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**Subthalamic nucleus stimulation impairs motivation:  
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3 **Subthalamic nucleus stimulation impairs motivation: implication for apathy in**  
4  
5 **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.

## STN-DBS and Apathy in Parkinson's Disease

## 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).<sup>1</sup> 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 influence these symptoms, for better or for worse.<sup>2, 3</sup> 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,<sup>4-6</sup> is the most frequently observed non-motor  
9 complication of PD and deeply contributes to worsen the patient's quality of life<sup>2, 5, 7-12</sup>.  
10 Importantly, apathy has been reported to occur, or be exacerbated, in some patients under  
11 STN-DBS, as blunted affects<sup>8-10, 13-16</sup>. 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.<sup>17</sup> 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 (D<sub>2</sub>R and D<sub>3</sub>R)<sup>18, 19</sup> and 2) functional imaging studies  
18 in PD patients<sup>9, 17</sup> and some preclinical data indicating that at least some forms of apathy are  
19 related to the degenerative process and DA loss.<sup>20</sup>

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<sup>15, 21, 22</sup> or with incorrect location of  
23 electrodes in the associative or limbic part of the STN.<sup>23</sup> Thus, apathy in patients under STN-  
24 DBS was also proposed to be a major side-effect of STN-DBS itself.<sup>15, 21-23</sup> There is now an  
25 abundance of experimental and clinical studies demonstrating that 1) the STN is involved in  
26 reward and motivational processes,<sup>24-31</sup> 2) manipulating the STN can modify motivational  
27 behaviors<sup>32-37</sup> and 3) STN-DBS can alleviate dopamine dysregulation syndrome in some PD

## STN-DBS and Apathy in Parkinson's Disease

1 patients<sup>14, 38, 39</sup> and be a conceivable approach to treat addictive disorders<sup>40-45</sup>. Yet, a  
2 possible direct impact of STN-DBS on motivation in PD is not unanimously supported.

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

14 In the present study, we explored a potential effect of bilateral STN-DBS on  
15 motivation, by using a wireless micro-stimulation system enabling chronic continuous  
16 stimulation in rats during several weeks<sup>54</sup>. We first investigated the consequences of bilateral  
17 chronic STN-DBS in naïve rats and then in a preclinical model of neuropsychiatric symptoms  
18 related to PD that we have developed, using bilateral but partial denervation of the dorsal  
19 striatum (DS) by 6-hydroxydopamine (6-OHDA) lesion of SNc.<sup>20, 55</sup> Because D<sub>2</sub>R and D<sub>3</sub>R  
20 agonists, such as pramipexole (PPX), can alleviate pre and post STN-DBS apathy in PD  
21 patients<sup>18, 19, 56</sup> as well as in preclinical models<sup>20, 57</sup> and because we reported that STN-DBS  
22 reduces the level of D<sub>2</sub>R and D<sub>3</sub>R in the nucleus accumbens (NAc) of rats,<sup>58</sup> our working  
23 hypothesis was that post-STN-DBS apathy may be due to an alteration of DA transmission  
24 induced by STN-DBS itself. Thus, we also investigated the effect of STN-DBS with or without  
25 chronic treatment with PPX.

## 1 **Materials and Methods**

### 2 **Animals**

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

### 10 ***Bilateral 6-OHDA lesions, bilateral implantation of electrodes and deep brain 11 stimulation of subthalamic nucleus***

12 See supplemental informations

### 14 **Experimental design**

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

19 Rats were trained to self-administer a 2.5% sucrose solution before and after SNc lesion and  
20 electrodes implantation (Only the self-administration after electrode implantation is  
21 represented). After 10 to 15 days, stable performances were obtained (less than 20%  
22 performance variation over three consecutive sessions) and STN-DBS was turned ON.  
23 Pharmacological procedures were applied after a new stabilization period: PPX (Sigma, 0.3  
24 mg.kg<sup>-1</sup> in 0.9% NaCl, 1 ml/kg) or vehicle was administered (sub-cutaneous) twice a day, 3h  
25 before the beginning of behavioral tests (i.e. injection at 7 am; test at 10 am) for and then at  
26 5 pm, during 20 days. This protocol, known to increase the expression of D<sub>2</sub>R and D<sub>3</sub>R,<sup>59</sup>  
27 was chosen to explore the chronic effects of PPX.<sup>60</sup> STN-DBS and PPX treatment were

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1  
2  
3 1 uninterrupted until rat euthanasia. After several days of sucrose self-administration, rats were  
4  
5 2 submitted to a two-bottle choice procedure, as well as to a stepping test and  
6  
7 3 locomotor/ambulatory activity evaluation in an open area<sup>55</sup> (Figure 1A). At the end of the  
8  
9 4 experiment, rats were euthanized and brains were processed for histological control of lesion  
10  
11 5 and implantations.  
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15  
16 7 See supplemental data for full description of behavioral procedures, quantification of the  
17  
18 8 extent of the striatal DA denervation and control of electrode implantation.  
19  
20 9

**Data and statistical analysis**

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22 10  
23  
24 11 Data are shown as means  $\pm$  SEM and were analyzed by one or two-way ANOVAs, repeated  
25  
26 12 or not as specified in Results. Concerning operant sucrose self-administration, the different  
27  
28 13 experimental periods (Pre-STN-DBS, STN-DBS and STN-DBS + PPX) were analyzed  
29  
30 14 independently by distinct repeated measure ANOVAs for figures 2A and 4A. When indicated,  
31  
32 15 post hoc analyses were carried out with the Student Newman-Keuls procedure.  
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## STN-DBS and Apathy in Parkinson's Disease

**1 Results****2 *Histological controls***

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

8 Bilateral lesion of SNc (Figure 1E, percent of TH-IR loss, left SNc:  $73 \pm 5$ ; right SNc:  
9  $74 \pm 5$ ) was obtained by 6-OHDA injection. The injection produced an important denervation  
10 of the dorsal striatum in its lateral portion (Figure 1F, left dorsal striatum:  $68 \pm 5$ ; right dorsal  
11 striatum:  $74 \pm 6$ ), along its rostro-caudal extent as revealed by decreased tyrosine  
12 hydroxylase immunoreactivity. As the lesion has been shown to specifically affect SNc,  
13 barely impacting VTA (Figure 1G, left VTA:  $11 \pm 8$ ; right VTA:  $20 \pm 4$ ; Two way ANOVA,  
14 Structure x Lesion interaction:  $F_{1,22} = 7.654$ ,  $p < .0151$ ), NAc was almost totally preserved  
15 from denervation (Figure 1H, left NAc:  $21 \pm 3$ ; right NAc:  $24 \pm 4$ ; Two way ANOVA, Structure  
16 x Lesion interaction:  $F_{1,22} = 125.758$ ,  $p < .001$ ).

**18 *STN-DBS induces a motivational deficit in normal rats that is reversed by the D<sub>2</sub>R/D<sub>3</sub>R***  
**19 *agonist pramipexole***

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

## STN-DBS and Apathy in Parkinson's Disease

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2  
3 1 Figure S2A, two way ANOVA, STN-DBS effect:  $F_{1,42} = 10.480$ ,  $p = .002$ ). PPX completely  
4  
5 2 rescued the self-administration performances of stimulated rats from the second day of  
6  
7 3 treatment, without bringing performances superior to baseline or to Control + Veh rat levels.  
8  
9 4 (Figure 2A, STN-DBS + PPX period, repeated measure ANOVA, STN-DBS x PPX  
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11 5 interaction:  $F_{1,58} = 4.658$ ,  $p = .0351$ ; Session x PPX interaction:  $F_{6,348} = 2.412$ ,  $p = .0269$ ).  
12  
13 6 Both STN-DBS and PPX effects remained stable until the end of self-administration  
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15 7 experimentation (Figure 2B, two ways ANOVA, STN-DBS x PPX interaction:  $F_{1,64} = 7.178$ ,  $p$   
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17 8 = .009). In order to determine whether the decrease of operant performances induced by  
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19 9 STN-DBS was due to impairment in the consummatory or preparatory components of  
20  
21 10 motivated behaviors, we evaluated the sensitivity to the motivational properties of sucrose  
22  
23 11 (consummatory behavior) in a two-bottle choice procedure. The preference for the sucrose  
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25 12 solution that was used in the operant self-administration experiment over water was high and  
26  
27 13 not altered by STN-DBS or PPX (Figure 2C, two way ANOVA, STN-DBS x PPX interaction:  
28  
29 14  $F_{1,61} = .966$ ,  $p = .330$ ). Therefore, the self-administration paradigm and the sucrose  
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31 15 preference test indicate that STN-DBS affected the preparatory component of motivated  
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33 16 behaviors during the operant task and that PPX specifically corrected this impairment.

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36 17 In addition, STN-DBS-induced preparatory component deficit and subsequent self-  
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38 18 administration deficiency cannot be attributed to motor impairment, because STN-DBS did  
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40 19 not induce any significant locomotor change during the first 20 minutes of the open area test,  
41  
42 20 corresponding to the exploratory phase when locomotor activity is high, facilitating detection  
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44 21 of motor deficit (Figure 3A, two way ANOVA, 0-20 min:  $F_{1,48} = .513$ ;  $p = .477$ ). Exploration  
45  
46 22 and locomotor activity then progressively decreased to a basal level during the last 2 periods  
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48 23 (20 to 60 min). Although it did not reach significance, STN-DBS tended to reduce ambulatory  
49  
50 24 activity during this phase. (Figure 3A, STN-DBS effect, Two way ANOVA, 20-40 min:  $F_{1,48} =$   
51  
52 25  $3.311$ ,  $p = .075$ ; 40-60 min:  $F_{1,48} = 3.525$ ,  $p = .067$ ) This effect of STN-DBS is unlikely to  
53  
54 26 reflect a motor deficit but rather a decrease in general behavioral activity, because  
55  
56 27 ambulatory speed during this test phase was not changed by the stimulation (Figure 3B,  
57  
58 28 STN-DBS effect, Two way ANOVA,  $F_{1,48} = .196$ ,  $p = .660$ ). Moreover, fine motor skills of left

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

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

13  
14 ***STN-DBS exacerbates motivational deficit in a rodent model of PD apathetic***  
15 ***symptoms and affective disorders***

16 We sought to confirm whether STN-DBS would also affect motivation in a  
17 pathological context. We used a rodent model of PD that we developed<sup>55</sup> and that exhibits  
18 strong motivational deficits, without locomotor alterations.

