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**Subthalamic nucleus stimulation impairs motivation: implication for apathy in
Parkinson’s disease**

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STN-DBS and Apathy in Parkinson's Disease

ABSTRACT

Background: Apathy is one of the most disabling neuropsychiatric symptoms in Parkinson's disease (PD) patients, and has a higher prevalence in patients under subthalamic nucleus deep brain stimulation (STN-DBS). Indeed, despite its effectiveness for alleviating PD motor symptoms, its neuropsychiatric repercussion has not been fully uncovered yet. Because it can be alleviated by dopaminergic therapies, especially D_2 and D_3 dopaminergic receptor (D_2R/D_3R) agonists, the commonest explanation proposed for apathy after STN-DBS is a too strong reduction of dopaminergic treatments.

Objectives: Whether or not STN-DBS can induce apathetic behaviors remains an important matter of concern. We aimed at unambiguously addressing this question of the motivational effects of chronic STN-DBS.

Methods: We longitudinally assessed the motivational effects of chronic STN-DBS, by using innovative wireless micro-stimulators allowing continuous stimulation of STN in freely moving rats, and a pharmacological therapeutic approach.

Results: We showed for the first time that STN-DBS induces a motivational deficit in naïve rats and intensifies those existing in a rodent model of PD neuropsychiatric symptoms. As reported from clinical studies, this loss of motivation was fully reversed by chronic treatment with pramipexole, a D_2R/D_3R agonist.

Conclusion: Taken together, these data provide experimental evidence that chronic STN-DBS by itself can induce a loss of motivation, reminiscent of apathy, independently of the dopaminergic neurodegenerative process or reduction of dopamine replacement therapy, presumably reflecting a dopaminergic driven deficit. Therefore, our data help to clarify and reconcile conflicting clinical observations by highlighting some of the mechanisms of the neuropsychiatric side-effects induced by chronic STN-DBS.

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1 Introduction

2 Subthalamic nucleus deep brain stimulation (STN-DBS) is a neurosurgical treatment
3 that efficiently alleviates the motor symptoms of Parkinson’s disease (PD).¹ However, a
4 plethora of psychiatric manifestations and cognitive deficits have been recently identified as
5 an integral part of the clinical picture of the disease and STN-DBS has been suggested to
6 influencethese symptoms, for better or for worse.^{2, 3} Apathy, which can be simplistically
7 defined as a loss of motivation or a reduction in goal-directed behaviors accompanied by loss
8 of emotions and flattening of affect,⁴⁻⁶ is the most frequently observed non-motor
9 complication of PD and deeply contributes to worsen the patient’s quality of life^{2, 5, 7-12}.
10 Importantly, apathy has been reported to occur, or be exacerbated, in some patients under
11 STN-DBS, as blunted affects^{8-10, 13-16}. Yet, the clear repercussion of STN-DBS on apathy
12 remains to be elucidated.

13 Because dopaminergic replacement therapy (DRT) is reduced during STN-DBS,
14 apathy in patients under STN-DBS is commonly attributed to the resurgence of pre-existing
15 symptoms revealed by DRT reduction or withdrawal.¹⁷ This assumption is also supported by
16 1) the alleviation of apathy after STN-DBS by dopaminergic agonists, especially those
17 targeting the D2 and D3 DA receptors (D₂R and D₃R)^{18, 19} and 2) functional imaging studies
18 in PD patients^{9, 17} and some preclinical data indicating that at least some forms of apathy are
19 related to the degenerative process and DA loss.²⁰

20 However, in several studies, the occurrence of apathy in patients under STN-DBS
21 was not correlated with the reduction of DRT but with DBS-induced changes in glucose
22 metabolism within the associative and limbic circuitry^{15, 21, 22} or with incorrect location of
23 electrodes in the associative or limbic part of the STN.²³ Thus, apathy in patients under STN-
24 DBS was also proposed to be a major side-effect of STN-DBS itself.^{15, 21-23} There is now an
25 abundance of experimental and clinical studies demonstrating that 1) the STN is involved in
26 reward and motivational processes,²⁴⁻³¹ 2) manipulating the STN can modify motivational
27 behaviors³²⁻³⁷ and 3) STN-DBS can alleviate dopamine dysregulation syndrome in some PD

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patients^{14, 38, 39} and be a conceivable approach to treat addictive disorders⁴⁰⁻⁴⁵. Yet, a possible direct impact of STN-DBS on motivation in PD is not unanimously supported.

This lack of consensus concerning the origin of apathy in patients under STN-DBS is a critical issue. Whereas the prevalence of apathy before STN-DBS is about 25%^{13, 46, 47}, this percentage ranges from 8 % to 60 % during STN-DBS^{14, 17, 21, 48}, according to the diagnostic approach used, whether established according to cut-off scores on severity scales, instruments rated by caregivers, or clinical diagnostic criteria⁴⁷. Thus, it considerably compromises the benefits of STN-DBS on motor symptoms.⁵ Investigating this question in patients is difficult because it is impossible to avoid the impact of the progressive process of degeneration and reduction of DRT during STN-DBS. In addition, the animal studies that have sought to explore the limbic and mood effects of STN-DBS may not have combined appropriate behavioral approaches to assess motivation with bilateral and continuous STN-DBS^{41, 49, 50} as clinically applied most of the time in studies reporting on apathy^{5, 15, 19, 21, 51-53}.

In the present study, we explored a potential effect of bilateral STN-DBS on motivation, by using a wireless micro-stimulation system enabling chronic continuous stimulation in rats during several weeks⁵⁴. We first investigated the consequences of bilateral chronic STN-DBS in naïve rats and then in a preclinical model of neuropsychiatric symptoms related to PD that we have developed, using bilateral but partial denervation of the dorsal striatum (DS) by 6-hydroxydopamine (6-OHDA) lesion of SNc.^{20, 55} Because D₂R and D₃R agonists, such as pramipexole (PPX), can alleviate pre and post STN-DBS apathy in PD patients^{18, 19, 56} as well as in preclinical models^{20, 57} and because we reported that STN-DBS reduces the level of D₂R and D₃R in the nucleus accumbens (NAc) of rats,⁵⁸ our working hypothesis was that post-STN-DBS apathy may be due to an alteration of DA transmission induced by STN-DBS itself. Thus, we also investigated the effect of STN-DBS with or without chronic treatment with PPX.

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3 1 **Materials and Methods**

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6 2 **Animals**

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8 3 Experiments were performed on adult male Sprague-Dawley rats (Janvier, Le Genest-Saint-
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10 4 Isle, France) weighing approximately 350g (8 weeks old) at the time of surgery. Animals
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12 5 were individually housed under standard laboratory conditions (12 h light/dark cycle, with
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14 6 lights on at 7 am) with food and water available *ad libitum* during all the experimental
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16 7 procedures. Protocols used complied with the European Union 2010 Animal Welfare Act and
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18 8 the French directive 2010/63.
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23 10 **Bilateral 6-OHDA lesions, bilateral implantation of electrodes and deep brain**
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25 11 **stimulation of subthalamic nucleus**

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27 12 See supplemental informations
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31 14 **Experimental design**

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33 15 After self-administration training and both surgeries, rats were subjected to a sequence of
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35 16 behavioral tests, with one resting day between the different tests (Figure 1A). In each
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37 17 experiment, all conditions were counter-balanced among the different test chambers and
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39 18 each apparatus was thoroughly cleaned after each trial or session.

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41 19 Rats were trained to self-administer a 2.5% sucrose solution before and after SNc lesion and
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43 20 electrodes implantation (Only the self-administration after electrode implantation is
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45 21 represented). After 10 to 15 days, stable performances were obtained (less than 20%
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47 22 performance variation over three consecutive sessions) and STN-DBS was turned ON.
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49 23 Pharmacological procedures were applied after a new stabilization period: PPX (Sigma, 0.3
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51 24 mg.kg⁻¹ in 0.9% NaCl, 1 ml/kg) or vehicle was administered (sub-cutaneous) twice a day, 3h
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53 25 before the beginning of behavioral tests (i.e. injection at 7 am; test at 10 am) for and then at
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55 26 5 pm, during 20 days. This protocol, known to increase the expression of D₂R and D₃R,⁵⁹
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57 27 was chosen to explore the chronic effects of PPX.⁶⁰ STN-DBS and PPX treatment were
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uninterrupted until rat euthanasia. After several days of sucrose self-administration, rats were submitted to a two-bottle choice procedure, as well as to a stepping test and locomotor/ambulatory activity evaluation in an open area⁵⁵ (Figure 1A). At the end of the experiment, rats were euthanized and brains were processed for histological control of lesion and implantations.

See supplemental data for full description of behavioral procedures, quantification of the extent of the striatal DA denervation and control of electrode implantation.

Data and statistical analysis

Data are shown as means $\pm$ SEM and were analyzed by one or two-way ANOVAs, repeated or not as specified in Results. Concerning operant sucrose self-administration, the different experimental periods (Pre-STN-DBS, STN-DBS and STN-DBS + PPX) were analyzed independently by distinct repeated measure ANOVAs for figures 2A and 4A. When indicated, post hoc analyses were carried out with the Student Newman-Keuls procedure.

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Results

Histological controls

Figure 1B provides the different electrode positions in left and right STN for the stimulated animals. Figures 1C and D illustrate two examples of the position of an electrode tip within the STN, stimulated respectively with the lowest (100 μ A) and the highest (225 μ A) intensity used in the study. See also supplemental figure 1 for additional examples of STN stimulated at 100 μ A or 225 μ A, still unaltered after chronic stimulation.

Bilateral lesion of SNc (Figure 1E, percent of TH-IR loss, left SNc: 73 ± 5 ; right SNc: 74 ± 5) was obtained by 6-OHDA injection. The injection produced an important denervation of the dorsal striatum in its lateral portion (Figure 1F, left dorsal striatum: 68 ± 5 ; right dorsal striatum: 74 ± 6), along its rostro-caudal extent as revealed by decreased tyrosine hydroxylase immunoreactivity. As the lesion has been shown to specifically affect SNc, barely impacting VTA (Figure 1G, left VTA: 11 ± 8 ; right VTA: 20 ± 4 ; Two way ANOVA, Structure x Lesion interaction: $F_{1,22} = 7.654, p < .0151$), NAc was almost totally preserved from denervation (Figure 1H, left NAc: 21 ± 3 ; right NAc: 24 ± 4 ; Two way ANOVA, Structure x Lesion interaction: $F_{1,22} = 125.758, p < .001$).

