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Limbic Stimulation Drives Mania in STN-DBS in Parkinson Disease: A Prospective Study

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In this one-year prospective study, Parkinson's disease (PD) patients with or without mania following STN-DBS were compared to investigate risk and etiological factors, clinical management and consequences. Eighteen (16.2%) out of 111 consecutive PD patients developed mania, of whom 17 were males. No preoperative risk factor was identified. Postoperative mania was related to ventral limbic subthalamic stimulation in 15 (83%) patients, and resolved as stimulation was relocated to the sensorimotor STN, besides discontinuation or reduction of dopamine agonists and use of low-dose clozapine in 12 patients, while motor and nonmotor outcomes were similar. These findings underpin the prominent role of limbic subthalamic stimulation in postoperative mania.

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Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) is a remarkable treatment for patients with advanced Parkinson's disease (PD).^{1, 2} However, subsequent changes of mood have been reported, including depression, apathy, and mania.^{3–7} Regarding postoperative

mania, several studies pinpoint the role of the stimulation of ventral STN and substantia nigra,^{4, 8–10} while others suggest the role of preexisting risks factors including male sex and neuropsychiatric disorders.^{10, 11} However, most of these series are small, and/or retrospective. We therefore decided to conduct a prospective study assessing the incidence, risk factors, management and impact on long-term clinical outcome of postoperative mania following STN-DBS in PD.

Methods

Study Design and Patients

This is a bicentric ancillary study to the French multicentric, prospective Predictive Factors and Subthalamic Stimulation in Parkinson's Disease study (PREDISTIM) (<https://clinicaltrials.gov/ct2/show/NCT02360683>). Consecutive PD patients undergoing STN-DBS at the Lyon

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and Strasbourg University Hospitals were included between May 2015 and January 2020. In the present study, the STN was the unique target for DBS in all PD patients as the PREDISTIM study aimed at determining the predictive factors of outcome after STN DBS. All patients gave their informed written consent and the PREDISTIM study was approved by the CPP Nord-Ouest IV Ethical Committee (N° IDRCB: 2013 A0019342). All patients were implanted bilaterally in the STN with stereotactic implantation based on preoperative 3 T MR scans, micro-recording and awake macro-stimulation, using Medtronic (quadripolar 3389 leads and Activa PC* implanted pulse generator (IPG), Minneapolis, MN) or Boston devices (directional Cartesia leads and Vercise* or Gevia* rechargeable IPG, Valencia, CA). A postoperative CT scan was performed the day of surgery to ensure the absence of complication and was used for electrode registration.

Clinical Evaluation and Outcomes

Patients were evaluated at the baseline preoperative visit, at hospital discharge after implantation and one year after surgery. Occurrence of mania up to one year following STN-DBS surgery was diagnosed based on semistructured interviews conducted by neurologists and neuropsychologists using the core and supportive clinical features of DSM-5 criteria (A-C). Notably, hospitalization was required and prolonged for all patients with mania, notwithstanding regular hospitalization for stimulation onset. Demographic and clinical data were assessed at baseline and one year follow-up using the MDS-UPDRS part I, III and IV; the Montreal Cognitive Assessment (MoCA); the Hamilton Depression Scale (HAM-D); the Hamilton Anxiety Rating Scale (HAM-A); the Lille Apathy Rating Scale (LARS); the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) and Ardouin Scale of Behavior in Parkinson's Disease (ASBPD). Furthermore, past history of impulse control disorders (ICD) or other neuropsychiatric disorders was recorded. Daily levodopa equivalent dose (LEDD) was calculated for total oral dopamine replacement therapy and for dopamine agonists. Total electrical energy delivery (TEED) was calculated and active contacts were categorized as ventral for the two leads at the tip of the electrode and as dorsal for the two other ones. Three-dimensional coordinates of the electrode active contacts in MNI space and volume of tissue activated (VTA) were determined using the Lead-DBS 2.5.2 toolbox after registration of postoperative CT scan to preoperative MRI and spatial normalization (supplementary methods), using a tripartite atlas of subthalamic territories.¹²

Statistical Analysis

Patients with mania and patients without mania following STN-DBS surgery were compared to determine preoperative risk factors, postoperative clinical management, and long-term prognosis. Demographic and clinical data were summarized as mean (standard deviation) or median (interquartile range) and compared using the *Khi2* independence, Student's *t*-test or Wilcoxon-Mann-Whitney test as appropriate, and Fischer's exact test for categorical data. Group-comparison of active contacts coordinates, TEED and bilateral average of the limbic VTA overlap within the stimulated STN was performed considering the climax of manic symptoms for patients with mania and the regular hospital discharge for patients without mania, respectively. In addition, we performed multivariable regression to compare the respective role of preoperative clinical factors and limbic VTA overlap. Missing data for clinical scores related to length of clinical evaluation were reported without imputation.

