3 (0–1120)	277.1 ± 252.8 (0–1060)	344.4 ± 314.5 (0–1000)	334.5 ± 243.9 (0–900)	0.776
Follow-up	149.7 ± 136.1 (0–450)	124.7 ± 124.4 (0–360)	100.0 ± 131.1 (0–300)	124.1 ± 118.9 (0–300)	0.745
TEED (μJ)	120.8 ± 39.9 (51.8–292.9)	112.4 ± 24.8 (75.7–167.2)	106.8 ± 47.9 (50.4–162.3)	109.5 ± 29.4 (55.9–152.6)	0.847

Values are reported as average ± standard deviation; minimum and maximum values are reported in brackets

DA dopamine agonists, *LEDD* L-dopa equivalent daily dosage, *UPDRS* Unified Parkinson's Disease Rating Scale, *mg* milligrams, *TEED* total electrical energy delivered, *μJ* microjoules

P value: Kruskal–Wallis and Cramer's *V* tests

Overall, there was a reduction in the prevalence of hypersexuality (12–8.0 %; $p = 0.047$), gambling (10.7–5.3 %; $p = 0.033$), and DDS (4.7–0 %; $p < 0.001$). There were no changes in the prevalence of multiple ICD (9.3–6.7 %; $p = 0.197$), compulsive shopping (6.7–5.3 %; $p = 0.617$), and punding (2.0–3.3 %; $p = 0.414$) (Fig. 1).