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

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2  
3 1 50% from day one of stimulation (Figure 4A, STN-DBS period, repeated measure ANOVA,  
4  
5 2 STN-DBS effect  $F_{1,15} = 4.249$ ,  $p = .0571$ ), as observed in non-lesioned/control stimulated rats  
6  
7 3 (Figure S2A, two way ANOVA, STN-DBS effect:  $F_{1,42} = 10.48$ ,  $p = .002$  and no STN-DBS x  
8  
9 4 Lesion interaction:  $F_{1,42} = 1,112$ ,  $p = .298$ ). As for non-lesioned animals, PPX completely  
10  
11 5 alleviated this STN-DBS-induced deficit from the second day of treatment (STN-DBS + PPX  
12  
13 6 period, repeated measure ANOVA, STN-DBS x PPX x Session interaction effect  $F_{9,108} =$   
14  
15 7  $2.712$ ,  $p = .0069$ ). Both STN-DBS and PPX effects remained stable until the end of the  
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17 8 experiment (Figure 4B, two way ANOVA, STN-DBS x PPX interaction:  $F_{1,16} = .826$ ,  $p = .377$ ).  
18  
19 9 We also assessed the consummatory components of motivated behaviors, with the two-  
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21 10 bottle choice procedure and we found that neither STN-DBS nor PPX modified the  
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23 11 preference for sucrose (Figure 4C, two way ANOVA, STN-DBS x PPX interaction:  $F_{1,20} =$   
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25 12  $.341$ ,  $p = .567$ ).

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28 13 PPX or STN-DBS tended to reduce ambulatory activity in the open area test while  
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30 14 when they were combined, on average they promoted a high level of activity but with high  
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32 15 variability (Figure 5A, two way ANOVA, STN-DBS x PPX interaction:  $F_{1,14} = 5.759$ ,  $p = .031$ ).  
33  
34 16 These effects are likely to reflect changes in behavioral activity rather than alteration of  
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36 17 motor skills *per se*, first because neither PPX nor STN-DBS affected the ambulatory speed  
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38 18 during the open area test (Figure 5B, Two way ANOVA, STN-DBS x PPX interaction  $F_{1,48} =$   
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40 19  $.214$ ,  $p = .650$ ) and second, adjustments during the stepping test were not impacted by either  
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42 20 treatment (Figure 5B, two ways ANOVA, STN-DBS x PPX interaction: left to right moves, left  
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44 21 limb:  $F_{1,18} = .184$ ,  $p = .673$ ; right limb:  $F_{1,18} = .653$ ,  $p = .983$ ; right to left moves, left limb:  $F_{1,18}$   
45  
46 22  $= .0017$ ,  $p = .915$ ; right limb:  $F_{1,18} = .764$ ,  $p = .393$ ).

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48  
49 23 Taken together, these results suggest that STN-DBS exacerbates the loss of  
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51 24 motivation induced by the dopaminergic lesion and reduce behavioral activity, effects that  
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53 25 were alleviated by PPX.  
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## STN-DBS and Apathy in Parkinson's Disease

**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 D<sub>2</sub>R/D<sub>3</sub>R 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.,<sup>41, 49</sup>), 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 patients<sup>1</sup> as well as in studies describing apathy under STN-DBS<sup>17, 21, 48, 61-64</sup>. Furthermore, a preclinical study in rat has clearly demonstrated that it reduces tissue damage compared to bipolar stimulation.<sup>65</sup> Moreover, although monopolar stimulation is more likely to affect the surrounding STN fibers than bipolar stimulation, it was applied at intensities below 225  $\mu$ A to minimize current spreading as previously demonstrated.<sup>66</sup> The motivational dimension of apathy especially concerns hum-drum daily tasks that are neither challenging nor particularly effortful.<sup>4</sup> 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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1 behavioral activity, as observed in apathy.<sup>9</sup> While we previously provided strong evidence  
2 that the dopaminergic denervation can account for the loss of motivation in PD, here we  
3 report that STN-DBS by itself could induce or exacerbate this motivational impairment via  
4 DA-driven mechanisms, independent of the hypodopaminergy induced by DRT reduction.  
5 Furthermore, the present study provides a missing link, reconciling apparently contradictory  
6 clinical observations on the origin of post-operative apathy in stimulated PD patients.

7         The myriad of reported neuropsychiatric side effects of STN-DBS in PD patients<sup>3</sup> has  
8 triggered several animal studies to understand their phenomenology. These studies have  
9 demonstrated the possible implication of STN-DBS in PD-related depression<sup>49, 67</sup> or potent  
10 effects on impulsive behaviors,<sup>68</sup> but few of them tackled the effects on pure motivational  
11 processes. As far as we know, only one report mentions data that could be interpreted as a  
12 transient reduced motivation under STN-DBS.<sup>69</sup> However, another study showed no effect of  
13 STN-DBS on operant activity in a fixed-ratio schedule of reinforcement and even described  
14 an increase in performance in obtaining a sucrose pellet during a progressive ratio  
15 schedule.<sup>41</sup> Major differences between this previous study and our protocol are likely to  
16 account for these discrepancies. Indeed, Rouaud et al., used acute bipolar stimulation  
17 conditions compared to our chronic monopolar STN-DBS; interestingly, psychiatric side  
18 effects of STN-DBS strongly depend on electrode polarity. For example, acute depressive  
19 states following regular monopolar STN-DBS are greatly reduced by switching to the scarcer  
20 bipolar STN-DBS.<sup>70, 71</sup> Moreover, the design of the operant task was different enough to yield  
21 diverging results. In particular, our study avoided food-restriction. Whereas all the studies  
22 having inactivated the STN found an increase in motivation for food in restricted animals, one  
23 study demonstrated that this effect was completely occluded in rats fed *ad libitum*.<sup>37</sup> Finally,  
24 while the conditioned place preference revealed an effect of STN-DBS on the rewarding  
25 properties of sucrose in this study,<sup>41</sup> we did not find any modification of this parameter during  
26 the two bottle choice test.

27         The STN can be functionally and anatomically subdivided into motor, associative and  
28 limbic sub-territories.<sup>72-74</sup> Then it is part of the three respective basal ganglia loops.<sup>73, 74</sup> In PD



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

9 In patients, apathy occurring after STN-DBS can be treated by dopaminergic  
10 agonists, including those targeting the D<sub>2</sub>R and D<sub>3</sub>R.<sup>18, 19</sup> This, and the fact that  
11 methylphenidate can alleviate fatigue<sup>76</sup>, which is a related and/or confounding symptom of  
12 apathy<sup>77</sup>, has prompted the hypothesis that a strong hypodopaminergic state revealed by  
13 reduction of DRT, rather than STN-DBS *per se*, may be responsible for the resurgence of  
14 apathy.<sup>13</sup> Using a pharmacological protocol allowing exploration of the chronic effects of PPX  
15 and known to increase D<sub>2</sub>R and D<sub>3</sub>R expression,<sup>59</sup> we demonstrated that PPX, a D<sub>2</sub>R/D<sub>3</sub>R  
16 agonist, fully rescued the motivational deficit induced by STN-DBS in control and lesioned  
17 rats. It should be noted that this pharmacological protocol was not able to reverse the loss of  
18 motivation due to the dopaminergic lesion, indicating that even if both the lesion and STN-  
19 DBS effects on motivation could be driven by dopaminergic mechanisms, these could be  
20 significantly different. This suggests that STN-DBS may impact on behavior via its own  
21 effects on DA transmission, which is consistent with previous animal model studies showing  
22 that STN-DBS modulates DA system.<sup>58, 78-82</sup> The three so-called basal ganglia limbic,  
23 associative and motor loops including the STN are not completely segregated; the different  
24 structures involved are functionally interconnected<sup>83</sup> by an ascending striato-midbrain-striatal  
25 spiraling circuitry.<sup>84</sup> Moreover, beyond this complex organization, which has yet to be  
26 demonstrated in rats, SNc and VTA are overlapping structures<sup>85</sup> and the whole striatum is  
27 characterized by a dense local microcircuitry<sup>86, 87</sup> which could also contribute to this  
28 interconnection. Thus, STN-DBS may modulate DA transmission within the basal ganglia

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1 and, through these subcortical interactions, disrupt the complex chain of events that  
2 transforms intentions into adapted action, and thereby influence non-motor functions.<sup>6, 9</sup>  
3 Nonetheless, we cannot exclude a potential involvement of the structures surrounding the  
4 STN . It is unlikely that the electric field emanating from the electrode is restrained to the  
5 STN borders and DBS of some of these structures in the vicinity of the STN, such as the  
6 lateral hypothalamus, can also modulate DA transmission<sup>88</sup>. We previously found that short  
7 STN-DBS can decrease the level of D<sub>2</sub>R and D<sub>3</sub>R within the NAc.<sup>58</sup> Given the critical  
8 implication of the D<sub>2</sub>R and D<sub>3</sub>R in motivational processes,<sup>89-92</sup> our data suggest a causal  
9 involvement of these receptors in the motivational deficit that we observed. In addition, D<sub>2</sub>R  
10 and D<sub>3</sub>R are expressed in several other non-motor structures impacted by PPX treatment<sup>93</sup>  
11 and some of them are part of down-stream circuits with metabolic activities known to be  
12 affected by STN-DBS.<sup>22, 94</sup> Thus, beyond the NAc, both STN-DBS and PPX effects could  
13 differentially engage some common system responsible for behavior changes highlighted in  
14 this study. However, dopaminergic agonists do not always efficiently alleviate apathy under  
15 STN-DBS<sup>22</sup>. Non dopaminergic lesions frequently occur during the course of disease<sup>95, 96</sup>,  
16 and serotonin for example is proposed to participate in PD apathy<sup>97</sup>. In rats, STN-DBS has  
17 been shown to decrease serotonin release promoting depressive like behavior.<sup>49, 98</sup> Thus,  
18 we cannot completely exclude the implication of other neurotransmitters in the loss of  
19 motivation observed in patients or in this study.