STN-DBS induces a motivational deficit in normal rats that is reversed by the D_2R/D_3R agonist pramipexole

Before STN-DBS was switched ON, rats were trained for 10 days in the operant task (only the last 3 days of training are represented in figure 2A). Groups were formed to have equivalent performance levels (Figure 2A, Pre STN-DBS period, repeated measure ANOVA, Session x STN-DBS x PPX interaction, $F_{2,122} = 1.334, p = .2672$). From day one of stimulation, STN-DBS induced a dramatic decrease of about 40% in instrumental responding for the sucrose solution in both stimulated groups before pharmacological treatment (STN-DBS + Veh and STN-DBS + PPX) as compared with the pre STN-DBS levels (Figure 2A, STN-DBS period, repeated measure ANOVA, STN-DBS effect: $F_{1,54} = 9.615, p = .0031$;

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Figure S2A, two way ANOVA, STN-DBS effect: $F_{1,42} = 10.480$, $p = .002$). PPX completely rescued the self-administration performances of stimulated rats from the second day of treatment, without bringing performances superior to baseline or to Control + Veh rat levels. (Figure 2A, STN-DBS + PPX period, repeated measure ANOVA, STN-DBS x PPX interaction: $F_{1,58} = 4.658$, $p = .0351$; Session x PPX interaction: $F_{6,348} = 2.412$, $p = .0269$). Both STN-DBS and PPX effects remained stable until the end of self-administration experimentation (Figure 2B, two ways ANOVA, STN-DBS x PPX interaction: $F_{1,64} = 7.178$, $p = .009$). In order to determine whether the decrease of operant performances induced by STN-DBS was due to impairment in the consummatory or preparatory components of motivated behaviors, we evaluated the sensitivity to the motivational properties of sucrose (consummatory behavior) in a two-bottle choice procedure. The preference for the sucrose solution that was used in the operant self-administration experiment over water was high and not altered by STN-DBS or PPX (Figure 2C, two way ANOVA, STN-DBS x PPX interaction: $F_{1,61} = .966$, $p = .330$). Therefore, the self-administration paradigm and the sucrose preference test indicate that STN-DBS affected the preparatory component of motivated behaviors during the operant task and that PPX specifically corrected this impairment.

In addition, STN-DBS-induced preparatory component deficit and subsequent self-administration deficiency cannot be attributed to motor impairment, because STN-DBS did not induce any significant locomotor change during the first 20 minutes of the open area test, corresponding to the exploratory phase when locomotor activity is high, facilitating detection of motor deficit (Figure 3A, two way ANOVA, 0-20 min: $F_{1,48} = .513$; $p = .477$). Exploration and locomotor activity then progressively decreased to a basal level during the last 2 periods (20 to 60 min). Although it did not reach significance, STN-DBS tended to reduce ambulatory activity during this phase. (Figure 3A, STN-DBS effect, Two way ANOVA, 20-40 min: $F_{1,48} = 3.311$, $p = .075$; 40-60 min: $F_{1,48} = 3.525$, $p = .067$) This effect of STN-DBS is unlikely to reflect a motor deficit but rather a decrease in general behavioral activity, because ambulatory speed during this test phase was not changed by the stimulation (Figure 3B, STN-DBS effect, Two way ANOVA, $F_{1,48} = .196$, $p = .660$). Moreover, fine motor skills of left

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and right limbs assessed using a stepping test were not affected by the stimulation, confirming the absence of any motor deficit induced by chronic and bilateral STN-DBS (Figure 3C). As STN-DBS, PPX had no impact on fine motor skills (Figure 3C, two way ANOVA, STN-DBS x PPX interaction: left to right moves, left limb: $F_{1,55} = .110$, $p = .742$; right limb $F_{1,55} = .000442$, $p = .983$; right to left moves, left limb: $F_{1,55} = .0135$, $p = .908$; right limb: $F_{1,55} = .0557$, $p = .814$), but caused a significant increase in locomotor activity in the open area test (Figure 3A, PPX effect, Two way ANOVA, 20-40 min: $F_{1,48} = 5.686$, $p = .021$; 40-60 min: $F_{1,48} = 5.047$, $p = .030$). Interestingly, the combined effect of the behavioral hypoactivity induced by STN-DBS and hyperactivity due to PPX resulted in normalization of the general activity during the last 2 phases of the open area test (Figure 3A).

Taken together, these results suggest that STN-DBS induced a clear motivational deficit that was alleviated by the D_2R/D_3R agonist, reminiscent of apathy in PD.

STN-DBS exacerbates motivational deficit in a rodent model of PD apathetic symptoms and affective disorders

We sought to confirm whether STN-DBS would also affect motivation in a pathological context. We used a rodent model of PD that we developed⁵⁵ and that exhibits strong motivational deficits, without locomotor alterations.

Before STN-DBS was switched-ON, rats were trained again for 10 days in the operant task (only the last 3 days of training are represented in figure 4A). All groups obtained equivalent performance levels (Figure 4A, 3 last days of Pre STN-DBS period, repeated measure ANOVA, Session x STN-DBS x PPX interaction, $F_{2,32} = 1.088$, $p = .3490$). As previously demonstrated,⁵⁵ 6-OHDA rats showed a marked and significant decrease in self-administration of sucrose as compared to non-lesioned animals (Figure S2A, two way ANOVA, Lesion effect: $F_{1,42} = 26.592$, $p = < .001$; Figure S2B, two way ANOVA, Lesion effect: $F_{1,50} = 26.368$, $p = < .001$) which was not reversed by PPX treatment alone (Figure S2B, two way ANOVA, PPX effect: $F_{1,50} = .150$, $p = .701$). Despite this important instrumental deficit induced by the lesion, STN-DBS was still able to reduce operant behavior by about

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50% from day one of stimulation (Figure 4A, STN-DBS period, repeated measure ANOVA, STN-DBS effect $F_{1,15} = 4.249$, $p = .0571$), as observed in non-lesioned/control stimulated rats (Figure S2A, two way ANOVA, STN-DBS effect: $F_{1,42} = 10.48$, $p = .002$ and no STN-DBS x Lesion interaction: $F_{1,42} = 1.112$, $p = .298$). As for non-lesioned animals, PPX completely alleviated this STN-DBS-induced deficit from the second day of treatment (STN-DBS + PPX period, repeated measure ANOVA, STN-DBS x PPX x Session interaction effect $F_{9,108} = 2.712$, $p = .0069$). Both STN-DBS and PPX effects remained stable until the end of the experiment (Figure 4B, two way ANOVA, STN-DBS x PPX interaction: $F_{1,16} = .826$, $p = .377$). We also assessed the consummatory components of motivated behaviors, with the two-bottle choice procedure and we found that neither STN-DBS nor PPX modified the preference for sucrose (Figure 4C, two way ANOVA, STN-DBS x PPX interaction: $F_{1,20} = .341$, $p = .567$).

PPX or STN-DBS tended to reduce ambulatory activity in the open area test while when they were combined, on average they promoted a high level of activity but with high variability (Figure 5A, two way ANOVA, STN-DBS x PPX interaction: $F_{1,14} = 5.759$, $p = .031$). These effects are likely to reflect changes in behavioral activity rather than alteration of motor skills *per se*, first because neither PPX nor STN-DBS affected the ambulatory speed during the open area test (Figure 5B, Two way ANOVA, STN-DBS x PPX interaction $F_{1,48} = .214$, $p = .650$) and second, adjustments during the stepping test were not impacted by either treatment (Figure 5B, two ways ANOVA, STN-DBS x PPX interaction: left to right moves, left limb: $F_{1,18} = .184$, $p = .673$; right limb: $F_{1,18} = .653$, $p = .983$; right to left moves, left limb: $F_{1,18} = .0017$, $p = .915$; right limb: $F_{1,18} = .764$, $p = .393$).

Taken together, these results suggest that STN-DBS exacerbates the loss of motivation induced by the dopaminergic lesion and reduce behavioral activity, effects that were alleviated by PPX.

Discussion

Combining a relevant *in vivo* model of neuropsychiatric PD symptoms, chronic bilateral STN-DBS in awake and freely moving animals and a pharmacological approach, we provide strong evidence for a direct deleterious effect of STN-DBS on motivation. STN-DBS induces a significant deficit in motivated behavior, due neither to a reward sensitivity deficit related to a potential anhedonic effect, nor to motor deficits. This behavioral effect was completely reversed by the activation of D₂R/D₃R with PPX, revealing the potential critical role of DA in this STN-DBS motivational effect.

It is essential to better understand the pathophysiology of neuropsychiatric symptoms of PD and how they respond to current treatments such as STN-DBS. Here, we tried to be as close as possible to the clinical situation in PD, especially for the stimulation conditions. While most preclinical studies have been performed with acute STN-DBS that was applied daily only during the tasks and experiments (e.g.,^{41, 49}), the novel stimulation system we used allowed continuous STN-DBS for several days. In addition, we used monopolar stimulation. Indeed, it is the most widely applied in PD patients¹ as well as in studies describing apathy under STN-DBS^{17, 21, 48, 61-64}. Furthermore, a preclinical study in rat has clearly demonstrated that it reduces tissue damage compared to bipolar stimulation.⁶⁵ Moreover, although monopolar stimulation is more likely to affect the surrounding STN fibers than bipolar stimulation, it was applied at intensities below 225 μ A to minimize current spreading as previously demonstrated.⁶⁶ The motivational dimension of apathy especially concerns hum-drum daily tasks that are neither challenging nor particularly effortful.⁴ A sucrose self-administration procedure with a 2.5 % solution, in a fixed ratio 1 schedule, in non-food-deprived rats, is an appropriate way to operationalize a simple effort with a relatively moderate rewarding outcome. This approach has allowed us to demonstrate a clear effect of STN-DBS on motivated behaviors during an operant task. The decrease of baseline ambulatory activity detected during the open area test, unrelated to motor impairment, further suggests that the STN-DBS-induced operant deficit may be considered as a decrease in the maintenance of

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behavioral activity, as observed in apathy.⁹ While we previously provided strong evidence that the dopaminergic denervation can account for the loss of motivation in PD, here we report that STN-DBS by itself could induce or exacerbate this motivational impairment via DA-driven mechanisms, independent of the hypodopaminergy induced by DRT reduction. Furthermore, the present study provides a missing link, reconciling apparently contradictory clinical observations on the origin of post-operative apathy in stimulated PD patients.