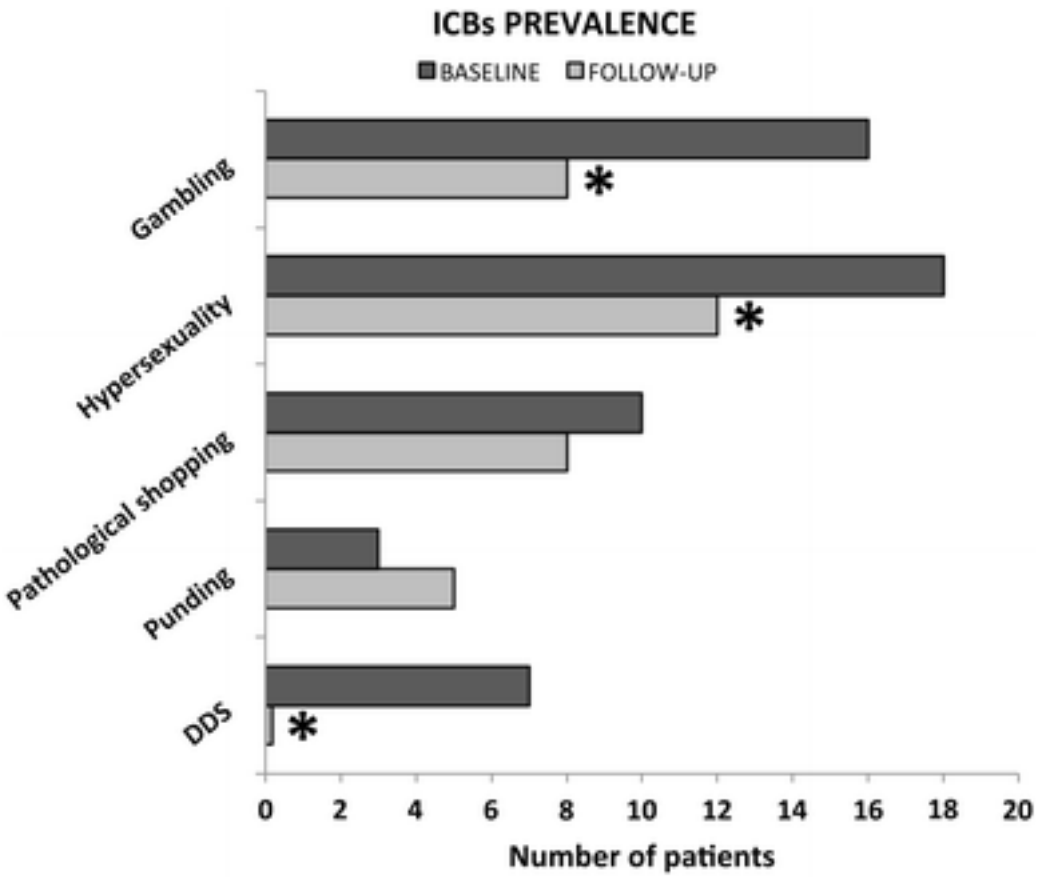

Fig. 1
Impulsive control behaviors (baseline and follow-up). Number of patients with ICB before and after surgery. There was a significant reduction in the prevalence of gambling, hypersexuality, and DDS. No significant changes were observed in the prevalence of compulsive shopping and punding. *Significant difference between pre- and post-surgical prevalence ($p < 0.05$). *DDS* dopamine dysregulation syndrome

Dyskinesia and UPDRS-III motor score

Baseline data showed no significant differences in motor symptoms, dyskinesia severity (item 33 of UPDRS), and dyskinesia duration (item 32 of UPDRS) between patients with and without ICB (Table 1). Repeated-measure ANOVA showed a different improvement (Table 2) of dyskinesia duration and severity in the four groups ($p = 0.033$ and $p = 0.035$), with new-onset ICB patients reporting lower

amelioration compared to other groups (post hoc comparisons: $p \leq 0.035$ and $p \leq 0.029$). There were no differences in UPDRS-III motor score between new-onset, remitting, persistent, and no ICB (Table 2).

Dopaminergic therapies and Stimulation Parameters

There were no differences in dopaminergic therapy (total LEDD, dopamine agonist LEDD, or use of dopamine agonists) between patients with and without ICB at baseline (Table 1). The LEDD post-surgical reduction was evident in all groups (−29.6 % in new-onset ICB; −28.3 % in remitting ICB; −21.0 % in persistent ICB; −37.3 % in no ICB), although the cohort with persistent ICB maintained higher total LEDD compared to other groups ($p = 0.021$; Table 2). Stimulation parameters and TEED did not differ across all ICB groups (Table 2).

Demographic features

There was a higher prevalence of ICBs in men at baseline (88.5 % men; 11.5 % women; $p = 0.001$) (Table 1), while the gender distribution significantly changed after STN-DBS (the prevalence of women increased from 11.5 to 42.1 %; $p = 0.018$) (Table 2). Age was younger both in patients with ICBs at baseline (56.9 ± 5.5 vs. 59.6 ± 6.9 years; $p = 0.045$) and in new-onset ICBs patients (59.1 ± 7.3 years) compared to no ICBs (64.2 ± 7.5 years), persistent ICB (61.8 ± 8.5 years) and remitting ICBs (61.1 ± 7.8 years) ($p = 0.042$).

Cognitive and neuropsychological data

Cognitive and neuropsychological data were similar between patients with and without ICBs at baseline. Post-surgical data revealed higher prevalence of obsessive–compulsive ($p = 0.042$) traits of personality disorder in persistent ICBs, and higher prevalence of borderline ($p = 0.007$), schizoid ($p = 0.046$) and schizotypal ($p = 0.010$) traits of personality disorder in new-onset ICBs (Table 3). There were no changes in cognitive performance between baseline and follow-up among new-onset, remitting, persistent, and no ICB groups (Table 4). No baseline differences were observed in BDI ($p = 0.368$), anxiety (STAI-X1, $p = 0.415$; STAI-X2, $p = 0.149$), and apathy ($p = 0.400$) scores, while post-surgical data showed a trend for BDI worsening in new-onset ICBs and persistent ICBs (Table 4).