20 As previously reported,<sup>99</sup> PPX at 0.3 mg/kg induces hyperlocomotricity in the open  
21 area test in control rats. This hyperactivity is unlikely to be responsible for the reversion of  
22 the self-administration deficit observed in PPX-treated STN-DBS rats since first, the level of  
23 non-stimulated treated rats remains similar to that of control rats, and second, PPX induced  
24 hypoactivity in non-stimulated lesioned rats whereas it also reversed the operant deficit  
25 induced by STN-DBS in those lesioned rats. This hypoactivity promoted by PPX in lesioned  
26 rats has previously been reported during the 120 minutes post injection window in control  
27 animals<sup>99</sup> and could rely on a sedating effect mediated by the presynaptic D<sub>3</sub>R<sup>100</sup>. We chose  
28 to separate the behavioral test from injection by 3h to avoid this effect. Since we previously



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1 demonstrated that the 6-OHDA lesion modifies D<sub>3</sub>R expression within the dorsolateral part of  
2 the striatum<sup>101</sup>, local imbalance between pre and post synaptic D<sub>2</sub>R and/or D<sub>3</sub>R expression  
3 or activity<sup>102</sup> could be responsible for DA transmission blunting, thus promoting this  
4 hypoactivity. Very intriguingly, in some rats of both the control and lesioned groups, the  
5 combination of STN-DBS and PPX induced a very high- level of activity that could emphasize  
6 the importance of individual traits, as demonstrated for the expression or severity of impulse  
7 control disorder in PD<sup>103-105</sup> or compulsive drug taking.<sup>106</sup> Thus, depending on complex  
8 interactions with dopaminergic treatments and according to pre-existing individual traits,  
9 STN-DBS could also lead to the development of hyperdopaminergic states reminiscent of  
10 hypomanic behaviors also observed in PD patients under STN-DBS.<sup>62, 74, 107, 108</sup>

11 Altogether, these data bring coherence to clinical observations that seemed  
12 contradictory until today: apathy in PD patients, at least its motivational dimension, could be  
13 induced by STN-DBS itself and attenuated by activation of D<sub>2</sub>R/D<sub>3</sub>R, regardless of (or in  
14 addition to) DRT reduction and the DA-mediated hypofunction. More detailed molecular  
15 analysis or techniques such as optogenetics could enable us to clarify the structures or sub-  
16 territories involved in this STN-DBS induced DA-driven loss of motivation. While it is beyond  
17 the scope of the present study, it would be also of interest to further investigate the effect of  
18 STN-DBS on the emotional and affective component of apathy, as STN has been proposed  
19 to be involved in such processes<sup>109</sup>.

20 STN-DBS has been shown to prevent cocaine or heroin re-escalation intake in rats<sup>40</sup>,  
21<sup>44</sup> and to reduce dopamine dysregulation syndrome or addictive behavior such as  
22 pathological gambling.<sup>110-114</sup> Thus, STN-DBS is currently explored as an effective treatment  
23 for addiction.<sup>45, 115</sup> However, our results suggest that this apparent beneficial effect could be  
24 underlain by a general motivational deficit. In rats, inhibiting the STN can abolish affective  
25 responses for salient reward<sup>109</sup> and STN-DBS can induce depression-like behaviors.<sup>49, 67, 116</sup>  
26 Furthermore, PD patients for whom addictive behavior was reduced under STN-DBS can  
27 also co-express apathy.<sup>14, 110</sup> These convergent facts are raising the question of the nature of  
28 this apparent "anti-addictive" effect of STN-DBS. This neurosurgical treatment could rather

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2  
3 1 induce a state of negative affect, comparable to a certain extent to the blunted dopaminergic  
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5 2 transmission observed during prolonged drug consumption<sup>117-119</sup> , increasing the risk of  
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7 3 addictive behavior resurgence in the same way as drugs of abuse withdrawal syndrome  
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9 4 promotes relapse.<sup>120</sup>  
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11 5 Thus, this new insight calls for reconsideration of the role of STN-DBS on mood in PD  
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13 6 to improve patient care and quality of life, and more broadly, to rethink the use of STN-DBS  
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15 7 in psychiatry.  
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For Peer Review

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**12 Author contributions**

13 YV, SB, SC and MS were responsible for the conception and the design of the study. YV,  
14 SB, CC and RM carried out the stereotaxic surgeries and the post-surgery monitoring of the  
15 animals. YV, CC and SB performed the neuroanatomical analysis of electrode implantation  
16 and lesions. YV and SB carried out the behavioral experiments and analysis. LKLG and PS  
17 provided micro-stimulators as well as training and advice for their use. YV and SB wrote the  
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## STN-DBS and Apathy in Parkinson's Disease

## References

1. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol* 2009;8(1):67-81.
2. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 2009;8(5):464-474.
3. Castrioto A, Lhommee E, Moro E, Krack P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. *Lancet Neurol* 2014;13(3):287-305.
4. Marin RS. Apathy: Concept, Syndrome, Neural Mechanisms, and Treatment. *Semin Clin Neuropsychiatry* 1996;1(4):304-314.
5. Martinez-Fernandez R, Pelissier P, Quesada JL, et al. Postoperative apathy can neutralise benefits in quality of life after subthalamic stimulation for Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry* 2016;87(3):311-318.
6. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex* 2006;16(7):916-928.
7. Chagraoui A, Boukharz L, Thibaut F, Anouar Y, Maltete D. The pathophysiological mechanisms of motivational deficits in Parkinson's disease. *Progress in neuro-psychopharmacology & biological psychiatry* 2018;81:138-152.
8. Chaudhuri KR, Odin P. The challenge of non-motor symptoms in Parkinson's disease. *Prog Brain Res* 2010;184:325-341.
9. Pagonabarraga J, Kulisevsky J, Strafella AP, Krack P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *Lancet Neurol* 2015;14(5):518-531.
10. Sierra M, Carnicella S, Strafella AP, et al. Apathy and Impulse Control Disorders: Yin & Yang of Dopamine Dependent Behaviors. *Journal of Parkinson's disease* 2015;5(3):625-636.
11. Maier F, Lewis CJ, Horstkoetter N, et al. Subjective perceived outcome of subthalamic deep brain stimulation in Parkinson's disease one year after surgery. *Parkinsonism & related disorders* 2016;24:41-47.
12. Maier F, Lewis CJ, Horstkoetter N, et al. Patients' expectations of deep brain stimulation, and subjective perceived outcome related to clinical measures in Parkinson's disease: a mixed-method approach. *Journal of neurology, neurosurgery, and psychiatry* 2013;84(11):1273-1281.
13. Aarsland D, Bronnick K, Alves G, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry* 2009;80(8):928-930.
14. Abbes M, Lhommee E, Thobois S, et al. Subthalamic stimulation and neuropsychiatric symptoms in Parkinson's disease: results from a long-term follow-up cohort study. *Journal of neurology, neurosurgery, and psychiatry* 2018;89(8):836-843.
15. Drapier D, Peron J, Leray E, et al. Emotion recognition impairment and apathy after subthalamic nucleus stimulation in Parkinson's disease have separate neural substrates. *Neuropsychologia* 2008;46(11):2796-2801.
16. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol* 2008;7(7):605-614.
17. Thobois S, Ardouin C, Lhommee E, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain : a journal of neurology* 2010;133(Pt 4):1111-1127.

## STN-DBS and Apathy in Parkinson's Disease

18. Thobois S, Lhomme E, Klinger H, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain : a journal of neurology* 2013;136(Pt 5):1568-1577.
19. Czernecki V, Schupbach M, Yaici S, et al. Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom. *Movement disorders : official journal of the Movement Disorder Society* 2008;23(7):964-969.
20. Magnard R, Vachez Y, Carcenac C, et al. What can rodent models tell us about apathy and associated neuropsychiatric symptoms in Parkinson's disease? *Transl Psychiatry* 2016;6:e753.
21. Drapier D, Drapier S, Sauleau P, et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? *Journal of neurology* 2006;253(8):1083-1091.
22. Le Jeune F, Drapier D, Bourguignon A, et al. Subthalamic nucleus stimulation in Parkinson disease induces apathy: a PET study. *Neurology* 2009;73(21):1746-1751.
23. Zoon TJ, de Bie RM, Schuurman PR, van den Munckhof P, Denys D, Fiege M. Resolution of apathy after dorsal instead of ventral subthalamic deep brain stimulation for Parkinson's disease. *Journal of neurology* 2019.
24. Breyse E, Pelloux Y, Baunez C. The Good and Bad Differentially Encoded within the Subthalamic Nucleus in Rats(1,2,3). *eNeuro* 2015;2(5).
25. Darbaky Y, Baunez C, Arecchi P, Legallet E, Apicella P. Reward-related neuronal activity in the subthalamic nucleus of the monkey. *Neuroreport* 2005;16(11):1241-1244.
26. Espinosa-Parrilla JF, Baunez C, Apicella P. Modulation of neuronal activity by reward identity in the monkey subthalamic nucleus. *The European journal of neuroscience* 2015;42(1):1705-1717.
27. Lardeux S, Pernaud R, Paleressompoulle D, Baunez C. Beyond the reward pathway: coding reward magnitude and error in the rat subthalamic nucleus. *J Neurophysiol* 2009;102(4):2526-2537.
28. Montanari C, Giorla E, Pelloux Y, Baunez C. Subthalamic nucleus mediates the modulation on cocaine self-administration induced by ultrasonic vocalization playback in rats. *Addiction biology* 2018.
29. Lardeux S, Paleressompoulle D, Pernaud R, Cador M, Baunez C. Different populations of subthalamic neurons encode cocaine vs. sucrose reward and predict future error. *J Neurophysiol* 2013;110(7):1497-1510.
30. Justin Rossi P, Peden C, Castellanos O, Foote KD, Gunduz A, Okun MS. The human subthalamic nucleus and globus pallidus internus differentially encode reward during action control. *Human brain mapping* 2017;38(4):1952-1964.
31. Zenon A, Duclos Y, Carron R, et al. The human subthalamic nucleus encodes the subjective value of reward and the cost of effort during decision-making. *Brain : a journal of neurology* 2016;139(Pt 6):1830-1843.
32. Baunez C, Amalric M, Robbins TW. Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2002;22(2):562-568.
33. Baunez C, Dias C, Cador M, Amalric M. The subthalamic nucleus exerts opposite control on cocaine and 'natural' rewards. *Nat Neurosci* 2005;8(4):484-489.
34. Bezzina G, Boon FS, Hampson CL, et al. Effect of quinolinic acid-induced lesions of the subthalamic nucleus on performance on a progressive-ratio schedule of reinforcement: a quantitative analysis. *Behavioural brain research* 2008;195(2):223-230.
35. Uslaner JM, Dell'Orco JM, Pevzner A, Robinson TE. The influence of subthalamic nucleus lesions on sign-tracking to stimuli paired with food and drug rewards: facilitation of incentive salience attribution? *Neuropsychopharmacology* 2008;33(10):2352-2361.