Results

Eighteen (16.2%) out of 111 consecutive PD patients developed mania (Table 1), 17 of whom were males. Manic symptoms started during the first week following STN-DBS in 15 patients. Three patients had a delayed onset of mania at 19, 30, and 180 days following the change of active contacts to optimize motor response. Rate of occurrence was similar in Lyon (13 (17.1%) out of 76 patients) and Strasbourg (5 (14.3%) out of 35 patients, $p = 0.7$).

Age, disease duration, preoperative motor and non-motor impairment did not predict the occurrence of postoperative mania (Tables 1 and S1). Before surgery, patients had normal to low levels of hyperdopaminergic symptoms, depression and anxiety, similar in both groups, although preoperative severity of apathy was greater in patients who developed mania (LARS score (IQR) -25.0 (-29.0 , -23.5), odds ratio (OR) (95% confidence interval (95% CI)) 1.08 (0.98 – 1.19)). Similarly, both groups had the same past history of neuropsychiatric disorders, and no patients with mania had a personal history of bipolar disorder. In addition, no preoperative difference was observed in terms of dopamine replacement therapy and psychotropic medication.

Contrastingly, the active contact of stimulation in the STN clearly differed in patients with mania and those without. Indeed, active contacts were located in the medial and ventral part of the STN in patients at the climax of manic symptoms, consistent with greater VTA overlap with the limbic subthalamic territory (median (IQR) 15.0% (8.7 , 28.2) for patients with mania; 5.6% (0.9 , 11.0) for patients without mania; $p = 0.002$) (Fig).

TABLE 1. Preoperative Demographic and Clinical Risk Factors for the Occurrence of Postoperative Mania Following STN-DBS in Patients with Parkinson's Disease

	PD patients without post-operative mania (n = 93)	PD patients with post-operative mania (n = 18)	<i>p</i>
Baseline evaluation, before STN-DBS surgery			
Sex (M/F)	70 (75%)/ 23 (25%)	17 (94%)/ 1 (5.6%)	0.11
Age (yr)	61 (54, 66)	58 (54, 64)	0.52
Disease duration (yr)	9 (7, 12)	8 (8, 11)	0.18
MDS-UPDRS part I	10.0 (6.0, 12.5)	9.0 (5.2, 14.2)	0.82
MDS-UPDRS part III (off medication)	41 (32, 52)*	40 (32, 50)	0.96
MDS-UPDRS part III (on medication)	11 (6, 15)*	12 (8, 17)	0.35
MDS-UPDRS part IV	9.0 (6.5, 10.0)	8.5 (5.2, 10.8)	0.66
MOCA score	28.00 (26.00, 29.00)□	27.00 (26.00, 29.75)	0.9
HAM-D score	3.00 (2.00, 6.00)	4.00 (2.00, 6.00)*	0.74
HAM-A score	3.0 (1.0, 6.0)	3.0 (1.0, 5.0)*	0.96
LARS score	-29.0 (-33.0, -25.2)	-25.0 (-29.0, -23.5)‡	0.05
QUIP-RS score	2.0 (0.0, 4.0)□	3.0 (1.0, 5.0)‡	0.38
ASBPD hypodopaminergic disorders	2.00 (1.00, 3.50)†	3.00 (1.00, 4.00)	0.38
ASBPD non-motor fluctuations	1.00 (0, 2.00)†	1.00 (0.25, 2.75)	0.16
ASBPD hyperdopaminergic behaviors	2.00 (1.00, 4.00)†	2.00 (1.25, 4.00)	0.41
Active or previous mood disorder	61 (67%)†	12 (67%)	0.98
Active or previous ICD	54 (59%)†	13 (72%)	0.3
Active or previous DDS	4 (4.4%)†	1 (5.6%)	0.99
LEDD, total (mg)	1,462 (1,098, 1800)	1,482 (1,203, 1764)	0.94
LEDD, dopamine agonists (mg)	220 (37, 310)	232 (74, 354)	0.41
Antidepressant medication (yes)	16 (17%)	6 (33%)	0.19
Anxiolytic medication (yes)	19 (20%)	2 (11%)	0.52
Antipsychotic medication (yes)	2 (2.2%)	1 (5.6%)	0.41

Data are presented as median (interquartile range) for continuous variable or number (percent) for categorical variables.