Table 3
Pre-operative SCID-II questionnaire score

	No ICB (*n* = 113)	**Remitting ICB (*n* = 18)**	**Persistent ICB (*n* = 8)**	**New-onset ICB (*n* = 11)**	***P***
Cluster A: odd-eccentric					
Paranoid	13.3 % (1.8 ± 1.4)	5.6 % (2.1 ± 1.3)	12.5 % (2.0 ± 1.1)	18.2 % (2.2 ± 1.3)	0.762
Schizoid	11.5 % (2.2 ± 1.2)	5.6 % (1.8 ± 0.9)	0.0 % (2.1 ± 0.6)	36.4 % (2.8 ± 1.7)	0.046
Schizotypal	1.8 % (1.3 ± 1.5)	0.0 % (0.7 ± 0.7)	0.0 % (0.4 ± 1.1)	18.2 % (2.3 ± 1.6)	0.010
Cluster B: dramatic-emotional					
Antisocial	6.2 % (0.7 ± 1.3)	16.7 % (1.6 ± 2.7)	12.5 % (1.0 ± 1.2)	18.2 % (1.0 ± 1.3)	0.293
Borderline	11.5 % (1.9 ± 1.8)	11.1 % (2.1 ± 2.1)	37.5 % (3.0 ± 2.4)	45.5 % (3.9 ± 2.2)	0.007
Histrionic	16.8 % (1.9 ± 1.4)	11.1 % (2.1 ± 1.2)	37.5 % (2.8 ± 1.9)	18.2 % (2.6 ± 1.8)	0.426
Narcissistic	23.0 % (2.9 ± 2.0)	27.8 % (3.2 ± 2.0)	25.0 % (3.6 ± 2.7)	36.4 % (3.5 ± 2.1)	0.784
Cluster C: anxious-fearful					
Avoidant	32.7 % (2.6 ± 1.9)	22.2 % (2.0 ± 1.5)	12.5 % (1.7 ± 1.4)	36.4 % (2.5 ± 1.9)	0.524
Dependent	12.4 % (2.4 ± 1.8)	16.7 % (2.3 ± 2.0)	12.5 % (2.9 ± 1.3)	18.2 % (2.3 ± 1.6)	0.921
Obsessive–compulsive	33.6 % (3.3 ± 2.2)	16.7 % (3.3 ± 2.1)	62.5 % (4.6 ± 2.1)	9.1 % (3.5 ± 1.1)	0.042

Values are reported as percentage of subjects reporting a pathological score in each SCID-II trait of personality; raw scores are reported in brackets (average ± standard deviation)

P value: Cramer's V test

Cluster A: (a) *paranoid* = paranoia, suspiciousness and generalized mistrust of others; (b) *schizoid* = lack of interest in social relationships, solitary lifestyle; (c) *schizotypal* = social anxiety, paranoia, and unconventional beliefs

Cluster B: (a) *antisocial* = pervasive pattern of disregard for, or violation of, the rights of others; (b) *borderline* = impulsivity, inconsistent interpersonal relationships, and poor self-image; (c) *histrionic* = inappropriately seductive behavior and excessive need for approval; (d) *narcissistic* = excessive preoccupation with personal adequacy, prestige and vanity

Cluster C: (a) *avoidant* = pervasive pattern of social inhibition and avoidance of social interaction despite a strong desire to be close to others; (b) *dependent* = pervasive psychological dependence on other people; (c) *obsessive–compulsive* = perfectionism, excessive attention to details, and mental and interpersonal control

Table 4

Neuropsychological profile (baseline and follow-up)