The myriad of reported neuropsychiatric side effects of STN-DBS in PD patients³ has triggered several animal studies to understand their phenomenology. These studies have demonstrated the possible implication of STN-DBS in PD-related depression^{49, 67} or potent effects on impulsive behaviors,⁶⁸ but few of them tackled the effects on pure motivational processes. As far as we know, only one report mentions data that could be interpreted as a transient reduced motivation under STN-DBS.⁶⁹ However, another study showed no effect of STN-DBS on operant activity in a fixed-ratio schedule of reinforcement and even described an increase in performance in obtaining a sucrose pellet during a progressive ratio schedule.⁴¹ Major differences between this previous study and our protocol are likely to account for these discrepancies. Indeed, Rouaud et al., used acute bipolar stimulation conditions compared to our chronic monopolar STN-DBS; interestingly, psychiatric side effects of STN-DBS strongly depend on electrode polarity. For example, acute depressive states following regular monopolar STN-DBS are greatly reduced by switching to the scarcer bipolar STN-DBS.^{70, 71} Moreover, the design of the operant task was different enough to yield diverging results. In particular, our study avoided food-restriction. Whereas all the studies having inactivated the STN found an increase in motivation for food in restricted animals, one study demonstrated that this effect was completely occluded in rats fed *ad libitum*.³⁷ Finally, while the conditioned place preference revealed an effect of STN-DBS on the rewarding properties of sucrose in this study,⁴¹ we did not find any modification of this parameter during the two bottle choice test.

The STN can be functionally and anatomically subdivided into motor, associative and limbic sub-territories.⁷²⁻⁷⁴ Then it is part of the three respective basal ganglia loops.^{73, 74} In PD

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patients, DBS is tailored to stimulate the motor part of the STN, and so to impact the whole motor circuitry. However, an inaccurate electrode placement within the STN can engage the circuitries involving its associative or limbic part rather than the motor one,⁷⁵ potentially leading to non-motor side effects,^{70, 74} apathy in particular. In line with this assumption, a very recent study succeeded in alleviating post STN-DBS apathy in patients by displacing the electrode from the limbic STN to the motor part,²³ demonstrating that apathy under STN-DBS could rely on a mechanism caused by the stimulation of the limbic part of the STN. Our data suggest that the dopaminergic system might be involved in this mechanism, at least in part.

In patients, apathy occurring after STN-DBS can be treated by dopaminergic agonists, including those targeting the D₂R and D₃R.^{18, 19} This, and the fact that methylphenidate can alleviate fatigue⁷⁶, which is a related and/or confounding symptom of apathy⁷⁷, has prompted the hypothesis that a strong hypodopaminergic state revealed by reduction of DRT, rather than STN-DBS *per se*, may be responsible for the resurgence of apathy.¹³ Using a pharmacological protocol allowing exploration of the chronic effects of PPX and known to increase D₂R and D₃R expression,⁵⁹ we demonstrated that PPX, a D₂R/D₃R agonist, fully rescued the motivational deficit induced by STN-DBS in control and lesioned rats. It should be noted that this pharmacological protocol was not able to reverse the loss of motivation due to the dopaminergic lesion, indicating that even if both the lesion and STN-DBS effects on motivation could be driven by dopaminergic mechanisms, these could be significantly different. This suggests that STN-DBS may impact on behavior via its own effects on DA transmission, which is consistent with previous animal model studies showing that STN-DBS modulates DA system.^{58, 78-82} The three so-called basal ganglia limbic, associative and motor loops including the STN are not completely segregated; the different structures involved are functionally interconnected⁸³ by an ascending striato-midbrain-striatal spiraling circuitry.⁸⁴ Moreover, beyond this complex organization, which has yet to be demonstrated in rats, SNc and VTA are overlapping structures⁸⁵ and the whole striatum is characterized by a dense local microcircuitry^{86, 87} which could also contribute to this interconnection. Thus, STN-DBS may modulate DA transmission within the basal ganglia

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and, through these subcortical interactions, disrupt the complex chain of events that transforms intentions into adapted action, and thereby influence non-motor functions.^{6, 9} Nonetheless, we cannot exclude a potential involvement of the structures surrounding the STN. It is unlikely that the electric field emanating from the electrode is restrained to the STN borders and DBS of some of these structures in the vicinity of the STN, such as the lateral hypothalamus, can also modulate DA transmission⁸⁸. We previously found that short STN-DBS can decrease the level of D₂R and D₃R within the NAc.⁵⁸ Given the critical implication of the D₂R and D₃R in motivational processes,⁸⁹⁻⁹² our data suggest a causal involvement of these receptors in the motivational deficit that we observed. In addition, D₂R and D₃R are expressed in several other non-motor structures impacted by PPX treatment⁹³ and some of them are part of down-stream circuits with metabolic activities known to be affected by STN-DBS.^{22, 94} Thus, beyond the NAc, both STN-DBS and PPX effects could differentially engage some common system responsible for behavior changes highlighted in this study. However, dopaminergic agonists do not always efficiently alleviate apathy under STN-DBS²². Non dopaminergic lesions frequently occur during the course of disease^{95, 96}, and serotonin for example is proposed to participate in PD apathy⁹⁷. In rats, STN-DBS has been shown to decrease serotonin release promoting depressive like behavior.^{49, 98} Thus, we cannot completely exclude the implication of other neurotransmitters in the loss of motivation observed in patients or in this study.

As previously reported,⁹⁹ PPX at 0.3 mg/kg induces hyperlocomotricity in the open area test in control rats. This hyperactivity is unlikely to be responsible for the reversion of the self-administration deficit observed in PPX-treated STN-DBS rats since first, the level of non-stimulated treated rats remains similar to that of control rats, and second, PPX induced hypoactivity in non-stimulated lesioned rats whereas it also reversed the operant deficit induced by STN-DBS in those lesioned rats. This hypoactivity promoted by PPX in lesioned rats has previously been reported during the 120 minutes post injection window in control animals⁹⁹ and could rely on a sedating effect mediated by the presynaptic D₃R¹⁰⁰. We chose to separate the behavioral test from injection by 3h to avoid this effect. Since we previously

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demonstrated that the 6-OHDA lesion modifies D₃R expression within the dorsolateral part of the striatum¹⁰¹, local imbalance between pre and post synaptic D₂R and/or D₃R expression or activity¹⁰² could be responsible for DA transmission blunting, thus promoting this hypoactivity. Very intriguingly, in some rats of both the control and lesioned groups, the combination of STN-DBS and PPX induced a very high- level of activity that could emphasize the importance of individual traits, as demonstrated for the expression or severity of impulse control disorder in PD¹⁰³⁻¹⁰⁵ or compulsive drug taking.¹⁰⁶ Thus, depending on complex interactions with dopaminergic treatments and according to pre-existing individual traits, STN-DBS could also lead to the development of hyperdopaminergic states reminiscent of hypomanic behaviors also observed in PD patients under STN-DBS.^{62, 74, 107, 108}

Altogether, these data bring coherence to clinical observations that seemed contradictory until today: apathy in PD patients, at least its motivational dimension, could be induced by STN-DBS itself and attenuated by activation of D₂R/D₃R, regardless of (or in addition to) DRT reduction and the DA-mediated hypofunction. More detailed molecular analysis or techniques such as optogenetics could enable us to clarify the structures or sub-territories involved in this STN-DBS induced DA-driven loss of motivation. While it is beyond the scope of the present study, it would be also of interest to further investigate the effect of STN-DBS on the emotional and affective component of apathy, as STN has been proposed to be involved in such processes¹⁰⁹.

STN-DBS has been shown to prevent cocaine or heroin re-escalation intake in rats⁴⁰,⁴⁴ and to reduce dopamine dysregulation syndrome or addictive behavior such as pathological gambling.¹¹⁰⁻¹¹⁴ Thus, STN-DBS is currently explored as an effective treatment for addiction.^{45, 115} However, our results suggest that this apparent beneficial effect could be underlain by a general motivational deficit. In rats, inhibiting the STN can abolish affective responses for salient reward¹⁰⁹ and STN-DBS can induce depression-like behaviors.^{49, 67, 116} Furthermore, PD patients for whom addictive behavior was reduced under STN-DBS can also co-express apathy.^{14, 110} These convergent facts are raising the question of the nature of this apparent “anti-addictive” effect of STN-DBS. This neurosurgical treatment could rather

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1 induce a state of negative affect, comparable to a certain extent to the blunted dopaminergic
2 transmission observed during prolonged drug consumption¹¹⁷⁻¹¹⁹ , increasing the risk of
3 addictive behavior resurgence in the same way as drugs of abuse withdrawal syndrome
4 promotes relapse.¹²⁰

5 Thus, this new insight calls for reconsideration of the role of STN-DBS on mood in PD
6 to improve patient care and quality of life, and more broadly, to rethink the use of STN-DBS
7 in psychiatry.

For Peer Review

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Author contributions

YV, SB, SC and MS were responsible for the conception and the design of the study. YV, SB, CC and RM carried out the stereotaxic surgeries and the post-surgery monitoring of the animals. YV, CC and SB performed the neuroanatomical analysis of electrode implantation and lesions. YV and SB carried out the behavioral experiments and analysis. LKLG and PS provided micro-stimulators as well as training and advice for their use. YV and SB wrote the paper with the help of the other authors.

Supplementary information accompanies this paper.

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Figures legends

FIGURE 1: Experimental design and electrode implantation.

(A) Time course of the study, groups of animals and histological controls

After learning the sucrose self-administration task, lesion and implantation of electrodes, rats were divided into a stimulated and a non-stimulated group according to their performances, to constitute initially equal performance groups. Then, after 4 days of subthalamic nucleus deep brain stimulation (STN-DBS) with further sucrose self-administration, pramipexole (PPX) or vehicle (Veh) was injected twice a day into half of the stimulated (Non lesioned rats: STN-DBS + PPX, n = 8; STN-DBS + Veh, n = 13; lesioned rats: Lesion + STN-DBS + PPX, n = 5; Lesion + STN-DBS + Veh, n = 5) and non-stimulated rats (Control + PPX, n = 22; Control + Veh, n = 22; Lesioned rats: Lesion + PPX, n = 4; Lesion + Veh, n = 6) for 20 days. During this time, sucrose self-administration was continued for several days and then followed successively by other behavioral tests: the two-bottle choice test, the stepping test and finally the open area test. **(B)** Positions of bilateral DBS electrode tips in left and right STNs of stimulated animals in representative coronal sections (anteroposterior relative to Bregma: -3.60 mm; -3.80 mm; -4.16 mm), reproduced from Paxinos and Watson.¹²¹ Each bar represents the placement of one electrode. **(C)** and **(D)** Example of electrode trace within the left STN stimulated at 100 μ A **(C)** or 225 μ A **(D)**, after Cresyl violet staining. Scale bar: 1 mm. IC, Internal Capsule; LH, Lateral Hypothalamus; ZI, Zona Incerta.