Missing data: *n = 1; †n = 2; ‡n = 3; ||n = 4–9; □n = 10–18.

ASBPD = Ardouin Scale of Behavior in Parkinson's Disease; DDS = dopamine dysregulation syndrome; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Scale; ICD = impulse control disorders; LARS = Lille Apathy Rating Scale; LEDD = levodopa equivalent daily dose; MDS-UPDRS = Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; TEED = Total Electrical Energy Delivery.

Significant VTA overlap with the right substantia nigra was found in one patient with mania. Bilateral ventral active contacts were used in 12 (67%) out of 18 patients with mania versus 24 (27%) out of 90 patients without mania ($p = 0.004$) and the use of at least one ventral contact was found in 15 (83%) out of 18 patients with mania versus 44 (47%) out of 90 patients without mania,

whereas TEED was similar in both groups (Table S2). Moreover, limbic VTA overlap within the STN was associated with mania (OR (95% CI) 1.14 (1.06 to 1.25)), independently of age (OR (95% CI) 1.01 (0.92–1.12)), UPDRS-III off score (OR (95% CI) 1.01 (0.96–1.06)), QUIP-RS score (OR (95% CI) 0.97 (0.73–1.21)) and LARS score (OR (95% CI) 1.12 (0.97–1.29)).

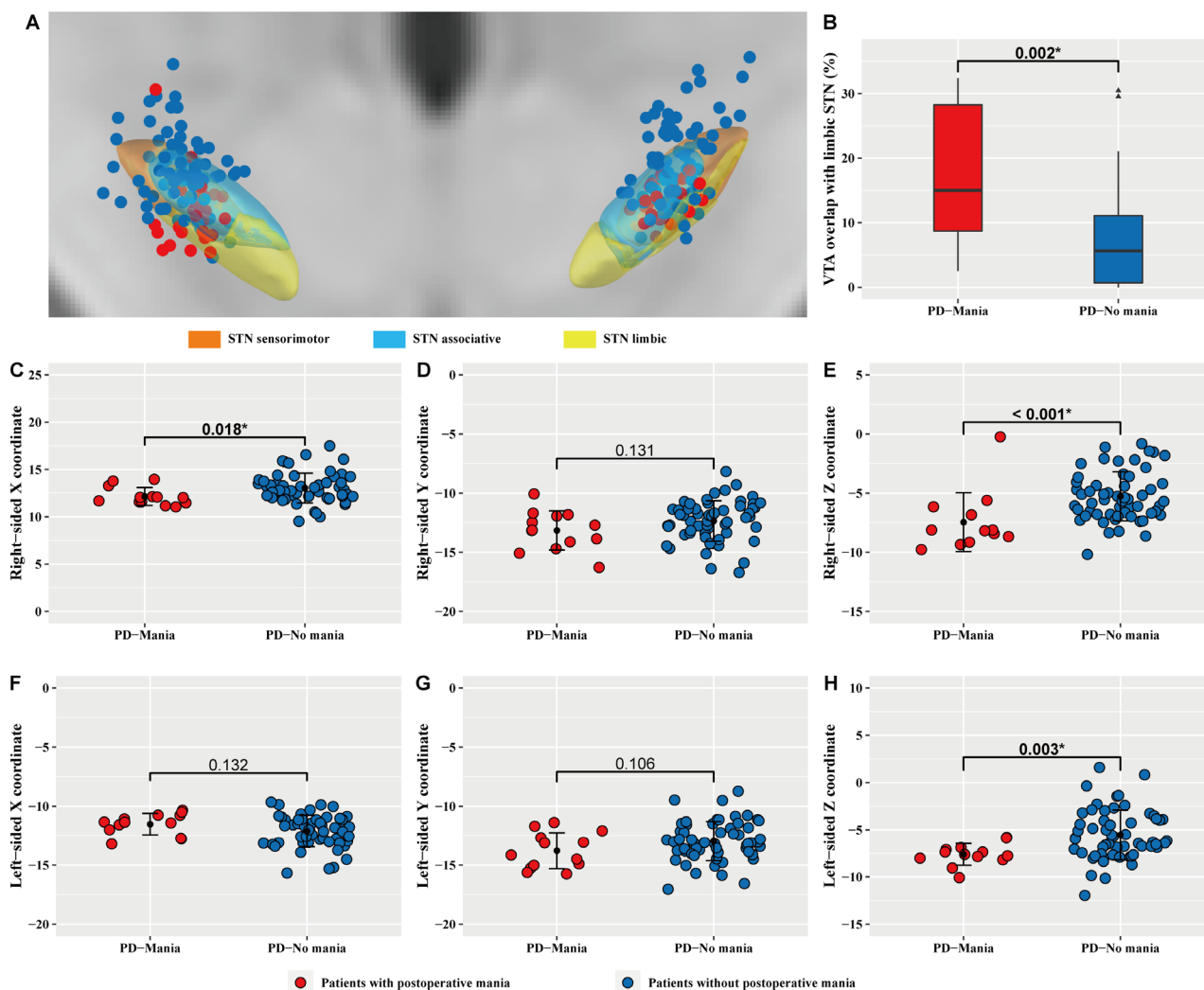


FIGURE: Electrodes active contacts position relative to the tripartite subthalamic nuclei (STN) (orange = sensorimotor, light blue = associative, yellow = limbic) in coronal view (A), percent overlap of the volume of tissue activated with the limbic STN (B) and three-dimensional coordinates of the right (C-E) and left (F-H) electrodes contacts for patients with mania (red) and patients without mania (blue). Active contacts are represented at the climax of manic symptoms for patients with postoperative mania, and at hospital discharge for patients without mania serving as reference for comparison.