	No ICB (113)		**Remitting ICB (18)**		**Persistent ICB (8)**		**New-onset ICB (11)**		***P***
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	
MMSE	28.8 ± 1.2	27.5 ± 2.7	28.9 ± 1.4	27.3 ± 3.2	27.8 ± 3.0	26.8 ± 3.8	29.3 ± 1.0	28.0 ± 2.7	0.409
Reasoning									
CPM47	28.0 ± 4.6	24.9 ± 7.1	29.4 ± 4.5	24.6 ± 9.1	28.1 ± 5.5	25.2 ± 11.7	30.3 ± 4.5	28.0 ± 11.5	0.916
Memory									
Digit span	5.3 ± 1.1	4.9 ± 0.9	5.4 ± 1.1	4.8 ± 1.1	5.2 ± 0.8	5.0 ± 1.0	5.2 ± 1.1	5.4 ± 1.5	0.563
Verbal span	4.2 ± 0.8	3.9 ± 0.8	4.6 ± 1.0	4.2 ± 1.0	4.3 ± 0.7	4.2 ± 1.1	4.4 ± 0.5	4.4 ± 0.8	0.783
Sp	4.4 ±	4.1 ± 0	4.6 ±	4.2 ± 1	4.6 ±	4.0 ±	4.6 ±	4.3 ±	0.

	No ICB (113)		Remitting ICB (18)		Persistent ICB (8)		New-onset ICB (11)		*P*
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	
atial span	0.7	.7	1.0	.1	1.1	0.7	0.8	0.7	532
PAL	12.0 ± 3.0	10.6 ± 3.1	12.1 ± 3.5	10.3 ± 2.0	11.4 ± 2.9	10.6 ± 3.2	11.8 ± 3.8	12.9 ± 3.7	0.146
Attentional–executive functions									
DCT	45.2 ± 10.1	38.7 ± 12.3	49.3 ± 6.9	42.0 ± 11.0	46.2 ± 11.8	45.0 ± 18.7	46.0 ± 8.4	47.5 ± 11.4	0.698
Trail making A	43.7 ± 16.1	99.8 ± 106.8	30.2 ± 11.5	79.2 ± 75.4	37.5 ± 17.6	103.6 ± 135.7	59.7 ± 23.9	81.8 ± 78.6	0.191
Trail making B	178.4 ± 116.5	286.2 ± 197.6	174.7 ± 141.4	269.7 ± 188.1	166.7 ± 179.5	246.4 ± 220.8	165.8 ± 150.3	214.1 ± 220.5	0.934
Nelson MCSTc	5.7 ± 0.7	4.9 ± 1.5	5.8 ± 0.3	5.5 ± 0.7	5.8 ± 0.1	5.4 ± 1.3	5.4 ± 1.5	5.3 ± 1.4	0.516
Nelson MCSTp	1.7 ± 2.0	3.2 ± 3.3	1.1 ± 1.5	2.4 ± 2.1	1.5 ± 1.6	1.6 ± 2.5	1.9 ± 1.8	2.2 ± 4.5	0.914
FAB	16.4 ± 1.5	13.1 ± 3.5	17.8 ± 0.5	13.4 ± 4.4	15.0 ± 2.9	14.5 ± 5.0	17.2 ± 0.9	16.0 ± 2.7	0.833
PVF	43.1 ± 16.0	26.3 ± 12.8	46.4 ± 21.9	29.2 ± 13.4	47.8 ± 19.6	33.0 ± 12.6	42.3 ± 12.7	36.0 ± 12.5	0.497

	No ICB (113)		Remitting ICB (18)		Persistent ICB (8)		New-onset ICB (11)		*P*
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	
Language									
CVF	20.9 ± 5.3	16.8 ± 5.5	23.3 ± 7.0	18.5 ± 5.8	23.0 ± 7.5	18.6 ± 3.4	23.5 ± 5.8	19.8 ± 5.0	0.736
Mood depression									
BDI	11.3 ± 7.3	12.9 ± 8.2	10.1 ± 6.8	10.5 ± 8.3	9.8 ± 7.4	15.4 ± 11.6	12.5 ± 6.1	15.9 ± 11.3	0.108
Anxiety									
STAI-X1	42.0 ± 11.0	43.9 ± 11.0	43.0 ± 9.7	41.5 ± 7.1	47.2 ± 15.9	39.4 ± 6.5	45.7 ± 13.2	41.7 ± 12.5	0.212
STAI-X2	43.5 ± 10.0	46.0 ± 10.6	42.0 ± 9.6	41.7 ± 9.4	42.7 ± 9.9	46.3 ± 11.1	46.7 ± 8.8	48.2 ± 9.7	0.787
APATHY									
MAS	11.5 ± 5.4	16.1 ± 6.7	10.0 ± 5.6	14.7 ± 4.9	14.1 ± 4.7	± 5.4	11.8 ± 5.1	15.6 ± 8.3	0.700