(E) and **(F)** Representative photomicrographs of coronal sections stained for tyrosine hydroxylase (TH) in striatal (bottom, 1.6 mm to bregma) and mesencephalic (top, -5.6 mm to bregma) regions from naïve (top) and lesioned (bottom) rats.¹²¹ Scale bar = 1 mm. **(G, H)** Quantification of TH ImmunoReactivity (IR) loss in the midbrain **(G)** and the striatum **(H)**, expressed as the percentage difference compared to the mean value obtained for sham operated animals. The SNc bilateral lesion produced an important but partial denervation of

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the dorsal striatum. The ventral tegmental area and the nucleus accumbens were preserved from the lesion. Control + Veh: $n = 22$; Lesion: $n = 20$. Control + Veh versus Lesion: $*p < .05$; $***p < .001$. DS: dorsal striatum; NAc: nucleus accumbens; SNc: substantia nigra compacta, VTA: ventral tegmental area.

FIGURE 2: Subthalamic nucleus deep brain stimulation (STN-DBS) induces a deficit of preparatory behaviors in 2.5% sucrose self-administration that is rescued by pramipexole (PPX). **(A)** Time course of the sucrose self-administration experiment. STN-DBS induced a significant decrease of the number of sucrose deliveries. PPX induced a total reversion of this deficit. **(B)** Mean sucrose deliveries over the last 3 days of experiment. **(C)** STN-DBS and PPX did not alter the preference for sucrose. Control + Veh: $n = 22$; Control + PPX: $n = 22$; STN-DBS + Veh: $n = 13$; STN-DBS + PPX: $n = 8$. Data shown as means $\pm$ SEM. Control + Veh versus STN-DBS + Veh: $*p < .05$; $**p < .01$; STN-DBS + Veh versus STN-DBS + PPX: $\#p < .05$; $##p < .01$.

FIGURE 3: Subthalamic nucleus deep brain stimulation (STN-DBS) and pramipexole (PPX) promote hypo and hyper locomotor activity respectively but do not impair motor abilities. **(A)** Total distance travelled during a 1h open area test. STN-DBS induced a non-significant tendency towards decreased basal locomotor activity that was counteracted by treatment with PPX. In control rats, PPX induced a dramatic increase in the distance traveled. **(B)** STN-DBS and PPX did not change the mean ambulatory speed during the last 2 periods of the open area test. **(C)** STN-DBS and/or PPX did not alter the fine motor skills of front limbs as demonstrated by adjusting steps in the course of the stepping test. Control + Veh: $n = 22$; Control + PPX: $n = 22$; STN-DBS + Veh: $n = 6$; STN-DBS + PPX: $n = 8$. Data shown as means $\pm$ SEM. Control + PPX versus Control + Veh: $*p < .05$.

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FIGURE 4: STN-DBS exacerbates the deficit of preparatory behaviors of the existing motivational deficit in a rodent model of the neuropsychiatric symptoms of PD. **(A)** Time course of the sucrose self-administration experiment. STN-DBS decreased the number of sucrose deliveries. PPX induced a complete reversion of this deficit. **(B)** Mean sucrose deliveries over the last 5 days of experiment. **(C)** STN-DBS and PPX did not alter the preference for sucrose in 6-OHDA rats. Lesion + Veh: n = 6; Lesion + PPX: n = 4; Lesion + STN-DBS + Veh: n = 5; Lesion + STN-DBS + PPX: n = 5. Data shown as means $\pm$ SEM. Lesion + Veh versus Lesion + STN-DBS + Veh: $*p < .05$; Lesion + STN-DBS + Veh versus Lesion + STN-DBS + PPX: $\#p < .05$.

FIGURE 5: Subthalamic nucleus deep brain stimulation (STN-DBS) or pramipexole (PPX) individually promote hypoactivity but do not impair motor abilities. **(A)** Total distance traveled during a 1h open area test. STN-DBS induced a non-significant tendency towards decreased basal locomotor activity. In non-stimulated rats, PPX induced a dramatic decrease in the distance traveled. The combination of both treatments increased activity. **(B)** STN-DBS and PPX did not change the mean ambulatory speed during the open area test. **(C)** STN-DBS and/or PPX did not alter the fine motor skills of front limbs as demonstrated by adjusting steps in the course of the stepping test. Lesion + Veh: n = 6; Lesion + PPX: n = 4; Lesion + STN-DBS + Veh: n = 5; Lesion + STN-DBS + PPX: n = 5. Data shown as means $\pm$ SEM. Lesion + PPX versus Lesion + STN-DBS + PPX: $*p < .05$.

**Subthalamic nucleus stimulation impairs motivation: implication for apathy in
Parkinson's disease**

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ABSTRACT

Background: Apathy is one of the most disabling neuropsychiatric symptoms in Parkinson's disease (PD) patients, and has a higher prevalence in patients under subthalamic nucleus deep brain stimulation (STN-DBS). Indeed, despite its effectiveness for alleviating PD motor symptoms, its neuropsychiatric repercussion has not been fully uncovered yet. Because it can be alleviated by dopaminergic therapies, especially D₂ and D₃ dopaminergic receptor (D₂R/D₃R) agonists, the commonest explanation proposed for apathy after STN-DBS is a too strong reduction of dopaminergic treatments.

Objectives: Whether or not STN-DBS can induce apathetic behaviors remains an important matter of concern. We aimed at unambiguously addressing this question of the motivational effects of chronic STN-DBS.

Methods: We longitudinally assessed the motivational effects of chronic STN-DBS, by using innovative wireless micro-stimulators allowing continuous stimulation of STN in freely moving rats, and a pharmacological therapeutic approach.

Results: We showed for the first time that STN-DBS induces a motivational deficit in naïve rats and intensifies those existing in a rodent model of PD neuropsychiatric symptoms. As reported from clinical studies, this loss of motivation was fully reversed by chronic treatment with pramipexole, a D₂R/D₃R agonist.

Conclusion: Taken together, these data provide experimental evidence that chronic STN-DBS by itself can induce a loss of motivation, reminiscent of apathy, independently of the dopaminergic neurodegenerative process or reduction of dopamine replacement therapy, presumably reflecting a dopaminergic driven deficit. Therefore, our data help to clarify and reconcile conflicting clinical observations by highlighting some of the mechanisms of the neuropsychiatric side-effects induced by chronic STN-DBS.

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1 Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) is a neurosurgical treatment that efficiently alleviates the motor symptoms of Parkinson's disease (PD).¹ However, a plethora of psychiatric manifestations and cognitive deficits have been recently identified as an integral part of the clinical picture of the disease and STN-DBS has been suggested to influence these symptoms, for better or for worse.^{2, 3} Apathy, which can be simplistically defined as a loss of motivation or a reduction in goal-directed behaviors accompanied by loss of emotions and flattening of affect,⁴⁻⁶ is the most frequently observed non-motor complication of PD and deeply contributes to worsen the patient's quality of life^{2, 5, 7-12}. Importantly, apathy has been reported to occur, or be exacerbated, in some patients under STN-DBS, as blunted affects^{8-10, 13-16}. Yet, the clear repercussion of STN-DBS on apathy remains to be elucidated.

Because dopaminergic replacement therapy (DRT) is reduced during STN-DBS, apathy in patients under STN-DBS is commonly attributed to the resurgence of pre-existing symptoms revealed by DRT reduction or withdrawal.¹⁷ This assumption is also supported by 1) the alleviation of apathy after STN-DBS by dopaminergic agonists, especially those targeting the D2 and D3 DA receptors (D₂R and D₃R)^{18, 19} and 2) functional imaging studies in PD patients^{9, 17} and some preclinical data indicating that at least some forms of apathy are related to the degenerative process and DA loss.²⁰

However, in several studies, the occurrence of apathy in patients under STN-DBS was not correlated with the reduction of DRT but with DBS-induced changes in glucose metabolism within the associative and limbic circuitry^{15, 21, 22} or with incorrect location of electrodes in the associative or limbic part of the STN.²³ Thus, apathy in patients under STN-DBS was also proposed to be a major side-effect of STN-DBS itself.^{15, 21-23} There is now an abundance of experimental and clinical studies demonstrating that 1) the STN is involved in reward and motivational processes,²⁴⁻³¹ 2) manipulating the STN can modify motivational behaviors³²⁻³⁷ and 3) STN-DBS can alleviate dopamine dysregulation syndrome in some PD

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patients^{14, 38, 39} and be a conceivable approach to treat addictive disorders⁴⁰⁻⁴⁵. Yet, a possible direct impact of STN-DBS on motivation in PD is not unanimously supported.

This lack of consensus concerning the origin of apathy in patients under STN-DBS is a critical issue. Whereas the prevalence of apathy before STN-DBS is about 25%^{13, 46, 47}, this percentage ranges from 8 % to 60 % during STN-DBS^{14, 17, 21, 48}, according to the diagnostic approach used, whether established according to cut-off scores on severity scales, instruments rated by caregivers, or clinical diagnostic criteria⁴⁷. Thus, it considerably compromises the benefits of STN-DBS on motor symptoms.⁵ Investigating this question in patients is difficult because it is impossible to avoid the impact of the progressive process of degeneration and reduction of DRT during STN-DBS. In addition, the animal studies that have sought to explore the limbic and mood effects of STN-DBS may not have combined appropriate behavioral approaches to assess motivation with bilateral and continuous STN-DBS^{41, 49, 50} as clinically applied most of the time in studies reporting on apathy^{5, 15, 19, 21, 51-53}.

In the present study, we explored a potential effect of bilateral STN-DBS on **motivation**, by using a wireless micro-stimulation system enabling chronic continuous stimulation in rats during several weeks⁵⁴. We first investigated the consequences of bilateral chronic STN-DBS in naïve rats and then in a preclinical model of neuropsychiatric symptoms related to PD that we have developed, using bilateral but partial denervation of the dorsal striatum (DS) by 6-hydroxydopamine (6-OHDA) lesion of SNc.^{20, 55} Because D₂R and D₃R agonists, such as pramipexole (PPX), can alleviate pre and post STN-DBS apathy in PD patients^{18, 19, 56} as well as in preclinical models^{20, 57} and because we reported that STN-DBS reduces the level of D₂R and D₃R in the nucleus accumbens (NAc) of rats,⁵⁸ our working hypothesis was that post-STN-DBS apathy may be due to an alteration of DA transmission induced by STN-DBS itself. Thus, we also investigated the effect of STN-DBS with or without chronic treatment with PPX.