## STN-DBS and Apathy in Parkinson's Disease

- 1  
2  
3 1 36. Maillard CA, Edwards DA. [Subthalamic lesions eliminate sexual behavior in the  
4 2 male rat]. *Journal de physiologie* 1988;83(1):50-55.
- 5 3 37. Pratt WE, Choi E, Guy EG. An examination of the effects of subthalamic nucleus  
6 4 inhibition or mu-opioid receptor stimulation on food-directed motivation in the non-deprived  
7 5 rat. *Behavioural brain research* 2012;230(2):365-373.
- 8 6 38. Eusebio A, Witjas T, Cohen J, et al. Subthalamic nucleus stimulation and compulsive  
9 7 use of dopaminergic medication in Parkinson's disease. *Journal of neurology, neurosurgery,*  
10 8 *and psychiatry* 2013;84(8):868-874.
- 11 9 39. Lhomme E, Klinger H, Thobois S, et al. Subthalamic stimulation in Parkinson's  
12 10 disease: restoring the balance of motivated behaviours. *Brain : a journal of neurology*  
13 11 2012;135(Pt 5):1463-1477.
- 14 12 40. Pelloux Y, Degoulet M, Tiran-Cappello A, et al. Subthalamic nucleus high frequency  
15 13 stimulation prevents and reverses escalated cocaine use. *Molecular psychiatry*  
16 14 2018;23(12):2266-2276.
- 17 15 41. Rouaud T, Lardeux S, Panayotis N, Paleressompoulle D, Cador M, Baunez C.  
18 16 Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. *Proceedings*  
19 17 *of the National Academy of Sciences of the United States of America* 2010;107(3):1196-  
20 18 1200.
- 21 19 42. Adams WK, Vonder Haar C, Tremblay M, et al. Deep-Brain Stimulation of the  
22 20 Subthalamic Nucleus Selectively Decreases Risky Choice in Risk-Preferring Rats. *eNeuro*  
23 21 2017;4(4).
- 24 22 43. Hachem-Delaunay S, Fournier ML, Cohen C, et al. Subthalamic nucleus high-  
25 23 frequency stimulation modulates neuronal reactivity to cocaine within the reward circuit.  
26 24 *Neurobiol Dis* 2015;80:54-62.
- 27 25 44. Wade CL, Kallupi M, Hernandez DO, et al. High-Frequency Stimulation of the  
28 26 Subthalamic Nucleus Blocks Compulsive-Like Re-Escalation of Heroin Taking in Rats.  
29 27 *Neuropsychopharmacology* 2017;42(9):1850-1859.
- 30 28 45. Creed M. Current and emerging neuromodulation therapies for addiction: insight from  
31 29 pre-clinical studies. *Curr Opin Neurobiol* 2018;49:168-174.
- 32 30 46. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: A multicenter  
33 31 assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease.  
34 32 *Movement disorders : official journal of the Movement Disorder Society* 2009;24(11):1641-  
35 33 1649.
- 36 34 47. Pagonabarraga J, Kulisevsky J. Apathy in Parkinson's Disease. *International review of*  
37 35 *neurobiology* 2017;133:657-678.
- 38 36 48. Castelli L, Perozzo P, Zibetti M, et al. Chronic deep brain stimulation of the  
39 37 subthalamic nucleus for Parkinson's disease: effects on cognition, mood, anxiety and  
40 38 personality traits. *European neurology* 2006;55(3):136-144.
- 41 39 49. Temel Y, Boothman LJ, Blokland A, et al. Inhibition of 5-HT neuron activity and  
42 40 induction of depressive-like behavior by high-frequency stimulation of the subthalamic  
43 41 nucleus. *Proc Natl Acad Sci U S A* 2007;104(43):17087-17092.
- 44 42 50. Temel Y, Tan S, Vlamings R, et al. Cognitive and limbic effects of deep brain  
45 43 stimulation in preclinical studies. *Front Biosci* 2009;14:1891-1901.
- 46 44 51. Czernecki V, Pillon B, Houeto JL, et al. Does bilateral stimulation of the subthalamic  
47 45 nucleus aggravate apathy in Parkinson's disease? *Journal of neurology, neurosurgery, and*  
48 46 *psychiatry* 2005;76(6):775-779.
- 49 47 52. Robert GH, Le Jeune F, Lozachmeur C, et al. Preoperative factors of apathy in  
50 48 subthalamic stimulated Parkinson disease: a PET study. *Neurology* 2014;83(18):1620-1626.
- 51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## STN-DBS and Apathy in Parkinson's Disease

- 1  
2  
3 1 53. Wang Y, Li Y, Zhang X, Xie A. Apathy following Bilateral Deep Brain Stimulation of  
4 2 Subthalamic Nucleus in Parkinson's Disease: A Meta-Analysis. *Parkinsons Dis*  
5 3 2018;2018:9756468.  
6 4 54. Forni C, Mainard O, Melon C, Goguenheim D, Kerkerian-Le Goff L, Salin P. Portable  
7 5 microstimulator for chronic deep brain stimulation in freely moving rats. *Journal of*  
8 6 *neuroscience methods* 2012;209(1):50-57.  
9 7 55. Drui G, Carnicella S, Carcenac C, et al. Loss of dopaminergic nigrostriatal neurons  
10 8 accounts for the motivational and affective deficits in Parkinson's disease. *Mol Psychiatry*  
11 9 2014;19(3):358-367.  
12 10 56. Leentjens AF, Koester J, Fruh B, Shephard DT, Barone P, Houben JJ. The effect of  
13 11 pramipexole on mood and motivational symptoms in Parkinson's disease: a meta-analysis of  
14 12 placebo-controlled studies. *Clin Ther* 2009;31(1):89-98.  
15 13 57. Favier M, Duran T, Carcenac C, Drui G, Savasta M, Carnicella S. Pramipexole  
16 14 reverses Parkinson's disease-related motivational deficits in rats. *Movement disorders :*  
17 15 *official journal of the Movement Disorder Society* 2014;29(7):912-920.  
18 16 58. Carcenac C, Favier M, Vachez Y, et al. Subthalamic deep brain stimulation differently  
19 17 alters striatal dopaminergic receptor levels in rats. *Movement disorders : official journal of the*  
20 18 *Movement Disorder Society* 2015;30(13):1739-1749.  
21 19 59. Tokunaga N, Choudhury ME, Nishikawa N, et al. Pramipexole upregulates dopamine  
22 20 receptor D(2) and D(3) expression in rat striatum. *J Pharmacol Sci* 2012;120(2):133-137.  
23 21 60. Micallef J, Rey M, Eusebio A, et al. Antiparkinsonian drug-induced sleepiness: a  
24 22 double-blind placebo-controlled study of L-dopa, bromocriptine and pramipexole in healthy  
25 23 subjects. *Br J Clin Pharmacol* 2009;67(3):333-340.  
26 24 61. Castelli L, Lanotte M, Zibetti M, et al. Apathy and verbal fluency in STN-stimulated  
27 25 PD patients. An observational follow-up study. *Journal of neurology* 2007;254(9):1238-1243.  
28 26 62. Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic  
29 27 nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease.  
30 28 *Journal of neurology, neurosurgery, and psychiatry* 2004;75(6):834-839.  
31 29 63. Gervais-Bernard H, Xie-Brustolin J, Mertens P, et al. Bilateral subthalamic nucleus  
32 30 stimulation in advanced Parkinson's disease: five year follow-up. *Journal of neurology*  
33 31 2009;256(2):225-233.  
34 32 64. Schupbach WM, Chastan N, Welter ML, et al. Stimulation of the subthalamic nucleus  
35 33 in Parkinson's disease: a 5 year follow up. *Journal of neurology, neurosurgery, and psychiatry*  
36 34 2005;76(12):1640-1644.  
37 35 65. Temel Y, Visser-Vandewalle V, van der Wolf M, et al. Monopolar versus bipolar high  
38 36 frequency stimulation in the rat subthalamic nucleus: differences in histological damage.  
39 37 *Neuroscience letters* 2004;367(1):92-96.  
40 38 66. Chaturvedi A, Lujan JL, McIntyre CC. Artificial neural network based  
41 39 characterization of the volume of tissue activated during deep brain stimulation. *Journal of*  
42 40 *neural engineering* 2013;10(5):056023.  
43 41 67. Creed MC, Hamani C, Nobrega JN. Effects of repeated deep brain stimulation on  
44 42 depressive- and anxiety-like behavior in rats: comparing entopeduncular and subthalamic  
45 43 nuclei. *Brain Stimul* 2013;6(4):506-514.  
46 44 68. Aleksandrova LR, Creed MC, Fletcher PJ, Lobo DS, Hamani C, Nobrega JN. Deep  
47 45 brain stimulation of the subthalamic nucleus increases premature responding in a rat gambling  
48 46 task. *Behavioural brain research* 2013;245:76-82.  
49 47 69. Darbaky Y, Forni C, Amalric M, Baunez C. High frequency stimulation of the  
50 48 subthalamic nucleus has beneficial antiparkinsonian effects on motor functions in rats, but  
51 49 less efficiency in a choice reaction time task. *Eur J Neurosci* 2003;18(4):951-956.  
52  
53  
54  
55  
56  
57  
58  
59  
60