Values are reported as average ± standard deviations

BDI beck depression inventory, *CPM47* Raven's colored progressive matrices, *CVF* category verbal fluency, *DCT* digit cancellation test, *FAB* frontal assessment battery, *PAL* paired associate learning, *PVF* phonemic verbal fluency, *MAS* Marin Apathy Scale, *MCTSc* modified card sorting test categories, *MCTSp* modified card sorting test perseveration, *STAI-X1* state anxiety inventory, *STAI-X2* trait anxiety inventory

P value: repeated measure ANOVA (baseline vs. follow-up changes)

Discussion

We confirmed a trend towards reduction of ICBs in PD patients treated with STN-DBS. However, selected features emerged as risk factors for persistent ICB (higher LEDD and obsessive compulsive personality trait) and new-onset ICB (younger age, borderline, schizoid and schizotypal traits of personality disorder), indicating that

the beneficial effects of STN-DBS on ICBs may be partially reduced in patients with less pronounced decrease in dopaminergic medications, younger age, and/or specific traits of personality disorders. Interestingly, we observed a different ICB gender distribution before and after STN-DBS surgery, suggesting a differential sensitivity between men and women to dopaminergic therapies reduction and/or STN-DBS modulation. Hypersexuality, gambling, and DDS were significantly improved, whereas punding, compulsive shopping and multiple ICD were not (trend toward improvement in the latter two). These data confirm and extend previous reports on the varying effects of STN-DBS on ICD and DDS [19–28], highlighting the presence of "risk factors" for ICB persistence.

The reduction of dopaminergic medications partly explains the beneficial effects of STN-DBS on selected ICBs; it has been suggested that the imbalanced impairment of the dorsal striatum motor area and the ventral striatum limbic area typical of PD might have a role in the development of ICB [35, 36]. Antiparkinsonian medications, while compensating for dopamine depletion of the motor dorsal striatum, could 'over-dose' the otherwise non-deficient limbic ventral striatum, thus facilitating the development of impulsive behaviors [37]. This theory is in agreement with the hypothesis that STN-DBS effects on ICBs should be primarily attributed to the post-surgical reduction of dopaminergic medications. It should be noted, however, that several STN-DBS studies reported mixed results [24–28], suggesting that other factors might be involved. Neuropsychiatric comorbidities and personality disorders have been frequently associated with ICBs in the general population, but their clinical relevance in PD has been poorly understood and insufficiently recognized [11]. Greater obsessive–compulsive symptoms and novelty seeking behaviors interact in the pathophysiology of PD-associated ICBs [6]. A substantial range (23–92 %) of non-PD pathological gamblers have at least one personality disorder, namely obsessive–compulsive, borderline, antisocial, narcissistic, or dependent personality [38, 39], and recent evidences support the hypothesis that PD patients with Cluster A personality disturbances might be at higher risk of developing ICBs [40]. We observed that patients with traits of obsessive compulsive personality disorder had higher risk of falling in the category of persistent ICB, and that patients with traits of borderline, schizoid and schizotypal personality disorder were at higher risk of developing new-onset ICB after DBS, in spite of a significant reduction in dopaminergic therapies. There was a trend towards BDI worsening in the groups of new-onset ICB and persistent ICB, while no differences were observed in apathy score and other neuropsychological or cognitive outcomes. Our results also support the lack of correlation between cognitive impairment and impulsive behaviors [12, 41], arguing against a causative link between specific cognitive dysfunction and ICD.