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Materials and Methods**Animals**

Experiments were performed on adult male Sprague-Dawley rats (Janvier, Le Genest-Saint-Isle, France) weighing approximately 350g (8 weeks old) at the time of surgery. Animals were individually housed under standard laboratory conditions (12 h light/dark cycle, with lights on at 7 am) with food and water available *ad libitum* during all the experimental procedures. Protocols used complied with the European Union 2010 Animal Welfare Act and the French directive 2010/63.

Bilateral 6-OHDA lesions, bilateral implantation of electrodes and deep brain stimulation of subthalamic nucleus

See supplemental informations

Experimental design

After self-administration training and both surgeries, rats were subjected to a sequence of behavioral tests, with one resting day between the different tests (Figure 1A). In each experiment, all conditions were counter-balanced among the different test chambers and each apparatus was thoroughly cleaned after each trial or session.

Rats were trained to self-administer a 2.5% sucrose solution before and after SNc lesion and electrodes implantation (Only the self-administration after electrode implantation is represented). After 10 to 15 days, stable performances were obtained (less than 20% performance variation over three consecutive sessions) and STN-DBS was turned ON. Pharmacological procedures were applied after a new stabilization period: PPX (Sigma, 0.3 mg.kg⁻¹ in 0.9% NaCl, 1 ml/kg) or vehicle was administered (sub-cutaneous) twice a day, 3h before the beginning of behavioral tests (i.e. injection at 7 am; test at 10 am) for and then at 5 pm, during 20 days. This protocol, known to increase the expression of D₂R and D₃R,⁵⁹ was chosen to explore the chronic effects of PPX.⁶⁰ STN-DBS and PPX treatment were

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1 uninterrupted until rat euthanasia. After several days of sucrose self-administration, rats were
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3 submitted to a two-bottle choice procedure, as well as to a stepping test and
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5 locomotor/ambulatory activity evaluation in an open area⁵⁵ (Figure 1A). At the end of the
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7 experiment, rats were euthanized and brains were processed for histological control of lesion
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9 and implantations.
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17 8 extent of the striatal DA denervation and control of electrode implantation.
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22 10 **Data and statistical analysis**
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24 11 Data are shown as means $\pm$ SEM and were analyzed by one or two-way ANOVAs, repeated
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26 12 or not as specified in Results. Concerning operant sucrose self-administration, the different
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28 13 experimental periods (Pre-STN-DBS, STN-DBS and STN-DBS + PPX) were analyzed
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30 14 independently by distinct repeated measure ANOVAs for figures 2A and 4A. When indicated,
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32 15 post hoc analyses were carried out with the Student Newman-Keuls procedure.
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Results***Histological controls***

Figure 1B provides the different electrode positions in left and right STN for the stimulated animals. Figures 1C and D illustrate two examples of the position of an electrode tip within the STN, stimulated respectively with the lowest (100 μ A) and the highest (225 μ A) intensity used in the study. See also supplemental figure 1 for additional examples of STN stimulated at 100 μ A or 225 μ A, still unaltered after chronic stimulation.

Bilateral lesion of SNc (Figure 1E, percent of TH-IR loss, left SNc: 73 ± 5 ; right SNc: 74 ± 5) was obtained by 6-OHDA injection. The injection produced an important denervation of the dorsal striatum in its lateral portion (Figure 1F, left dorsal striatum: 68 ± 5 ; right dorsal striatum: 74 ± 6), along its rostro-caudal extent as revealed by decreased tyrosine hydroxylase immunoreactivity. As the lesion has been shown to specifically affect SNc, barely impacting VTA (Figure 1G, left VTA: 11 ± 8 ; right VTA: 20 ± 4 ; Two way ANOVA, Structure x Lesion interaction: $F_{1,22} = 7.654$, $p < .0151$), NAc was almost totally preserved from denervation (Figure 1H, left NAc: 21 ± 3 ; right NAc: 24 ± 4 ; Two way ANOVA, Structure x Lesion interaction: $F_{1,22} = 125.758$, $p < .001$).

STN-DBS induces a motivational deficit in normal rats that is reversed by the D_2R/D_3R agonist pramipexole

Before STN-DBS was switched ON, rats were trained for 10 days in the operant task (only the last 3 days of training are represented in figure 2A). Groups were formed to have equivalent performance levels (Figure 2A, Pre STN-DBS period, repeated measure ANOVA, Session x STN-DBS x PPX interaction, $F_{2,122} = 1.334$, $p = .2672$). From day one of stimulation, STN-DBS induced a dramatic decrease of about 40% in instrumental responding for the sucrose solution in both stimulated groups before pharmacological treatment (STN-DBS + Veh and STN-DBS + PPX) as compared with the pre STN-DBS levels (Figure 2A, STN-DBS period, repeated measure ANOVA, STN-DBS effect: $F_{1,54} = 9.615$, $p = .0031$;

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Figure S2A, two way ANOVA, STN-DBS effect: $F_{1,42} = 10.480$, $p = .002$). PPX completely rescued the self-administration performances of stimulated rats from the second day of treatment, without bringing performances superior to baseline or to Control + Veh rat levels. (Figure 2A, STN-DBS + PPX period, repeated measure ANOVA, STN-DBS x PPX interaction: $F_{1,58} = 4.658$, $p = .0351$; Session x PPX interaction: $F_{6,348} = 2.412$, $p = .0269$). Both STN-DBS and PPX effects remained stable until the end of self-administration experimentation (Figure 2B, two ways ANOVA, STN-DBS x PPX interaction: $F_{1,64} = 7.178$, $p = .009$). In order to determine whether the decrease of operant performances induced by STN-DBS was due to impairment in the consummatory or preparatory components of motivated behaviors, we evaluated the sensitivity to the motivational properties of sucrose (consummatory behavior) in a two-bottle choice procedure. The preference for the sucrose solution that was used in the operant self-administration experiment over water was high and not altered by STN-DBS or PPX (Figure 2C, two way ANOVA, STN-DBS x PPX interaction: $F_{1,61} = .966$, $p = .330$). Therefore, the self-administration paradigm and the sucrose preference test indicate that STN-DBS affected the preparatory component of motivated behaviors during the operant task and that PPX specifically corrected this impairment.

In addition, STN-DBS-induced preparatory component deficit and subsequent self-administration deficiency cannot be attributed to motor impairment, because STN-DBS did not induce any significant locomotor change during the first 20 minutes of the open area test, corresponding to the exploratory phase when locomotor activity is high, facilitating detection of motor deficit (Figure 3A, two way ANOVA, 0-20 min: $F_{1,48} = .513$; $p = .477$). Exploration and locomotor activity then progressively decreased to a basal level during the last 2 periods (20 to 60 min). Although it did not reach significance, STN-DBS tended to reduce ambulatory activity during this phase. (Figure 3A, STN-DBS effect, Two way ANOVA, 20-40 min: $F_{1,48} = 3.311$, $p = .075$; 40-60 min: $F_{1,48} = 3.525$, $p = .067$) This effect of STN-DBS is unlikely to reflect a motor deficit but rather a decrease in general behavioral activity, because ambulatory speed during this test phase was not changed by the stimulation (Figure 3B, STN-DBS effect, Two way ANOVA, $F_{1,48} = .196$, $p = .660$). Moreover, fine motor skills of left

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and right limbs assessed using a stepping test were not affected by the stimulation, confirming the absence of any motor deficit induced by chronic and bilateral STN-DBS (Figure 3C). As STN-DBS, PPX had no impact on fine motor skills (Figure 3C, two way ANOVA, STN-DBS x PPX interaction: left to right moves, left limb: $F_{1,55} = .110$, $p = .742$; right limb $F_{1,55} = .000442$, $p = .983$; right to left moves, left limb: $F_{1,55} = .0135$, $p = .908$; right limb: $F_{1,55} = .0557$, $p = .814$), but caused a significant increase in locomotor activity in the open area test (Figure 3A, PPX effect, Two way ANOVA, 20-40 min: $F_{1,48} = 5.686$, $p = .021$; 40-60 min: $F_{1,48} = 5.047$, $p = .030$). Interestingly, the combined effect of the behavioral hypoactivity induced by STN-DBS and hyperactivity due to PPX resulted in normalization of the general activity during the last 2 phases of the open area test (Figure 3A).

Taken together, these results suggest that STN-DBS induced a clear motivational deficit that was alleviated by the D_2R/D_3R agonist, reminiscent of apathy in PD.

STN-DBS exacerbates motivational deficit in a rodent model of PD apathetic symptoms and affective disorders

We sought to confirm whether STN-DBS would also affect motivation in a pathological context. We used a rodent model of PD that we developed⁵⁵ and that exhibits strong motivational deficits, without locomotor alterations.

Before STN-DBS was switched-ON, rats were trained again for 10 days in the operant task (only the last 3 days of training are represented in figure 4A). All groups obtained equivalent performance levels (Figure 4A, 3 last days of Pre STN-DBS period, repeated measure ANOVA, Session x STN-DBS x PPX interaction, $F_{2,32} = 1.088$, $p = .3490$). As previously demonstrated,⁵⁵ 6-OHDA rats showed a marked and significant decrease in self-administration of sucrose as compared to non-lesioned animals (Figure S2A, two way ANOVA, Lesion effect: $F_{1,42} = 26.592$, $p = < .001$; Figure S2B, two way ANOVA, Lesion effect: $F_{1,50} = 26.368$, $p = < .001$) which was not reversed by PPX treatment alone (Figure S2B, two way ANOVA, PPX effect: $F_{1,50} = .150$, $p = .701$). Despite this important instrumental deficit induced by the lesion, STN-DBS was still able to reduce operant behavior by about

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50% from day one of stimulation (Figure 4A, STN-DBS period, repeated measure ANOVA, STN-DBS effect $F_{1,15} = 4.249$, $p = .0571$), as observed in non-lesioned/control stimulated rats (Figure S2A, two way ANOVA, STN-DBS effect: $F_{1,42} = 10.48$, $p = .002$ and no STN-DBS x Lesion interaction: $F_{1,42} = 1.112$, $p = .298$). As for non-lesioned animals, PPX completely alleviated this STN-DBS-induced deficit from the second day of treatment (STN-DBS + PPX period, repeated measure ANOVA, STN-DBS x PPX x Session interaction effect $F_{9,108} = 2.712$, $p = .0069$). Both STN-DBS and PPX effects remained stable until the end of the experiment (Figure 4B, two way ANOVA, STN-DBS x PPX interaction: $F_{1,16} = .826$, $p = .377$). We also assessed the consummatory components of motivated behaviors, with the two-bottle choice procedure and we found that neither STN-DBS nor PPX modified the preference for sucrose (Figure 4C, two way ANOVA, STN-DBS x PPX interaction: $F_{1,20} = .341$, $p = .567$).