## STN-DBS and Apathy in Parkinson's Disease

- 1  
2  
3 1 70. Abulseoud OA, Kasasbeh A, Min HK, et al. Stimulation-Induced Transient Nonmotor  
4 2 Psychiatric Symptoms following Subthalamic Deep Brain Stimulation in Patients with  
5 3 Parkinson's Disease: Association with Clinical Outcomes and Neuroanatomical Correlates.  
6 4 *Stereotactic and functional neurosurgery* 2016;94(2):93-101.
- 7 5 71. Simmons DB, Dashtipour K. The Quantitative Measurement of Reversible Acute  
8 6 Depression after Subthalamic Deep Brain Stimulation in a Patient with Parkinson Disease.  
9 7 *Case reports in neurological medicine* 2015;2015:165846.
- 10 8 72. Alkemade A, Schnitzler A, Forstmann BU. Topographic organization of the human  
11 9 and non-human primate subthalamic nucleus. *Brain Struct Funct* 2015;220(6):3075-3086.
- 12 10 73. Lambert C, Zrinzo L, Nagy Z, et al. Confirmation of functional zones within the  
13 11 human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion  
14 12 weighted imaging. *NeuroImage* 2012;60(1):83-94.
- 15 13 74. Mallet L, Schupbach M, N'Diaye K, et al. Stimulation of subterritories of the  
16 14 subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of  
17 15 behavior. *Proc Natl Acad Sci U S A* 2007;104(25):10661-10666.
- 18 16 75. Stefurak T, Mikulis D, Mayberg H, et al. Deep brain stimulation for Parkinson's  
19 17 disease dissociates mood and motor circuits: a functional MRI case study. *Movement*  
20 18 *disorders : official journal of the Movement Disorder Society* 2003;18(12):1508-1516.
- 21 19 76. Roji R, Centeno C. The use of methylphenidate to relieve fatigue. *Current opinion in*  
22 20 *supportive and palliative care* 2017;11(4):299-305.
- 23 21 77. Skorvanek M, Gdovinova Z, Rosenberger J, et al. The associations between fatigue,  
24 22 apathy, and depression in Parkinson's disease. *Acta Neurol Scand* 2015;131(2):80-87.
- 25 23 78. Benazzouz A, Gao D, Ni Z, Benabid AL. High frequency stimulation of the STN  
26 24 influences the activity of dopamine neurons in the rat. *Neuroreport* 2000;11(7):1593-1596.
- 27 25 79. Min HK, Ross EK, Jo HJ, et al. Dopamine Release in the Nonhuman Primate Caudate  
28 26 and Putamen Depends upon Site of Stimulation in the Subthalamic Nucleus. *The Journal of*  
29 27 *neuroscience : the official journal of the Society for Neuroscience* 2016;36(22):6022-6029.
- 30 28 80. Bruet N, Windels F, Bertrand A, Feuerstein C, Poupard A, Savasta M. High frequency  
31 29 stimulation of the subthalamic nucleus increases the extracellular contents of striatal  
32 30 dopamine in normal and partially dopaminergic denervated rats. *J Neuropathol Exp Neurol*  
33 31 2001;60(1):15-24.
- 34 32 81. Kocobicak E, Jahanshahi A, Schonfeld L, Heschem SA, Temel Y, Tan S. Deep Brain  
35 33 Stimulation of the Rat Subthalamic Nucleus Induced Inhibition of Median Raphe  
36 34 Serotonergic and Dopaminergic Neurotransmission. *Turk Neurosurg* 2015;25(5):721-727.
- 37 35 82. Zhao XD, Cao YQ, Liu HH, Li FQ, You BM, Zhou XP. Long term high frequency  
38 36 stimulation of STN increases dopamine in the corpus striatum of hemiparkinsonian rhesus  
39 37 monkey. *Brain Res* 2009;1286:230-238.
- 40 38 83. Belin D, Everitt BJ. Cocaine seeking habits depend upon dopamine-dependent serial  
41 39 connectivity linking the ventral with the dorsal striatum. *Neuron* 2008;57(3):432-441.
- 42 40 84. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human  
43 41 imaging. *Neuropsychopharmacology : official publication of the American College of*  
44 42 *Neuropsychopharmacology* 2010;35(1):4-26.
- 45 43 85. Bjorklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. *Trends*  
46 44 *in neurosciences* 2007;30(5):194-202.
- 47 45 86. Gittis AH, Kreitzer AC. Striatal microcircuitry and movement disorders. *Trends in*  
48 46 *neurosciences* 2012;35(9):557-564.
- 49 47 87. Sesack SR, Grace AA. Cortico-Basal Ganglia reward network: microcircuitry.  
50 48 *Neuropsychopharmacology : official publication of the American College of*  
51 49 *Neuropsychopharmacology* 2010;35(1):27-47.
- 52  
53  
54  
55  
56  
57  
58  
59  
60



## STN-DBS and Apathy in Parkinson's Disease

- 1 88. Simon MJ, Higuera-Matas A, Roura-Martinez D, et al. Changes in D1 but not D2  
2 dopamine or mu-opioid receptor expression in limbic and motor structures after lateral  
3 hypothalamus electrical self-stimulation: A quantitative autoradiographic study. *Neurobiology*  
4 *of learning and memory* 2016;127:17-26.
- 5 89. Le Foll B, Goldberg SR, Sokoloff P. The dopamine D3 receptor and drug dependence:  
6 effects on reward or beyond? *Neuropharmacology* 2005;49(4):525-541.
- 7 90. Simpson EH, Winiger V, Biezonski DK, Haq I, Kandel ER, Kellendonk C. Selective  
8 overexpression of dopamine D3 receptors in the striatum disrupts motivation but not  
9 cognition. *Biol Psychiatry* 2014;76(10):823-831.
- 10 91. Drew MR, Simpson EH, Kellendonk C, et al. Transient overexpression of striatal D2  
11 receptors impairs operant motivation and interval timing. *The Journal of neuroscience : the*  
12 *official journal of the Society for Neuroscience* 2007;27(29):7731-7739.
- 13 92. Trifilieff P, Feng B, Urizar E, et al. Increasing dopamine D2 receptor expression in the  
14 adult nucleus accumbens enhances motivation. *Mol Psychiatry* 2013;18(9):1025-1033.
- 15 93. Ishibashi K, Ishii K, Oda K, Mizusawa H, Ishiwata K. Binding of pramipexole to  
16 extrastriatal dopamine D2/D3 receptors in the human brain: a positron emission tomography  
17 study using <sup>11</sup>C-FLB 457. *PloS one* 2011;6(3):e17723.
- 18 94. Knight EJ, Testini P, Min HK, et al. Motor and Nonmotor Circuitry Activation  
19 Induced by Subthalamic Nucleus Deep Brain Stimulation in Patients With Parkinson Disease:  
20 Intraoperative Functional Magnetic Resonance Imaging for Deep Brain Stimulation. *Mayo*  
21 *Clinic proceedings* 2015;90(6):773-785.
- 22 95. Carriere N, Besson P, Dujardin K, et al. Apathy in Parkinson's disease is associated  
23 with nucleus accumbens atrophy: a magnetic resonance imaging shape analysis. *Movement*  
24 *disorders : official journal of the Movement Disorder Society* 2014;29(7):897-903.
- 25 96. Reijnders JS, Scholtissen B, Weber WE, Aalten P, Verhey FR, Leentjens AF.  
26 Neuroanatomical correlates of apathy in Parkinson's disease: A magnetic resonance imaging  
27 study using voxel-based morphometry. *Movement disorders : official journal of the*  
28 *Movement Disorder Society* 2010;25(14):2318-2325.
- 29 97. Maillet A, Krack P, Lhommee E, et al. The prominent role of serotonergic  
30 degeneration in apathy, anxiety and depression in de novo Parkinson's disease. *Brain : a*  
31 *journal of neurology* 2016;139(Pt 9):2486-2502.
- 32 98. Creed MC, Hamani C, Bridgman A, Fletcher PJ, Nobrega JN. Contribution of  
33 decreased serotonin release to the antidyskinetic effects of deep brain stimulation in a rodent  
34 model of tardive dyskinesia: comparison of the subthalamic and entopeduncular nuclei. *The*  
35 *Journal of neuroscience : the official journal of the Society for Neuroscience*  
36 2012;32(28):9574-9581.
- 37 99. Chang WL, Breier MR, Yang A, Swerdlow NR. Disparate effects of pramipexole on  
38 locomotor activity and sensorimotor gating in Sprague-Dawley rats. *Pharmacol Biochem*  
39 *Behav* 2011;99(4):634-638.
- 40 100. Riddle JL, Rokosik SL, Napier TC. Pramipexole- and methamphetamine-induced  
41 reward-mediated behavior in a rodent model of Parkinson's disease and controls. *Behavioural*  
42 *brain research* 2012;233(1):15-23.
- 43 101. Favier M, Carcenac C, Drui G, et al. Implication of dorsostriatal D3 receptors in  
44 motivational processes: a potential target for neuropsychiatric symptoms in Parkinson's  
45 disease. *Sci Rep* 2017;7:41589.
- 46 102. Hurley MJ, Jenner P. What has been learnt from study of dopamine receptors in  
47 Parkinson's disease? *Pharmacol Ther* 2006;111(3):715-728.
- 48 103. Marin-Lahoz J, Pagonabarraga J, Martinez-Horta S, et al. Parkinson's Disease:  
49 Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. *Frontiers*  
50 *in psychiatry* 2018;9:465.