Clinical management of mania consisted first in discontinuation of dopamine agonists in 11 patients and reduction in 4 of 17 patients with preoperative dopamine agonists, with overall reduction of total LEDD in all patients. Low-dose clozapine therapy (12.5–25 mg) was initiated in 12 (66.7%) of 18 patients, besides cessation of antidepressant medication in three. In addition, the active contact of stimulation was relocated dorsally in patients with mania (Fig S1) and, one year after surgery, bilateral ventral stimulation was used in only five patients (31%) with postoperative mania. Following these adjustments mania reverted within one month in 13 (72%) patients and within two months in three patients, whereas mania was observed in two patients up to three and five months after the surgery, respectively, and reverted thereafter. Motor and nonmotor outcome was similar at one year

following STN-DBS for patients with or without postoperative mania, with a major improvement both in terms of motor complications and neuropsychiatric symptoms (Tables 2 and S2).

Discussion

In this prospective study, postoperative mania occurred in 16.2% patients after STN-DBS, which was mainly driven by limbic subthalamic stimulation. Mania usually resolved within one month after active clinical management and relocation of active contacts toward the dorsal, sensorimotor STN. Importantly, patients with mania had similar motor and nonmotor benefits one year after STN-DBS surgery, even though dopamine agonists were considerably reduced or stopped, demonstrating that the occurrence of

TABLE 2. Stimulation Contacts and Parameters after STN-DBS Surgery (at manic climax or hospital discharge, respectively) and Stimulation Parameters and Clinical Evolution One Year after STN-DBS in PD Patients with and without Postoperative Mania