PPX or STN-DBS tended to reduce ambulatory activity in the open area test while when they were combined, on average they promoted a high level of activity but with high variability (Figure 5A, two way ANOVA, STN-DBS x PPX interaction: $F_{1,14} = 5.759$, $p = .031$). These effects are likely to reflect changes in behavioral activity rather than alteration of motor skills *per se*, first because neither PPX nor STN-DBS affected the ambulatory speed during the open area test (Figure 5B, Two way ANOVA, STN-DBS x PPX interaction $F_{1,48} = .214$, $p = .650$) and second, adjustments during the stepping test were not impacted by either treatment (Figure 5B, two ways ANOVA, STN-DBS x PPX interaction: left to right moves, left limb: $F_{1,18} = .184$, $p = .673$; right limb: $F_{1,18} = .653$, $p = .983$; right to left moves, left limb: $F_{1,18} = .0017$, $p = .915$; right limb: $F_{1,18} = .764$, $p = .393$).

Taken together, these results suggest that STN-DBS exacerbates the loss of motivation induced by the dopaminergic lesion and reduce behavioral activity, effects that were alleviated by PPX.

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Discussion

Combining a relevant *in vivo* model of neuropsychiatric PD symptoms, chronic bilateral STN-DBS in awake and freely moving animals and a pharmacological approach, we provide strong evidence for a direct deleterious effect of STN-DBS on motivation. STN-DBS induces a significant deficit in motivated behavior, due neither to a reward sensitivity deficit related to a potential anhedonic effect, nor to motor deficits. This behavioral effect was completely reversed by the activation of D₂R/D₃R with PPX, revealing the potential critical role of DA in this STN-DBS motivational effect.

It is essential to better understand the pathophysiology of neuropsychiatric symptoms of PD and how they respond to current treatments such as STN-DBS. Here, we tried to be as close as possible to the clinical situation in PD, especially for the stimulation conditions. While most preclinical studies have been performed with acute STN-DBS that was applied daily only during the tasks and experiments (e.g.,^{41, 49}), the novel stimulation system we used allowed continuous STN-DBS for several days. In addition, we used monopolar stimulation. Indeed, it is the most widely applied in PD patients¹ as well as in studies describing apathy under STN-DBS^{17, 21, 48, 61-64}. Furthermore, a preclinical study in rat has clearly demonstrated that it reduces tissue damage compared to bipolar stimulation.⁶⁵ Moreover, although monopolar stimulation is more likely to affect the surrounding STN fibers than bipolar stimulation, it was applied at intensities below 225 μ A to minimize current spreading as previously demonstrated.⁶⁶ The motivational dimension of apathy especially concerns hum-drum daily tasks that are neither challenging nor particularly effortful.⁴ A sucrose self-administration procedure with a 2.5 % solution, in a fixed ratio 1 schedule, in non-food-deprived rats, is an appropriate way to operationalize a simple effort with a relatively moderate rewarding outcome. This approach has allowed us to demonstrate a clear effect of STN-DBS on motivated behaviors during an operant task. The decrease of baseline ambulatory activity detected during the open area test, unrelated to motor impairment, further suggests that the STN-DBS-induced operant deficit may be considered as a decrease in the maintenance of

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behavioral activity, as observed in apathy.⁹ While we previously provided strong evidence that the dopaminergic denervation can account for the loss of motivation in PD, here we report that STN-DBS by itself could induce or exacerbate **this motivational impairment** via DA-driven mechanisms, independent of the hypodopaminergy induced by DRT reduction. Furthermore, the present study provides a missing link, reconciling apparently contradictory clinical observations on the origin of post-operative apathy in stimulated PD patients.

The myriad of reported neuropsychiatric side effects of STN-DBS in PD patients³ has triggered several animal studies to understand their phenomenology. These studies have demonstrated the possible implication of STN-DBS in PD-related depression^{49, 67} or potent effects on impulsive behaviors,⁶⁸ but few of them tackled the effects on pure motivational processes. As far as we know, only one report mentions data that could be interpreted as a transient reduced motivation under STN-DBS.⁶⁹ However, another study showed no effect of STN-DBS on operant activity in a fixed-ratio schedule of reinforcement and even described an increase in performance in obtaining a sucrose pellet during a progressive ratio schedule.⁴¹ Major differences between this previous study and our protocol are likely to account for these discrepancies. Indeed, Rouaud et al., used acute bipolar stimulation conditions compared to our chronic monopolar STN-DBS; interestingly, psychiatric side effects of STN-DBS strongly depend on electrode polarity. For example, acute depressive states following regular monopolar STN-DBS are greatly reduced by switching to the scarcer bipolar STN-DBS.^{70, 71} Moreover, the design of the operant task was different enough to yield diverging results. In particular, our study avoided food-restriction. Whereas all the studies having inactivated the STN found an increase in motivation for food in restricted animals, one study demonstrated that this effect was completely occluded in rats fed *ad libitum*.³⁷ Finally, while the conditioned place preference revealed an effect of STN-DBS on the rewarding properties of sucrose in this study,⁴¹ we did not find any modification of this parameter during the two bottle choice test.

The STN can be functionally and anatomically subdivided into motor, associative and limbic sub-territories.⁷²⁻⁷⁴ Then it is part of the three respective basal ganglia loops.^{73, 74} In PD

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patients, DBS is tailored to stimulate the motor part of the STN, and so to impact the whole motor circuitry. However, an inaccurate electrode placement within the STN can engage the circuitries involving its associative or limbic part rather than the motor one,⁷⁵ potentially leading to non-motor side effects,^{70, 74} apathy in particular. In line with this assumption, a very recent study succeeded in alleviating post STN-DBS apathy in patients by displacing the electrode from the limbic STN to the motor part,²³ demonstrating that apathy under STN-DBS could rely on a mechanism caused by the stimulation of the limbic part of the STN. Our data suggest that the dopaminergic system might be involved in this mechanism, at least in part.

In patients, apathy occurring after STN-DBS can be treated by dopaminergic agonists, including those targeting the D₂R and D₃R.^{18, 19} This, and the fact that methylphenidate can alleviate fatigue⁷⁶, which is a related and/or confounding symptom of apathy⁷⁷, has prompted the hypothesis that a strong hypodopaminergic state revealed by reduction of DRT, rather than STN-DBS *per se*, may be responsible for the resurgence of apathy.¹³ Using a pharmacological protocol allowing exploration of the chronic effects of PPX and known to increase D₂R and D₃R expression,⁵⁹ we demonstrated that PPX, a D₂R/D₃R agonist, fully rescued the motivational deficit induced by STN-DBS in control and lesioned rats. It should be noted that this pharmacological protocol was not able to reverse the loss of motivation due to the dopaminergic lesion, indicating that even if both the lesion and STN-DBS effects on motivation could be driven by dopaminergic mechanisms, these could be significantly different. This suggests that STN-DBS may impact on behavior via its own effects on DA transmission, which is consistent with previous animal model studies showing that STN-DBS modulates DA system.^{58, 78-82} The three so-called basal ganglia limbic, associative and motor loops including the STN are not completely segregated; the different structures involved are functionally interconnected⁸³ by an ascending striato-midbrain-striatal spiraling circuitry.⁸⁴ Moreover, beyond this complex organization, which has yet to be demonstrated in rats, SNc and VTA are overlapping structures⁸⁵ and the whole striatum is characterized by a dense local microcircuitry^{86, 87} which could also contribute to this interconnection. Thus, STN-DBS may modulate DA transmission within the basal ganglia

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and, through these subcortical interactions, disrupt the complex chain of events that transforms intentions into adapted action, and thereby influence non-motor functions.^{6, 9} Nonetheless, we cannot exclude a potential involvement of the structures surrounding the STN. It is unlikely that the electric field emanating from the electrode is restrained to the STN borders and DBS of some of these structures in the vicinity of the STN, such as the lateral hypothalamus, can also modulate DA transmission⁸⁸. We previously found that short STN-DBS can decrease the level of D₂R and D₃R within the NAc.⁵⁸ Given the critical implication of the D₂R and D₃R in motivational processes,⁸⁹⁻⁹² our data suggest a causal involvement of these receptors in the motivational deficit that we observed. In addition, D₂R and D₃R are expressed in several other non-motor structures impacted by PPX treatment⁹³ and some of them are part of down-stream circuits with metabolic activities known to be affected by STN-DBS.^{22, 94} Thus, beyond the NAc, both STN-DBS and PPX effects could differentially engage some common system responsible for behavior changes highlighted in this study. However, dopaminergic agonists do not always efficiently alleviate apathy under STN-DBS²². Non dopaminergic lesions frequently occur during the course of disease^{95, 96}, and serotonin for example is proposed to participate in PD apathy⁹⁷. In rats, STN-DBS has been shown to decrease serotonin release promoting depressive like behavior.^{49, 98} Thus, we cannot completely exclude the implication of other neurotransmitters in the loss of motivation observed in patients or in this study.

As previously reported,⁹⁹ PPX at 0.3 mg/kg induces hyperlocomotricity in the open area test in control rats. This hyperactivity is unlikely to be responsible for the reversion of the self-administration deficit observed in PPX-treated STN-DBS rats since first, the level of non-stimulated treated rats remains similar to that of control rats, and second, PPX induced hypoactivity in non-stimulated lesioned rats whereas it also reversed the operant deficit induced by STN-DBS in those lesioned rats. This hypoactivity promoted by PPX in lesioned rats has previously been reported during the 120 minutes post injection window in control animals⁹⁹ and could rely on a sedating effect mediated by the presynaptic D₃R¹⁰⁰. We chose to separate the behavioral test from injection by 3h to avoid this effect. Since we previously

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demonstrated that the 6-OHDA lesion modifies D₃R expression within the dorsolateral part of the striatum¹⁰¹, local imbalance between pre and post synaptic D₂R and/or D₃R expression or activity¹⁰² could be responsible for DA transmission blunting, thus promoting this hypoactivity. Very intriguingly, in some rats of both the control and lesioned groups, the combination of STN-DBS and PPX induced a very high- level of activity that could emphasize the importance of individual traits, as demonstrated for the expression or severity of impulse control disorder in PD¹⁰³⁻¹⁰⁵ or compulsive drug taking.¹⁰⁶ Thus, depending on complex interactions with dopaminergic treatments and according to pre-existing individual traits, STN-DBS could also lead to the development of hyperdopaminergic states reminiscent of hypomanic behaviors also observed in PD patients under STN-DBS.^{62, 74, 107, 108}

Altogether, these data bring coherence to clinical observations that seemed contradictory until today: apathy in PD patients, at least its motivational dimension, could be induced by STN-DBS itself and attenuated by activation of D₂R/D₃R, regardless of (or in addition to) DRT reduction and the DA-mediated hypofunction. More detailed molecular analysis or techniques such as optogenetics could enable us to clarify the structures or sub-territories involved in this STN-DBS induced DA-driven loss of motivation. While it is beyond the scope of the present study, it would be also of interest to further investigate the effect of STN-DBS on the emotional and affective component of apathy, as STN has been proposed to be involved in such processes¹⁰⁹.