## STN-DBS and Apathy in Parkinson's Disease

- 1  
2  
3 1 104. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson  
4 2 disease: a cross-sectional study of 3090 patients. *Arch Neurol* 2010;67(5):589-595.  
5 3 105. Houeto JL, Magnard R, Dalley JW, Belin D, Carnicella S. Trait Impulsivity and  
6 4 Anhedonia: Two Gateways for the Development of Impulse Control Disorders in Parkinson's  
7 5 Disease? *Front Psychiatry* 2016;7:91.  
8 6 106. Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ. High impulsivity predicts the  
9 7 switch to compulsive cocaine-taking. *Science (New York, NY)* 2008;320(5881):1352-1355.  
10 8 107. Scangos KW, Shahlaie K. Acute Frequency-Dependent Hypomania Induced by  
11 9 Ventral Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: A Case Report.  
12 10 *Biological psychiatry* 2017;82(5):e39-e41.  
13 11 108. Welter ML, Schupbach M, Czernecki V, et al. Optimal target localization for  
14 12 subthalamic stimulation in patients with Parkinson disease. *Neurology* 2014;82(15):1352-  
15 13 1361.  
16 14 109. Pelloux Y, Meffre J, Giorla E, Baunez C. The subthalamic nucleus keeps you high on  
17 15 emotion: behavioral consequences of its inactivation. *Frontiers in behavioral neuroscience*  
18 16 2014;8:414.  
19 17 110. Ardouin C, Voon V, Worbe Y, et al. Pathological gambling in Parkinson's disease  
20 18 improves on chronic subthalamic nucleus stimulation. *Movement disorders : official journal*  
21 19 *of the Movement Disorder Society* 2006;21(11):1941-1946.  
22 20 111. Bandini F, Primavera A, Pizzorno M, Cocito L. Using STN DBS and medication  
23 21 reduction as a strategy to treat pathological gambling in Parkinson's disease. *Parkinsonism &*  
24 22 *related disorders* 2007;13(6):369-371.  
25 23 112. Knobel D, Aybek S, Pollo C, Vingerhoets FJ, Berney A. Rapid resolution of dopamine  
26 24 dysregulation syndrome (DDS) after subthalamic DBS for Parkinson disease (PD): a case  
27 25 report. *Cognitive and behavioral neurology : official journal of the Society for Behavioral and*  
28 26 *Cognitive Neurology* 2008;21(3):187-189.  
29 27 113. Witjas T, Baunez C, Henry JM, et al. Addiction in Parkinson's disease: impact of  
30 28 subthalamic nucleus deep brain stimulation. *Movement disorders : official journal of the*  
31 29 *Movement Disorder Society* 2005;20(8):1052-1055.  
32 30 114. Castrioto A, Carnicella S, Fraix V, Chabardes S, Moro E, Krack P. Reversing  
33 31 dopaminergic sensitization. *Movement disorders : official journal of the Movement Disorder*  
34 32 *Society* 2017;32(12):1679-1683.  
35 33 115. Pelloux Y, Baunez C. Deep brain stimulation for addiction: why the subthalamic  
36 34 nucleus should be favored. *Curr Opin Neurobiol* 2013;23(4):713-720.  
37 35 116. Tan SK, Janssen ML, Jahanshahi A, et al. High frequency stimulation of the  
38 36 subthalamic nucleus increases c-fos immunoreactivity in the dorsal raphe nucleus and afferent  
39 37 brain regions. *J Psychiatr Res* 2011;45(10):1307-1315.  
40 38 117. Martinez D, Gil R, Slifstein M, et al. Alcohol dependence is associated with blunted  
41 39 dopamine transmission in the ventral striatum. *Biological psychiatry* 2005;58(10):779-786.  
42 40 118. Barak S, Carnicella S, Yowell QV, Ron D. Glial cell line-derived neurotrophic factor  
43 41 reverses alcohol-induced allostasis of the mesolimbic dopaminergic system: implications for  
44 42 alcohol reward and seeking. *The Journal of neuroscience : the official journal of the Society*  
45 43 *for Neuroscience* 2011;31(27):9885-9894.  
46 44 119. Martinez D, Greene K, Broft A, et al. Lower level of endogenous dopamine in patients  
47 45 with cocaine dependence: findings from PET imaging of D(2)/D(3) receptors following acute  
48 46 dopamine depletion. *The American journal of psychiatry* 2009;166(10):1170-1177.  
49 47 120. Le Moal M, Koob GF. Drug addiction: pathways to the disease and  
50 48 pathophysiological perspectives. *Eur Neuropsychopharmacol* 2007;17(6-7):377-393.  
51 49 121. Paxinos G WC. *The rat brain in stereotaxic coordinates*. 1998.  
52  
53  
54  
55  
56  
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## STN-DBS and Apathy in Parkinson's Disease

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8 5 **Figures legends**  
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10 7 **FIGURE 1:** Experimental design and electrode implantation.

11 8 **(A)** Time course of the study, groups of animals and histological controls

12 9 After learning the sucrose self-administration task, lesion and implantation of electrodes, rats  
13 10 were divided into a stimulated and a non-stimulated group according to their performances,  
14 11 to constitute initially equal performance groups. Then, after 4 days of subthalamic nucleus  
15 12 deep brain stimulation (STN-DBS) with further sucrose self-administration, pramipexole  
16 13 (PPX) or vehicle (Veh) was injected twice a day into half of the stimulated (Non lesioned rats:  
17 14 STN-DBS + PPX, n = 8; STN-DBS + Veh, n = 13; lesioned rats: Lesion + STN-DBS + PPX, n  
18 15 = 5; Lesion + STN-DBS + Veh, n = 5) and non-stimulated rats (Control + PPX, n = 22;  
19 16 Control + Veh, n = 22; Lesioned rats: Lesion + PPX, n = 4; Lesion + Veh, n = 6) for 20 days.  
20 17 During this time, sucrose self-administration was continued for several days and then  
21 18 followed successively by other behavioral tests: the two-bottle choice test, the stepping test  
22 19 and finally the open area test. **(B)** Positions of bilateral DBS electrode tips in left and right  
23 20 STNs of stimulated animals in representative coronal sections (anteroposterior relative to  
24 21 Bregma: -3.60 mm; -3.80 mm; -4.16 mm), reproduced from Paxinos and Watson.<sup>121</sup> Each bar  
25 22 represents the placement of one electrode. **(C)** and **(D)** Example of electrode trace within the  
26 23 left STN stimulated at 100  $\mu$ A **(C)** or 225  $\mu$ A **(D)**, after Cresyl violet staining. Scale bar: 1 mm.  
27 24 IC, Internal Capsule; LH, Lateral Hypothalamus; ZI, Zona Incerta.

28 25 **(E)** and **(F)** Representative photomicrographs of coronal sections stained for tyrosine  
29 26 hydroxylase (TH) in striatal (bottom, 1.6 mm to bregma) and mesencephalic (top, -5.6 mm to  
30 27 bregma) regions from naïve (top) and lesioned (bottom) rats.<sup>121</sup> Scale bar = 1 mm. **(G, H)**  
31 28 Quantification of TH ImmunoReactivity (IR) loss in the midbrain **(G)** and the striatum **(H)**,  
32 29 expressed as the percentage difference compared to the mean value obtained for sham  
33 30 operated animals. The SNc bilateral lesion produced an important but partial denervation of

## STN-DBS and Apathy in Parkinson's Disease

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

5  
6 **FIGURE 2:** Subthalamic nucleus deep brain stimulation (STN-DBS) induces a deficit of  
7 preparatory behaviors in 2.5% sucrose self-administration that is rescued by pramipexole  
8 (PPX). **(A)** Time course of the sucrose self-administration experiment. STN-DBS induced a  
9 significant decrease of the number of sucrose deliveries. PPX induced a total reversion of  
10 this deficit. **(B)** Mean sucrose deliveries over the last 3 days of experiment. **(C)** STN-DBS  
11 and PPX did not alter the preference for sucrose.  
12 Control + Veh: n = 22; Control + PPX: n = 22; STN-DBS + Veh: n = 13; STN-DBS + PPX: n =  
13 8. Data shown as means  $\pm$  SEM. Control + Veh versus STN-DBS + Veh: \* $p < .05$ ; \*\* $p < .01$ ;  
14 STN-DBS + Veh versus STN-DBS + PPX: # $p < .05$ ; ## $p < .01$ .

15  
16 **FIGURE 3:** Subthalamic nucleus deep brain stimulation (STN-DBS) and pramipexole (PPX)  
17 promote hypo and hyper locomotor activity respectively but do not impair motor abilities. **(A)**  
18 Total distance travelled during a 1h open area test. STN-DBS induced a non-significant  
19 tendency towards decreased basal locomotor activity that was counteracted by treatment  
20 with PPX. In control rats, PPX induced a dramatic increase in the distance traveled. **(B)** STN-  
21 DBS and PPX did not change the mean ambulatory speed during the last 2 periods of the  
22 open area test. **(C)** STN-DBS and/or PPX did not alter the fine motor skills of front limbs as  
23 demonstrated by adjusting steps in the course of the stepping test. Control + Veh: n = 22;  
24 Control + PPX: n = 22; STN-DBS + Veh: n = 6; STN-DBS + PPX: n = 8. Data shown as  
25 means  $\pm$  SEM. Control + PPX versus Control + Veh: \* $p < .05$ .

## STN-DBS and Apathy in Parkinson's Disease

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3 1 **FIGURE 4:** STN-DBS exacerbates the deficit of preparatory behaviors of the existing  
4 motivational deficit in a rodent model of the neuropsychiatric symptoms of PD. **(A)** Time  
5 2 course of the sucrose self-administration experiment. STN-DBS decreased the number of  
6 3 sucrose deliveries. PPX induced a complete reversion of this deficit. **(B)** Mean sucrose  
7 4 deliveries over the last 5 days of experiment. **(C)** STN-DBS and PPX did not alter the  
8 5 preference for sucrose in 6-OHDA rats. Lesion + Veh: n = 6; Lesion + PPX: n = 4; Lesion +  
9 6 STN-DBS + Veh: n = 5; Lesion + STN-DBS + PPX: n = 5. Data shown as means  $\pm$  SEM.  
10 7  
11 8 Lesion + Veh versus Lesion + STN-DBS + Veh:  $*p < .05$ ; Lesion + STN-DBS + Veh versus  
12 9 Lesion + STN-DBS + PPX:  $\#p < .05$ .

10  
11 **FIGURE 5:** Subthalamic nucleus deep brain stimulation (STN-DBS) or pramipexole (PPX)  
12 individually promote hypoactivity but do not impair motor abilities. **(A)** Total distance traveled  
13 during a 1h open area test. STN-DBS induced a non-significant tendency towards decreased  
14 basal locomotor activity. In non-stimulated rats, PPX induced a dramatic decrease in the  
15 distance traveled. The combination of both treatments increased activity. **(B)** STN-DBS and  
16 PPX did not change the mean ambulatory speed during the open area test. **(C)** STN-DBS  
17 and/or PPX did not alter the fine motor skills of front limbs as demonstrated by adjusting  
18 steps in the course of the stepping test. Lesion + Veh: n = 6; Lesion + PPX: n = 4; Lesion +  
19 STN-DBS + Veh: n = 5; Lesion + STN-DBS + PPX: n = 5. Data shown as means  $\pm$  SEM.  
20 Lesion + PPX versus Lesion + STN-DBS + PPX:  $*p < .05$ .

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3 **Subthalamic nucleus stimulation impairs motivation: implication for apathy in**  
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41 **Running title:** STN-DBS and 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.