	PD patients without post-operative mania (n = 93)	PD patients with post-operative mania (n = 18)	<i>p</i>
After STN-DBS surgery			
Directional DBS electrodes (yes)	24 (26%)	9 (50%)	0.04
Active plots position (VV; VD; DD), bilateral	24 (27%); 20 (22%); 46 (51%)‡	12 (67%); 3 (17%); 3 (17%)	0.004
Active plot position (V; D), left STN	35 (39%); 55 (61%)‡	14 (78%); 4 (22%)	0.002
TEED (μJ), left STN	38 (28, 58)	32 (23, 49)	0.18
Active plot position (V; D), right STN	34 (37%); 58 (63%)*	13 (72%); 5 (28%)	0.006
TEED (μJ), right STN	34 (28, 49)	38 (23, 52)	0.75
LEDD, total (mg)	550 (370, 836)	385 (200, 810)	0.14
LEDD, dopamine agonists (mg)	40 (0, 150)	0 (0, 60)	0.046
1-year follow-up evaluation after STN-DBS			
	n = 86	n = 17	
Deaths/ Dementia/ loss of follow-up	2/ 2 / 3	0/ 0/ 1	0.12
Active plots position (VV;VD;DD), bilateral	18 (22%); 18 (22%); 44 (55%)	5 (31%); 4 (25%); 7 (44%)*	0.67
Active plot position (V; D), left STN	28 (35%); 52 (65%)	7 (47%); 8 (53%)*	0.39
TEED (μJ), left STN	72 (55, 92)†	44 (30, 69)*	0.005
Active plot position (V; D), right STN	28 (34%); 55 (66%)‡	5 (31%); 11 (69%)*	0.85
TEED (μJ), right STN	70 (49, 91)‡	51 (37, 84)*	0.2
LEDD, total (mg)	710 (562, 1,082)‡	803 (506, 1,125)*	0.83
LEDD, dopamine agonists (mg)	120 (0, 170)‡	0 (0, 10)*	0.001
MDS-UPDRS part I	8.0 (5.0, 12.0)‡	5.0 (3.0, 11.0)†	0.24
MDS-UPDRS part III (off-stim, off-med)	40 (32, 48)*	39 (32, 54)*	0.56
MDS-UPDRS part III (on-stim, off-med)	18 (13, 26)*	19 (14, 28)*	0.74
MDS-UPDRS part III (off-stim, on-med)	16 (12, 23)	20 (12, 24)*	0.52
MDS-UPDRS part III (on-stim, on-med)	10.0 (6.0, 13.0)	8.0 (8.0, 11.0)*	0.57
MDS-UPDRS part IV	3.0 (1.0, 5.5)‡	5.0 (3.0, 7.0)†	0.25
MOCA score	26.00 (25.00, 28.00)	26.50 (24.75, 28.00)*	0.98
HAM-D score	2.0 (1.0, 6.0)	2.0 (0.0, 4.5)†	0.36
HAM-A score	3.0 (1.0, 6.0)	1.0 (0.0, 4.0)†	0.092
LARS score	-28 (-31, -23)	-26 (-28, -21)†	0.33
QUIP-RS score	0.00 (0.00, 2.00)□	0.50 (0.00, 2.75)‡	0.49
ASBPD hypodopaminergic disorders	2.00 (1.00, 4.00)	2.00 (1.00, 4.00)	0.55
ASBPD non-motor fluctuations	0 (0, 0)	0 (0, 0)	0.59
ASBPD hyperdopaminergic behaviors	1.00 (0, 2.00)	2.00 (0, 3.00)	0.17

Data are presented as median (interquartile range) for continuous variable or number (percent) for categorical variables.

Missing data: *n = 1; †n = 2; ‡n = 3; ||n = 4–9; □n = 10–18.

ASBPD = Ardouin Scale of Behavior in Parkinson's Disease; D = dorsal; DDS = dopamine dysregulation syndrome; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Scale; ICD = impulse control disorders; LARS = Lille Apathy Rating Scale; LEDD = levodopa equivalent daily dose; MDS-UPDRS = Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; TEED = Total Electrical Energy Delivery; V = ventral.

mania in the immediate or short-term postoperative period is not a prognostic factor of outcome for STN-DBS implantation.