Finally, we found a correlation between new-onset ICB and reduced amelioration of post-surgical dyskinesia. The contention that ICBs may represent the neuropsychiatric equivalent of hyperdopaminergic motor complications [5–7] was

only supported in the persistent ICB cohort, which showed higher total post-STN-DBS LEDD, and a trend towards higher LEDD values before surgery. No associations were found with the magnitude of dopamine agonists reduction or with stimulation parameters as themselves influencing the ICBs outcome. However, more accurate evaluation of electrode placement will be necessary in future studies to analyze whether differences between stimulation of the ventral vs. dorsal portion of the STN play a differential role in whether ICBs remit or persistence.

This study has several limitations. The retrospective design and lack of randomization may have resulted in possible ascertainment biases, which limit the generalization of results. Our findings may only be applicable to the highly selected group of patients that fulfill the strict CAPSIT-PD clinical and neuropsychological criteria for STN-DBS eligibility. We did not use a specific scale for the assessment of ICB, such as the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating scale (QUIP-RS), which has been validated only in recent years [42]. Moreover, the list of ICBs that have been considered in this study is incomplete, since we did not include compulsive eating. Finally, we analyzed personality disorder traits in patients without overt abnormalities in personality structure, because all subjects with severe personality disorder or any other relevant neuropsychiatric comorbidity were excluded at the time of STN-DBS surgical selection.

In conclusion, our results suggest that: (a) hypersexuality, gambling, and DDS are significantly improved by STN-DBS and may be considered potential targets for surgical treatment; (b) Different mechanisms may be involved in presurgical versus new-onset postsurgical ICB; (c) ICBs appear unrelated to cognitive function; and (d) Higher LEDD and obsessive compulsive personality traits may increase the risk for persistent ICB after STN-DBS; (e) younger age, female gender, and specific personality traits (borderline, schizoid and schizotypal) may represent potential risk factors for ICB in the cohort of post-surgical STN-DBS patients. A prospective randomized controlled clinical trial will be required to confirm and extend these preliminary observations and further clarify the complex association between STN-DBS and impulsive behaviors in relationship with the clinical, demographic, pharmacological factors, and patient's pre-surgical neuropsychiatric assessment.

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Compliance with ethical standards

Conflicts of interest

Dr. Merola has received grant support from UCB Pharma and speaker honoraria from CSL Behring, UCB Pharma and Teva Pharmaceuticals. He has received personal compensation from Edge Consulting S.r.l., MediK S.r.l. and Sthetos S.r.l. Dr. Romagnolo has received grant support from AbbVie and travel grants from Novartis and Merck Serono. He has received personal compensation from Edge Consulting S.r.l. and Sthetos S.r.l. Dr. Rizzi declares no conflicts of interests. Dr. Rizzone received speaker and/or consulting honoraria from Medtronic, Lundbeck, UCB Pharma and AbbVie. Dr. Zibetti received speaker and/or consulting honoraria from Medtronic, Lundbeck, UCB Pharma and AbbVie. Prof. Lanotte received honoraria for lecturing and travel grants from Medtronic. Dr. Duker has served as a consultant for Merz Pharmaceuticals, US World Meds, and Auspex Pharmaceuticals and has received honoraria from UCB. Dr. Mandybur received honoraria for lecturing and travel grants from Medtronic. Dr. Espay is supported by the NIH (K23MH092735) and has received grant support from CleveMed/Great Lakes Neurotechnologies, Davis Phinney Foundation, and Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Solvay, Abbott, Chelsea Therapeutics, TEVA, Impax, Merz, Lundbeck, and Eli Lilly; honoraria from TEVA, UCB, the American Academy of Neurology, and the Movement Disorders Society; and publishing royalties from Lippincott Williams & Wilkins and Cambridge University Press. Prof. Lopiano received honoraria for lecturing and travel grants from Medtronic, UCB Pharma and AbbVie.

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Nothing to declare.

Ethical standards

The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The ethical committees approval was obtained (*Comitato Etico Interaziendale Città della Salute e della Scienza di Torino*; CS/855; Prot. no. 475/2016) and all patients gave their written informed consent to participate at the study.

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