## STN-DBS and Apathy in Parkinson's Disease

**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).<sup>1</sup> 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 influence these symptoms, for better or for worse.<sup>2, 3</sup> 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,<sup>4-6</sup> is the most frequently observed non-motor  
9 complication of PD and deeply contributes to worsen the patient's quality of life<sup>2, 5, 7-12</sup>.  
10 Importantly, apathy has been reported to occur, or be exacerbated, in some patients under  
11 STN-DBS, as blunted affects<sup>8-10, 13-16</sup>. 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.<sup>17</sup> 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 (D<sub>2</sub>R and D<sub>3</sub>R)<sup>18, 19</sup> and 2) functional imaging studies  
18 in PD patients<sup>9, 17</sup> and some preclinical data indicating that at least some forms of apathy are  
19 related to the degenerative process and DA loss.<sup>20</sup>

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<sup>15, 21, 22</sup> or with incorrect location of  
23 electrodes in the associative or limbic part of the STN.<sup>23</sup> Thus, apathy in patients under STN-  
24 DBS was also proposed to be a major side-effect of STN-DBS itself.<sup>15, 21-23</sup> There is now an  
25 abundance of experimental and clinical studies demonstrating that 1) the STN is involved in  
26 reward and motivational processes,<sup>24-31</sup> 2) manipulating the STN can modify motivational  
27 behaviors<sup>32-37</sup> and 3) STN-DBS can alleviate dopamine dysregulation syndrome in some PD



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1 patients<sup>14, 38, 39</sup> and be a conceivable approach to treat addictive disorders<sup>40-45</sup>. Yet, a  
2 possible direct impact of STN-DBS on motivation in PD is not unanimously supported.

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

14 In the present study, we explored a potential effect of bilateral STN-DBS on  
15 **motivation**, by using a wireless micro-stimulation system enabling chronic continuous  
16 stimulation in rats during several weeks<sup>54</sup>. We first investigated the consequences of bilateral  
17 chronic STN-DBS in naïve rats and then in a preclinical model of neuropsychiatric symptoms  
18 related to PD that we have developed, using bilateral but partial denervation of the dorsal  
19 striatum (DS) by 6-hydroxydopamine (6-OHDA) lesion of SNc.<sup>20, 55</sup> Because D<sub>2</sub>R and D<sub>3</sub>R  
20 agonists, such as pramipexole (PPX), can alleviate pre and post STN-DBS apathy in PD  
21 patients<sup>18, 19, 56</sup> as well as in preclinical models<sup>20, 57</sup> and because we reported that STN-DBS  
22 reduces the level of D<sub>2</sub>R and D<sub>3</sub>R in the nucleus accumbens (NAc) of rats,<sup>58</sup> our working  
23 hypothesis was that post-STN-DBS apathy may be due to an alteration of DA transmission  
24 induced by STN-DBS itself. Thus, we also investigated the effect of STN-DBS with or without  
25 chronic treatment with PPX.

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**1 Materials and Methods****2 Animals**

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

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

12 See supplemental informations

**14 Experimental design**

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

19 Rats were trained to self-administer a 2.5% sucrose solution before and after SNc lesion and  
20 electrodes implantation (Only the self-administration after electrode implantation is  
21 represented). After 10 to 15 days, stable performances were obtained (less than 20%  
22 performance variation over three consecutive sessions) and STN-DBS was turned ON.  
23 Pharmacological procedures were applied after a new stabilization period: PPX (Sigma, 0.3  
24 mg.kg<sup>-1</sup> in 0.9% NaCl, 1 ml/kg) or vehicle was administered (sub-cutaneous) twice a day, 3h  
25 before the beginning of behavioral tests (i.e. injection at 7 am; test at 10 am) for and then at  
26 5 pm, during 20 days. This protocol, known to increase the expression of D<sub>2</sub>R and D<sub>3</sub>R,<sup>59</sup>  
27 was chosen to explore the chronic effects of PPX.<sup>60</sup> STN-DBS and PPX treatment were

## STN-DBS and Apathy in Parkinson's Disease

1  
2  
3 1 uninterrupted until rat euthanasia. After several days of sucrose self-administration, rats were  
4  
5 2 submitted to a two-bottle choice procedure, as well as to a stepping test and  
6  
7 3 locomotor/ambulatory activity evaluation in an open area<sup>55</sup> (Figure 1A). At the end of the  
8  
9 4 experiment, rats were euthanized and brains were processed for histological control of lesion  
10  
11 5 and implantations.  
12  
13 6

15 7 See supplemental data for full description of behavioral procedures, quantification of the  
16  
17 8 extent of the striatal DA denervation and control of electrode implantation.  
18  
19 9

### 10 ***Data and statistical analysis***

11 Data are shown as means  $\pm$  SEM and were analyzed by one or two-way ANOVAs, repeated  
12  
13 or not as specified in Results. Concerning operant sucrose self-administration, the different  
14  
15 experimental periods (Pre-STN-DBS, STN-DBS and STN-DBS + PPX) were analyzed  
16  
17 independently by distinct repeated measure ANOVAs for figures 2A and 4A. When indicated,  
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19 post hoc analyses were carried out with the Student Newman-Keuls procedure.  
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## STN-DBS and Apathy in Parkinson's Disease

**1 Results****2 *Histological controls***

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

8 Bilateral lesion of SNc (Figure 1E, percent of TH-IR loss, left SNc:  $73 \pm 5$ ; right SNc:  
9  $74 \pm 5$ ) was obtained by 6-OHDA injection. The injection produced an important denervation  
10 of the dorsal striatum in its lateral portion (Figure 1F, left dorsal striatum:  $68 \pm 5$ ; right dorsal  
11 striatum:  $74 \pm 6$ ), along its rostro-caudal extent as revealed by decreased tyrosine  
12 hydroxylase immunoreactivity. As the lesion has been shown to specifically affect SNc,  
13 barely impacting VTA (Figure 1G, left VTA:  $11 \pm 8$ ; right VTA:  $20 \pm 4$ ; Two way ANOVA,  
14 Structure x Lesion interaction:  $F_{1,22} = 7.654$ ,  $p < .0151$ ), NAc was almost totally preserved  
15 from denervation (Figure 1H, left NAc:  $21 \pm 3$ ; right NAc:  $24 \pm 4$ ; Two way ANOVA, Structure  
16 x Lesion interaction:  $F_{1,22} = 125.758$ ,  $p < .001$ ).

**18 *STN-DBS induces a motivational deficit in normal rats that is reversed by the D<sub>2</sub>R/D<sub>3</sub>R***  
**19 *agonist pramipexole***

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

## STN-DBS and Apathy in Parkinson's Disease

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2  
3 1 Figure S2A, two way ANOVA, STN-DBS effect:  $F_{1,42} = 10.480$ ,  $p = .002$ ). PPX completely  
4  
5 2 rescued the self-administration performances of stimulated rats from the second day of  
6  
7 3 treatment, without bringing performances superior to baseline or to Control + Veh rat levels.  
8  
9 4 (Figure 2A, STN-DBS + PPX period, repeated measure ANOVA, STN-DBS x PPX  
10  
11 5 interaction:  $F_{1,58} = 4.658$ ,  $p = .0351$ ; Session x PPX interaction:  $F_{6,348} = 2.412$ ,  $p = .0269$ ).  
12  
13 6 Both STN-DBS and PPX effects remained stable until the end of self-administration  
14  
15 7 experimentation (Figure 2B, two ways ANOVA, STN-DBS x PPX interaction:  $F_{1,64} = 7.178$ ,  $p$   
16  
17 8 = .009). In order to determine whether the decrease of operant performances induced by  
18  
19 9 STN-DBS was due to impairment in the consummatory or preparatory components of  
20  
21 10 motivated behaviors, we evaluated the sensitivity to the motivational properties of sucrose  
22  
23 11 (consummatory behavior) in a two-bottle choice procedure. The preference for the sucrose  
24  
25 12 solution that was used in the operant self-administration experiment over water was high and  
26  
27 13 not altered by STN-DBS or PPX (Figure 2C, two way ANOVA, STN-DBS x PPX interaction:  
28  
29 14  $F_{1,61} = .966$ ,  $p = .330$ ). Therefore, the self-administration paradigm and the sucrose  
30  
31 15 preference test indicate that STN-DBS affected the preparatory component of motivated  
32  
33 16 behaviors during the operant task and that PPX specifically corrected this impairment.

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37 17 In addition, STN-DBS-induced preparatory component deficit and subsequent self-  
38  
39 18 administration deficiency cannot be attributed to motor impairment, because STN-DBS did  
40  
41 19 not induce any significant locomotor change during the first 20 minutes of the open area test,  
42  
43 20 corresponding to the exploratory phase when locomotor activity is high, facilitating detection  
44  
45 21 of motor deficit (Figure 3A, two way ANOVA, 0-20 min:  $F_{1,48} = .513$ ;  $p = .477$ ). Exploration  
46  
47 22 and locomotor activity then progressively decreased to a basal level during the last 2 periods  
48  
49 23 (20 to 60 min). Although it did not reach significance, STN-DBS tended to reduce ambulatory  
50  
51 24 activity during this phase. (Figure 3A, STN-DBS effect, Two way ANOVA, 20-40 min:  $F_{1,48} =$   
52  
53 25  $3.311$ ,  $p = .075$ ; 40-60 min:  $F_{1,48} = 3.525$ ,  $p = .067$ ) This effect of STN-DBS is unlikely to  
54  
55 26 reflect a motor deficit but rather a decrease in general behavioral activity, because  
56  
57 27 ambulatory speed during this test phase was not changed by the stimulation (Figure 3B,  
58  
59 28 STN-DBS effect, Two way ANOVA,  $F_{1,48} = .196$ ,  $p = .660$ ). Moreover, fine motor skills of left

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

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

13  
14 ***STN-DBS exacerbates motivational deficit in a rodent model of PD apathetic  
15 symptoms and affective disorders***

16 We sought to confirm whether STN-DBS would also affect motivation in a  
17 pathological context. We used a rodent model of PD that we developed<sup>55</sup> and that exhibits  
18 strong motivational deficits, without locomotor alterations.

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

## STN-DBS and Apathy in Parkinson's Disease

1  
2  
3 1 50% from day one of stimulation (Figure 4A, STN-DBS period, repeated measure ANOVA,  
4  
5 2 STN-DBS effect  $F_{1,15} = 4.249$ ,  $p = .0571$ ), as observed in non-lesioned/control stimulated rats  
6  
7 3 (Figure S2A, two way ANOVA, STN-DBS effect:  $F_{1,42} = 10.48$ ,  $p = .002$  and no STN-DBS x  
8  
9 4 Lesion interaction:  $F_{1,42} = 1,112$ ,  $p = .298$ ). As for non-lesioned animals, PPX completely  
10  
11 5 alleviated this STN-DBS-induced deficit from the second day of treatment (STN-DBS + PPX  
12  
13 6 period, repeated measure ANOVA, STN-DBS x PPX x Session interaction effect  $F_{9,108} =$   
14  
15 7  $2.712$ ,  $p = .0069$ ). Both STN-DBS and PPX effects remained stable until the end of the  
16  
17 8 experiment (Figure 4B, two way ANOVA, STN-DBS x PPX interaction:  $F_{1,16} = .826$ ,  $p = .377$ ).  
18  
19 9 We also assessed the consummatory components of motivated behaviors, with the two-  
20  
21 10 bottle choice procedure and we found that neither STN-DBS nor PPX modified the  
22  
23 11 preference for sucrose (Figure 4C, two way ANOVA, STN-DBS x PPX interaction:  $F_{1,20} =$   
24  
25 12  $.341$ ,  $p = .567$ ).