In contrast to previous retrospective reports,^{10, 11, 13} no preoperative risk factors of postoperative mania were identified, notably for pre-existing neuropsychiatric conditions and behavioral disorders,^{4, 5, 9–11, 14, 15} although further prospective studies are needed. In particular, 17 out of 18 patients with mania were males, consistent with over-representation of male patients in earlier reports.^{4, 5, 9–11, 14–16} Furthermore, patients with mania did not exhibit greater preoperative ICD and hyperdopaminergic behaviors evocative of limbic dopaminergic hypersensitivity.¹⁷ Interestingly, preoperative apathy may favor postoperative mania, as demonstrated for de novo ICD following STN-DBS,¹⁸ which may indicate abnormal limbic sensitization underlying the vulnerability to both hypo- and hyperdopaminergic behaviors depending on external stressors as DBS.¹⁹ In our study, postoperative ICD were not observed in manic patients, with reduction or cessation of dopamine agonists. Overall, postoperative mania is frequent and cannot be anticipated based on individual clinical characteristics, in line with studies indicating manic behaviors in 15 to 40% of patients undergoing STN-DBS.^{20, 21}

On the other hand, our study clearly emphasizes the major role of stimulating the ventromedial part of the STN as a trigger of mania, especially for bilateral stimulation of the limbic STN territory, independently of clinical factors. This suggests the role of direct limbic stimulation within the STN,^{13, 21} although functional territories are known to overlap.¹⁷ In addition to the stimulation of the limbic STN, the implication of the medial forebrain bundle either directly or via its connection to the STN is not excluded.^{16, 22} Besides this hypothesis, and because of the anatomical proximity between the STN and substantia nigra, one cannot also rule out a direct involvement of the substantia nigra notably its limbic part as suggested in previous studies.^{8, 9} On the opposite, energy delivery does not seem to be determinant,^{11, 14} provided that active contacts are stimulating limbic circuits. The direct involvement of the cortico-subcortical and mesocorticolimbic pathway was clearly shown using PET functional imaging, exhibiting the activation of the dorsal anterior cingulate cortex and medial prefrontal cortex elicited by ventromedial subthalamic and/or substantia nigra stimulation triggering hypomania.⁹ Accordingly, moving the active contacts from the ventral, limbic, to the dorsal, sensorimotor, part of the STN enables rapid and efficient management of mood elevation,^{9–11} with long-term motor and nonmotor benefits¹² and without reemergent mania. Therefore, our study is the first to show that mania was not a pejorative prognostic factor one year after STN-DBS surgery, provided that rapid postoperative management of DBS and oral treatments is initiated. Besides the relocation of stimulation, which is critical, a rapid reduction of oral dopamine

replacement therapy, notably dopamine agonist should be performed, which did not lead to postoperative withdrawal syndrome.⁷ In addition, low-dose clozapine or quetiapine therapy may be considered as needed. However, we cannot disentangle the relative efficacy of oral treatment versus DBS changes in our study. In addition, no rating scale was available to assess the evolution of mania severity in our study. Nevertheless, the rapid improvement of mania following the changes of stimulation contacts suggests the critical role of DBS by opposition to the delayed effect of medication changes. In favor of the crucial role of the topography of subthalamic stimulation, other studies demonstrated that mania could be reproduced up to five years after surgery using previously identified, ‘manic’ ventromedial active contacts.^{8, 9} Interestingly, mood changes can also be observed after DBS targeting the globus pallidus internus (GPi-DBS) when more ventral contacts of stimulation are used,²³ but, in the long-term, mood disorders were not different when comparing STN and GPi-DBS.²⁴

Overall, we demonstrate that 16% of PD patients undergoing STN-DBS experienced postoperative mania related to stimulation of the ventromedial limbic STN or nearby limbic structures or pathways. The switch to a more dorsal stimulation is a safe and effective strategy, besides discerning adjustment of oral medication, guaranteeing long-term motor and nonmotor benefits without reemergent mania. This strategy should be applied without delay once the first signs of mania occur because of the possible devastating consequences of prolonged or persistent mania for the patient, his caregiver and relatives.

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Author Contributions

SP, ZL, EM, DD, CT and ST contributed to the conception and design of the study; SP, ZL, MN, TD, CL,

OLB, MA, HK, NL, CP, JV, GP, ES, PM, ASR, DD, EM, CT and ST contributed to the acquisition and analysis of data; SP, ZL, MN, EM and ST contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

The authors declare no competing interest.