STN-DBS has been shown to prevent cocaine or heroin re-escalation intake in rats⁴⁰,⁴⁴ and to reduce dopamine dysregulation syndrome or addictive behavior such as pathological gambling.¹¹⁰⁻¹¹⁴ Thus, STN-DBS is currently explored as an effective treatment for addiction.^{45, 115} However, our results suggest that this apparent beneficial effect could be underlain by a general motivational deficit. In rats, inhibiting the STN can abolish affective responses for salient reward¹⁰⁹ and STN-DBS can induce depression-like behaviors.^{49, 67, 116} Furthermore, PD patients for whom addictive behavior was reduced under STN-DBS can also co-express apathy.^{14, 110} These convergent facts are raising the question of the nature of this apparent “anti-addictive” effect of STN-DBS. This neurosurgical treatment could rather

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1 induce a state of negative affect, comparable to a certain extent to the blunted dopaminergic
2 transmission observed during prolonged drug consumption¹¹⁷⁻¹¹⁹ , increasing the risk of
3 addictive behavior resurgence in the same way as drugs of abuse withdrawal syndrome
4 promotes relapse.¹²⁰

5 Thus, this new insight calls for reconsideration of the role of STN-DBS on mood in PD
6 to improve patient care and quality of life, and more broadly, to rethink the use of STN-DBS
7 in psychiatry.

For Peer Review

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Author contributions

YV, SB, SC and MS were responsible for the conception and the design of the study. YV, SB, CC and RM carried out the stereotaxic surgeries and the post-surgery monitoring of the animals. YV, CC and SB performed the neuroanatomical analysis of electrode implantation and lesions. YV and SB carried out the behavioral experiments and analysis. LKLG and PS provided micro-stimulators as well as training and advice for their use. YV and SB wrote the paper with the help of the other authors.

Supplementary information accompanies this paper.

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Figures legends**FIGURE 1:** Experimental design and electrode implantation.**(A)** Time course of the study, groups of animals and histological controls

After learning the sucrose self-administration task, lesion and implantation of electrodes, rats were divided into a stimulated and a non-stimulated group according to their performances, to constitute initially equal performance groups. Then, after 4 days of subthalamic nucleus deep brain stimulation (STN-DBS) with further sucrose self-administration, pramipexole (PPX) or vehicle (Veh) was injected twice a day into half of the stimulated (Non lesioned rats: STN-DBS + PPX, n = 8; STN-DBS + Veh, n = 13; lesioned rats: Lesion + STN-DBS + PPX, n = 5; Lesion + STN-DBS + Veh, n = 5) and non-stimulated rats (Control + PPX, n = 22; Control + Veh, n = 22; Lesioned rats: Lesion + PPX, n = 4; Lesion + Veh, n = 6) for 20 days. During this time, sucrose self-administration was continued for several days and then followed successively by other behavioral tests: the two-bottle choice test, the stepping test and finally the open area test. **(B)** Positions of bilateral DBS electrode tips in left and right STNs of stimulated animals in representative coronal sections (anteroposterior relative to Bregma: -3.60 mm; -3.80 mm; -4.16 mm), reproduced from Paxinos and Watson.¹²¹ Each bar represents the placement of one electrode. **(C)** and **(D)** Example of electrode trace within the left STN stimulated at 100 μ A **(C)** or 225 μ A **(D)**, after Cresyl violet staining. Scale bar: 1 mm. IC, Internal Capsule; LH, Lateral Hypothalamus; ZI, Zona Incerta.

(E) and **(F)** Representative photomicrographs of coronal sections stained for tyrosine hydroxylase (TH) in striatal (bottom, 1.6 mm to bregma) and mesencephalic (top, -5.6 mm to bregma) regions from naïve (top) and lesioned (bottom) rats.¹²¹ Scale bar = 1 mm. **(G, H)** Quantification of TH ImmunoReactivity (IR) loss in the midbrain **(G)** and the striatum **(H)**, expressed as the percentage difference compared to the mean value obtained for sham operated animals. The SNc bilateral lesion produced an important but partial denervation of

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the dorsal striatum. The ventral tegmental area and the nucleus accumbens were preserved from the lesion. Control + Veh: $n = 22$; Lesion: $n = 20$. Control + Veh versus Lesion: $*p < .05$; $***p < .001$. DS: dorsal striatum; NAc: nucleus accumbens; SNc: substantia nigra compacta, VTA: ventral tegmental area.

FIGURE 2: Subthalamic nucleus deep brain stimulation (STN-DBS) induces a deficit of preparatory behaviors in 2.5% sucrose self-administration that is rescued by pramipexole (PPX). **(A)** Time course of the sucrose self-administration experiment. STN-DBS induced a significant decrease of the number of sucrose deliveries. PPX induced a total reversion of this deficit. **(B)** Mean sucrose deliveries over the last 3 days of experiment. **(C)** STN-DBS and PPX did not alter the preference for sucrose. Control + Veh: $n = 22$; Control + PPX: $n = 22$; STN-DBS + Veh: $n = 13$; STN-DBS + PPX: $n = 8$. Data shown as means $\pm$ SEM. Control + Veh versus STN-DBS + Veh: $*p < .05$; $**p < .01$; STN-DBS + Veh versus STN-DBS + PPX: $\#p < .05$; $##p < .01$.

FIGURE 3: Subthalamic nucleus deep brain stimulation (STN-DBS) and pramipexole (PPX) promote hypo and hyper locomotor activity respectively but do not impair motor abilities. **(A)** Total distance travelled during a 1h open area test. STN-DBS induced a non-significant tendency towards decreased basal locomotor activity that was counteracted by treatment with PPX. In control rats, PPX induced a dramatic increase in the distance traveled. **(B)** STN-DBS and PPX did not change the mean ambulatory speed during the last 2 periods of the open area test. **(C)** STN-DBS and/or PPX did not alter the fine motor skills of front limbs as demonstrated by adjusting steps in the course of the stepping test. Control + Veh: $n = 22$; Control + PPX: $n = 22$; STN-DBS + Veh: $n = 6$; STN-DBS + PPX: $n = 8$. Data shown as means $\pm$ SEM. Control + PPX versus Control + Veh: $*p < .05$.

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FIGURE 4: STN-DBS exacerbates the deficit of preparatory behaviors of the existing motivational deficit in a rodent model of the neuropsychiatric symptoms of PD. **(A)** Time course of the sucrose self-administration experiment. STN-DBS decreased the number of sucrose deliveries. PPX induced a complete reversion of this deficit. **(B)** Mean sucrose deliveries over the last 5 days of experiment. **(C)** STN-DBS and PPX did not alter the preference for sucrose in 6-OHDA rats. Lesion + Veh: $n = 6$; Lesion + PPX: $n = 4$; Lesion + STN-DBS + Veh: $n = 5$; Lesion + STN-DBS + PPX: $n = 5$. Data shown as means $\pm$ SEM. Lesion + Veh versus Lesion + STN-DBS + Veh: $*p < .05$; Lesion + STN-DBS + Veh versus Lesion + STN-DBS + PPX: $\#p < .05$.

FIGURE 5: Subthalamic nucleus deep brain stimulation (STN-DBS) or pramipexole (PPX) individually promote hypoactivity but do not impair motor abilities. **(A)** Total distance traveled during a 1h open area test. STN-DBS induced a non-significant tendency towards decreased basal locomotor activity. In non-stimulated rats, PPX induced a dramatic decrease in the distance traveled. The combination of both treatments increased activity. **(B)** STN-DBS and PPX did not change the mean ambulatory speed during the open area test. **(C)** STN-DBS and/or PPX did not alter the fine motor skills of front limbs as demonstrated by adjusting steps in the course of the stepping test. Lesion + Veh: $n = 6$; Lesion + PPX: $n = 4$; Lesion + STN-DBS + Veh: $n = 5$; Lesion + STN-DBS + PPX: $n = 5$. Data shown as means $\pm$ SEM. Lesion + PPX versus Lesion + STN-DBS + PPX: $*p < .05$.

Figure 1

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After learning the sucrose self-administration task, lesion and implantation of electrodes, rats were divided into a stimulated and a non-stimulated group according to their performances, to constitute initially equal performance groups. Then, after 4 days of subthalamic nucleus deep brain stimulation (STN-DBS) with further sucrose self-administration, pramipexole (PPX) or vehicle (Veh) was injected twice a day into half of the stimulated (Non lesioned rats: STN-DBS + PPX, $n = 8$; STN-DBS + Veh, $n = 13$; lesioned rats: Lesion + STN-DBS + PPX, $n = 5$; Lesion + STN-DBS + Veh, $n = 5$) and non-stimulated rats (Control + PPX, $n = 22$; Control + Veh, $n = 22$; Lesioned rats: Lesion + PPX, $n = 4$; Lesion + Veh, $n = 6$) for 20 days. During this time, sucrose self-administration was continued for several days and then followed successively by other behavioral tests: the two-bottle choice test, the stepping test and finally the open area test. (B) Positions of bilateral DBS electrode tips in left and right STNs of stimulated animals in representative coronal sections (anteroposterior relative to Bregma: -3.60 mm; -3.80 mm; -4.16 mm), reproduced from Paxinos and Watson.¹¹⁹ Each bar represents the placement of one electrode. (C) and (D) Example of electrode trace

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5 (E) and (F) Representative photomicrographs of coronal sections stained for tyrosine hydroxylase (TH) in
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Figure 2

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Subthalamic nucleus stimulation impairs motivation: implication for apathy in Parkinson’s disease

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Supplemental Material and Methods

Bilateral 6-OHDA lesions

As previously described,¹⁻⁴ rats were first treated with desipramine hydrochloride (25 mg.kg⁻¹ in 0.9% NaCl, subcutaneously; Sigma; St Quentin-Fallavier, France) to protect noradrenergic neurons 30 min before 6-OHDA injection.⁵ They were then anesthetized with a mixture of xylazine (15 mg.kg⁻¹, i.p) and ketamine (100 mg.kg⁻¹, i.p) and secured in a Kopf stereotaxic apparatus (Phymep, Paris, France). As previously described², 6 µg of 6-OHDA dissolved in 2.3 µl sterile 0.9% NaCl with 0.2% ascorbic acid (Sigma), or 2.3 µl of vehicle (0.9% NaCl, 0.02% ascorbic acid) were injected bilaterally, at a flow rate of 0.5 µl min⁻¹. The stereotaxic coordinates of the injection site relative to bregma according to the stereotaxic atlas of Paxinos and Watson⁶ were as follows: anteroposterior (AP), -5.4 mm; mediolateral (L), ±1.8 mm, and dorsoventral (DV), -8.1 mm; with the incisor bar at +3.2 mm below the interaural plane. The cannulae were left in position for 5 min after each injection to allow absorption of the solution without spreading. After recovery from anesthesia, the animals were returned to the facility for 3 weeks, to allow the 6-OHDA lesion to develop and stabilize.