References

- Lhommée E, Wojtecki L, Czernecki V, et al. Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (EARLYSTIM trial): secondary analysis of an open-label randomised trial. *Lancet Neurol* 2018;17:223–231.
- Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 1998;339:1105–1111.
- Bejjani BP, Damier P, Arnulf I, et al. Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med* 1999;340:1476–1480.
- Kulisevsky J, Berthier ML, Gironell A, et al. Mania following deep brain stimulation for Parkinson's disease. *Neurology* 2002;59:1421–1424.
- Romito LM, Raja M, Daniele A, et al. Transient mania with hypersexuality after surgery for high frequency stimulation of the subthalamic nucleus in Parkinson's disease. *Mov Disord* 2002;17:1371–1374.
- Herzog J, Reiff J, Krack P, et al. Manic episode with psychotic symptoms induced by subthalamic nucleus stimulation in a patient with Parkinson's disease. *Mov Disord* 2003;18:1382–1384.
- Thobois S, Ardouin C, Lhommée E, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain* 2010;133:1111–1127.
- Ulla M, Thobois S, Lemaire JJ, et al. Manic behaviour induced by deep-brain stimulation in Parkinson's disease: evidence of substantia nigra implication? *J Neurol Neurosurg Psychiatry* 2006;77:1363–1366.
- Ulla M, Thobois S, Llorca PM, et al. Contact dependent reproducible hypomania induced by deep brain stimulation in Parkinson's disease: clinical, anatomical and functional imaging study. *J Neurol Neurosurg Psychiatry* 2011;82:607–614.
- Chopra A, Tye SJ, Lee KH, et al. Underlying neurobiology and clinical correlates of mania status after subthalamic nucleus deep brain stimulation in Parkinson's disease: a review of the literature. *J Neuropsychiatry Clin Neurosci* 2012;24:102–110.
- Seritan AL, Spiegel LL, Weinstein JL, et al. Elevated mood states in patients with Parkinson's disease treated with deep brain stimulation: diagnosis and management strategies. *J Neuropsychiatry Clin Neurosci* 2021;33:314–320.
- Dembek TA, Roediger J, Horn A, et al. Probabilistic sweet spots predict motor outcome for deep brain stimulation in Parkinson disease. *Ann Neurol* 2019;86:527–538.
- Welter ML, Schupbach M, Czernecki V, et al. Optimal target localization for subthalamic stimulation in patients with Parkinson disease. *Neurology* 2014;82:1352–1361.
- Chopra A, Tye SJ, Lee KH, et al. Voltage-dependent mania after subthalamic nucleus deep brain stimulation in Parkinson's disease: a case report. *Biol Psychiatry* 2011;70:e5–e7.
- Mandat TS, Hurwitz T, Honey CR. Hypomania as an adverse effect of subthalamic nucleus stimulation: report of two cases. *Acta Neurochir* 2006;148:895–898.
- Coenen VA, Honey CR, Hurwitz T, et al. Medial forebrain bundle stimulation as a pathophysiological mechanism for hypomania in subthalamic nucleus deep brain stimulation for Parkinson's disease. *Neurosurgery* 2009;64:1106–1115.
- Castrioto A, Lhommée E, Moro E, Krack P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. *Lancet Neurol* 2014;13:287–305.
- des Neiges Santin M, Vouilleminot P, Vrillon A, et al. Impact of subthalamic deep brain stimulation on impulse control disorders in Parkinson's disease: a prospective study. *Mov Disord* 2021;36:750–757.
- Theis H, Probst C, Fernagut PO, van Eimeren T. Unlucky punches: the vulnerability-stress model for the development of impulse control disorders in Parkinson's disease. *Npj Park Dis* 2021;7:1–8.
- Daniele A, Albanese A, Contarino MF, et al. Cognitive and behavioural effects of chronic stimulation of the subthalamic nucleus in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2003;74:175–182.
- Mosley PE, Smith D, Coyne T, et al. The site of stimulation moderates neuropsychiatric symptoms after subthalamic deep brain stimulation for Parkinson's disease. *NeuroImage Clin* 2018;18:996–1006.
- Coenen VA, Schumacher LV, Kaller C, et al. The anatomy of the human medial forebrain bundle: ventral tegmental area connections to reward-associated subcortical and frontal lobe regions. *NeuroImage Clin*. 2018;18:770–783.
- Okun MS, Fernandez HH, Wu SS, et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol* 2009;65:586–595.
- Wang JW, Zhang YQ, Zhang XH, et al. Cognitive and psychiatric effects of STN versus GPi deep brain stimulation in Parkinson's disease: a meta-analysis of randomized controlled trials. *Plos One* 2016; 11:e0156721.