Bilateral implantation of electrodes in the subthalamic nucleus

Rats were bilaterally implanted with monopolar electrodes consisting of platinum-iridium wire insulated with Teflon with a 400 μm exposed end (wire diameter, 110 μm insulated, 76 μm bare, PT-IR Teflon, Phymep, Paris, France). Stereotaxic coordinates (relative to bregma, according to the stereotaxic atlas of Paxinos and Watson⁶) were: AP, -3.8 mm; L, ± 2.4 mm, and DV, -7.8 mm; with the incisor bar at +3.2 mm below the interaural plane. The exposed end of the electrode, located in the STN, corresponded to the negative stimulation pole. A screw (Phymep, Paris, France, 0-80x1/16) fixed on the skull was used as the positive pole. Electrodes were soldered to corresponding contacts of the microstimulator support (ISENUSTIMV7, ISEN, Toulon, France) which was permanently fixed to the rat skull with dental cement (Superbond, Phymep, Paris, France). After recovery from anesthesia, animals were returned to the facility for 3 days, to allow recovery before the beginning of the behavioral experiments.

Subthalamic nucleus deep brain stimulation

Chronic long-lasting bilateral STN-DBS was performed using an electrical portable microstimulator system already validated in freely moving rats.⁷ This system has the advantages of leaving the animals free to move during behavioral tasks, of being removable and of allowing rapid and easy activation (ON/OFF), modulation of DBS parameters or battery change without strain of rats or anesthesia. Monopolar rather than bipolar electrodes were utilized because the former is the most widely applied in PD patients⁸ as well as in studies describing apathy under STN-DBS.⁹⁻¹⁵ Furthermore, a preclinical study in rat has clearly demonstrated that it reduces tissue damage compared to bipolar stimulation.¹⁶ The interface between electrodes and the microstimulator is a support with the top side designed as a platform to receive a microstimulator's plug in. The microstimulator is made up with classical structures allowing to regulate the frequency and the duty cycle. The power supply of the microstimulator consists of two 3 V flat lithium watch batteries (CR1220) connected in series.

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2
3 1 The frequency and pulse width used, 130 Hz and 60 μ s respectively, were similar to those
4
5 2 applied in humans. For each animal, the intensity was gradually increased until dyskinetic
6
7 3 movement of the contralateral forelimb appeared as previously described¹⁷ and then
8
9 4 adjusted just below this pro-dyskinetic threshold. This value was conserved throughout the
10
11 5 study. The stimulation intensity was 183 +/- 13 μ A on average and ranged between 100 and
12
13
14 6 225 μ A.
15

16 7
17
18 8 ***Behavioral procedures***
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20 9 Rats were not food or water deprived during the experimental procedures.
21

22 10 ***Sucrose self-administration***
23

24 11 Rats were trained to work for 2.5% sucrose reward, chosen for its relatively moderate
25
26 12 rewarding outcome, in a self-administration task in operant chambers (Med Associates, St
27
28 13 Albans, VT, USA) under a fixed ratio 1 reinforcement schedule. Rats were given the choice
29
30 14 between two levers: an active and reinforced one, delivering 0.2 ml sucrose solution in a
31
32 15 receptacle when pressed, and an inactive, non-reinforced lever, producing nothing¹⁻⁴.
33
34
35 16

36
37 17 ***Two bottle choice***
38

39 18 In their home cage, rats were given continuous access to two graduated 250 ml plastic
40
41 19 bottles (Techniplast, Lyon, France), for 3 days. One bottle contained tap water, whereas the
42
43 20 other contained 2.5% sucrose (Sigma) in tap water. Rats and bottles were weighed daily,
44
45 21 with the position of the bottles (left or right) alternated to control for side preference. The first
46
47 22 day was for acclimatation. The volumes of sucrose solution and water consumed on the
48
49 23 second and third days were averaged to determine preference for sucrose over water
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51 24 (sucrose intake/total intake, expressed as a percentage).
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1 *Stepping test*

2 Animals were moved sideways along a smooth-surfaced table over 90 cm and the number of
3 forelimb adjusting steps measured. The test was carried out three times for each paw.

5 *Open area*

6 Rats were placed in a dimly lit white Perspex (Castorama, Saint Martin d'Hères, France)
7 open arena (50 x 25 x 40cm) and horizontal distances traveled were recorded with a video-
8 tracking system to assess locomotor and basal activity (Viewpoint S.A., Champagne au Mont
9 d'Or, France), over a 1h period.

11 *Histological analysis*

12 Briefly, rats were sacrificed under chloral hydrate anesthesia at the end of the behavioral
13 experiments, intracardially perfused with NaCl (0.9%) and their brains frozen in cooled
14 isopentane (-40°C) and stored at -30°C. Serial coronal sections (14 µm-thick) of striatum,
15 mesencephalon and subthalamic nucleus were cut with a cryostat (Microm HM 500, Microm,
16 Francheville, France), collected on slides and stored at -30°C.

18 *Immunohistochemistry:*

19 Immunohistochemical analysis was performed as previously described.^{2, 17} 14 µm-thick
20 coronal sections from the striatum and the mesencephalon were incubated with an anti-TH
21 antibody, and then with a biotinylated goat anti-mouse IgG antibody. Immunoreactivity was
22 visualized with avidin-peroxidase conjugate.

24 *Quantification of the extent of the striatal DA denervation*

25 As described previously,² TH immunoreactivity (TH-IR) was quantified with the ICS
26 FrameWork computerized image analysis system (TRIBVN, 2.9.2 version, Châtillon, France)
27 coupled to a light microscope (Nikon, Eclipse 80i) and a Pike F-421C camera (ALLIED Vision
28 Technologies, Stadtroda, Germany) for digitalization of the DS and the NAc (+ 0.7 to 2.2 mm

1 anterior to bregma), and of the SNc and the ventral tegmental area (VTA), (-5.6 mm to -4.8
2 mm). For all measurements, masks from these different striatal and mesencephalic sub-
3 regions were drawn with the computer analysis system to ensure that appropriate
4 comparisons were made between homologous anatomical regions. For each striatal sub-
5 region, optical densities (OD) were measured and averaged. The OD value obtained for an
6 unlabeled area (the corpus callosum) was used as the background and was subtracted from
7 each of the OD values measured. OD were expressed as percentages relative to the mean
8 optical density values obtained for the homologous regions of the sham-operated animals.

9
10 *Histological control of electrodes implantation*

11 Sections through the subthalamic nucleus were stained with Cresyl violet and analyzed
12 under a light microscope (Nikon, Eclipse 80i, TRIBVN, Châtillon, France) coupled to the ICS
13 FrameWork computerized image analysis system (TRIBVN, 2.9.2 version, Châtillon, France)
14 in order to check the positions of electrodes. Animals with incorrect electrode locations were
15 excluded from the study.

16
17 **Supplemental Figure and Figure Legend:**

18 **FIGURE S1:** Example of electrode trace and tissue state in animals stimulated at 100 μ A **(A)**
19 or 225 μ A **(B)**, after Cresyl violet staining. Scale bar: 1 mm.

20
21 **FIGURE S2:** Comparison of the effects of STN-DBS **(A)** or PPX treatment **(B)** in control and
22 lesioned animals on the mean sucrose deliveries over the last 3 days of sucrose self-
23 administration experiment. Data shown as means $\pm$ SEM. **(A)** Control Sham: n = 22; Control
24 STN-DBS: n = 13; Lesion Sham n = 6; Lesion STN-DBS: n = 5. Control Sham versus Control
25 STN-DBS: *** $p < .001$; Control Sham versus Lesion sham: ### $p < .001$; Control STN-DBS
26 versus Lesion STN-DBS: ## $p < .01$. **(B)** Control Veh: n = 22; Control PPX: n = 22; Lesion

1 Veh: n = 6; Lesion PPX: n = 5. Control Veh versus Lesion Veh: $###p < .001$; Control PPX
2 versus Lesion PPX: $##p < .01$.

For Peer Review

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Supplemental figure 1

FIGURE S1: Example of electrode trace and tissue state in animals stimulated at 100 μ A (A) or 225 μ A (B), after Cresyl violet staining. Scale bar: 1 mm.

190x275mm (150 x 150 DPI)

Supplemental figure 2

FIGURE S2: Comparison of the effects of STN-DBS (A) or PPX treatment (B) in control and lesioned animals on the mean sucrose deliveries over the last 3 days of sucrose self-administration experiment. Data shown as means $\pm$ SEM. (A) Control Sham: $n = 22$; Control STN-DBS: $n = 13$; Lesion Sham $n = 6$; Lesion STN-DBS: $n = 5$. Control Sham versus Control STN-DBS: $***p < .001$; Control Sham versus Lesion sham: $###p < .001$; Control STN-DBS versus Lesion STN-DBS: $##p < .01$. (B) Control Veh: $n = 22$; Control PPX: $n = 22$; Lesion Veh: $n = 6$; Lesion PPX: $n = 5$. Control Veh versus Lesion Veh: $###p < .001$; Control PPX versus Lesion PPX: $##p < .01$.

190x275mm (150 x 150 DPI)