26  
27  
28 13 PPX or STN-DBS tended to reduce ambulatory activity in the open area test while  
29  
30 14 when they were combined, on average they promoted a high level of activity but with high  
31  
32 15 variability (Figure 5A, two way ANOVA, STN-DBS x PPX interaction:  $F_{1,14} = 5.759$ ,  $p = .031$ ).  
33  
34 16 These effects are likely to reflect changes in behavioral activity rather than alteration of  
35  
36 17 motors skills *per se*, first because neither PPX nor STN-DBS affected the ambulatory speed  
37  
38 18 during the open area test (Figure 5B, Two way ANOVA, STN-DBS x PPX interaction  $F_{1,48} =$   
39  
40 19  $.214$ ,  $p = .650$ ) and second, adjustments during the stepping test were not impacted by either  
41  
42 20 treatment (Figure 5B, two ways ANOVA, STN-DBS x PPX interaction: left to right moves, left  
43  
44 21 limb:  $F_{1,18} = .184$ ,  $p = .673$ ; right limb:  $F_{1,18} = .653$ ,  $p = .983$ ; right to left moves, left limb:  $F_{1,18}$   
45  
46 22  $= .0017$ ,  $p = .915$ ; right limb:  $F_{1,18} = .764$ ,  $p = .393$ ).

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49 23 Taken together, these results suggest that STN-DBS exacerbates the loss of  
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51 24 motivation induced by the dopaminergic lesion and reduce behavioral activity, effects that  
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53 25 were alleviated by PPX.  
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## STN-DBS and Apathy in Parkinson's Disease

**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 D<sub>2</sub>R/D<sub>3</sub>R 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.,<sup>41, 49</sup>), 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 patients<sup>1</sup> as well as in studies describing apathy under STN-DBS<sup>17, 21, 48, 61-64</sup>. Furthermore, a preclinical study in rat has clearly demonstrated that it reduces tissue damage compared to bipolar stimulation.<sup>65</sup> Moreover, although monopolar stimulation is more likely to affect the surrounding STN fibers than bipolar stimulation, it was applied at intensities below 225  $\mu$ A to minimize current spreading as previously demonstrated.<sup>66</sup> The motivational dimension of apathy especially concerns hum-drum daily tasks that are neither challenging nor particularly effortful.<sup>4</sup> 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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1 behavioral activity, as observed in apathy.<sup>9</sup> While we previously provided strong evidence  
2 that the dopaminergic denervation can account for the loss of motivation in PD, here we  
3 report that STN-DBS by itself could induce or exacerbate **this motivational impairment** via  
4 DA-driven mechanisms, independent of the hypodopaminergy induced by DRT reduction.  
5 Furthermore, the present study provides a missing link, reconciling apparently contradictory  
6 clinical observations on the origin of post-operative apathy in stimulated PD patients.

7       The myriad of reported neuropsychiatric side effects of STN-DBS in PD patients<sup>3</sup> has  
8 triggered several animal studies to understand their phenomenology. These studies have  
9 demonstrated the possible implication of STN-DBS in PD-related depression<sup>49, 67</sup> or potent  
10 effects on impulsive behaviors,<sup>68</sup> but few of them tackled the effects on pure motivational  
11 processes. As far as we know, only one report mentions data that could be interpreted as a  
12 transient reduced motivation under STN-DBS.<sup>69</sup> However, another study showed no effect of  
13 STN-DBS on operant activity in a fixed-ratio schedule of reinforcement and even described  
14 an increase in performance in obtaining a sucrose pellet during a progressive ratio  
15 schedule.<sup>41</sup> Major differences between this previous study and our protocol are likely to  
16 account for these discrepancies. Indeed, Rouaud et al., used acute bipolar stimulation  
17 conditions compared to our chronic monopolar STN-DBS; interestingly, psychiatric side  
18 effects of STN-DBS strongly depend on electrode polarity. For example, acute depressive  
19 states following regular monopolar STN-DBS are greatly reduced by switching to the scarcer  
20 bipolar STN-DBS.<sup>70, 71</sup> Moreover, the design of the operant task was different enough to yield  
21 diverging results. In particular, our study avoided food-restriction. Whereas all the studies  
22 having inactivated the STN found an increase in motivation for food in restricted animals, one  
23 study demonstrated that this effect was completely occluded in rats fed *ad libitum*.<sup>37</sup> Finally,  
24 while the conditioned place preference revealed an effect of STN-DBS on the rewarding  
25 properties of sucrose in this study,<sup>41</sup> we did not find any modification of this parameter during  
26 the two bottle choice test.

27       The STN can be functionally and anatomically subdivided into motor, associative and  
28 limbic sub-territories.<sup>72-74</sup> Then it is part of the three respective basal ganglia loops.<sup>73, 74</sup> In PD

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

9 In patients, apathy occurring after STN-DBS can be treated by dopaminergic  
10 agonists, including those targeting the D<sub>2</sub>R and D<sub>3</sub>R.<sup>18, 19</sup> This, and the fact that  
11 methylphenidate can alleviate fatigue<sup>76</sup>, which is a related and/or confounding symptom of  
12 apathy<sup>77</sup>, has prompted the hypothesis that a strong hypodopaminergic state revealed by  
13 reduction of DRT, rather than STN-DBS *per se*, may be responsible for the resurgence of  
14 apathy.<sup>13</sup> Using a pharmacological protocol allowing exploration of the chronic effects of PPX  
15 and known to increase D<sub>2</sub>R and D<sub>3</sub>R expression,<sup>59</sup> we demonstrated that PPX, a D<sub>2</sub>R/D<sub>3</sub>R  
16 agonist, fully rescued the motivational deficit induced by STN-DBS in control and lesioned  
17 rats. It should be noted that this pharmacological protocol was not able to reverse the loss of  
18 motivation due to the dopaminergic lesion, indicating that even if both the lesion and STN-  
19 DBS effects on motivation could be driven by dopaminergic mechanisms, these could be  
20 significantly different. This suggests that STN-DBS may impact on behavior via its own  
21 effects on DA transmission, which is consistent with previous animal model studies showing  
22 that STN-DBS modulates DA system.<sup>58, 78-82</sup> The three so-called basal ganglia limbic,  
23 associative and motor loops including the STN are not completely segregated; the different  
24 structures involved are functionally interconnected<sup>83</sup> by an ascending striato-midbrain-striatal  
25 spiraling circuitry.<sup>84</sup> Moreover, beyond this complex organization, which has yet to be  
26 demonstrated in rats, SNc and VTA are overlapping structures<sup>85</sup> and the whole striatum is  
27 characterized by a dense local microcircuitry<sup>86, 87</sup> which could also contribute to this  
28 interconnection. Thus, STN-DBS may modulate DA transmission within the basal ganglia

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1 and, through these subcortical interactions, disrupt the complex chain of events that  
2 transforms intentions into adapted action, and thereby influence non-motor functions.<sup>6, 9</sup>  
3 Nonetheless, we cannot exclude a potential involvement of the structures surrounding the  
4 STN . It is unlikely that the electric field emanating from the electrode is restrained to the  
5 STN borders and DBS of some of these structures in the vicinity of the STN, such as the  
6 lateral hypothalamus, can also modulate DA transmission<sup>88</sup>. We previously found that short  
7 STN-DBS can decrease the level of D<sub>2</sub>R and D<sub>3</sub>R within the NAc.<sup>58</sup> Given the critical  
8 implication of the D<sub>2</sub>R and D<sub>3</sub>R in motivational processes,<sup>89-92</sup> our data suggest a causal  
9 involvement of these receptors in the motivational deficit that we observed. In addition, D<sub>2</sub>R  
10 and D<sub>3</sub>R are expressed in several other non-motor structures impacted by PPX treatment<sup>93</sup>  
11 and some of them are part of down-stream circuits with metabolic activities known to be  
12 affected by STN-DBS.<sup>22, 94</sup> Thus, beyond the NAc, both STN-DBS and PPX effects could  
13 differentially engage some common system responsible for behavior changes highlighted in  
14 this study. However, dopaminergic agonists do not always efficiently alleviate apathy under  
15 STN-DBS<sup>22</sup>. Non dopaminergic lesions frequently occur during the course of disease<sup>95, 96</sup>,  
16 and serotonin for example is proposed to participate in PD apathy<sup>97</sup>. In rats, STN-DBS has  
17 been shown to decrease serotonin release promoting depressive like behavior.<sup>49, 98</sup> Thus,  
18 we cannot completely exclude the implication of other neurotransmitters in the loss of  
19 motivation observed in patients or in this study.

20 As previously reported,<sup>99</sup> PPX at 0.3 mg/kg induces hyperlocomotricity in the open  
21 area test in control rats. This hyperactivity is unlikely to be responsible for the reversion of  
22 the self-administration deficit observed in PPX-treated STN-DBS rats since first, the level of  
23 non-stimulated treated rats remains similar to that of control rats, and second, PPX induced  
24 hypoactivity in non-stimulated lesioned rats whereas it also reversed the operant deficit  
25 induced by STN-DBS in those lesioned rats. This hypoactivity promoted by PPX in lesioned  
26 rats has previously been reported during the 120 minutes post injection window in control  
27 animals<sup>99</sup> and could rely on a sedating effect mediated by the presynaptic D<sub>3</sub>R<sup>100</sup>. We chose  
28 to separate the behavioral test from injection by 3h to avoid this effect. Since we previously

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1 demonstrated that the 6-OHDA lesion modifies D<sub>3</sub>R expression within the dorsolateral part of  
2 the striatum<sup>101</sup>, local imbalance between pre and post synaptic D<sub>2</sub>R and/or D<sub>3</sub>R expression  
3 or activity<sup>102</sup> could be responsible for DA transmission blunting, thus promoting this  
4 hypoactivity. Very intriguingly, in some rats of both the control and lesioned groups, the  
5 combination of STN-DBS and PPX induced a very high- level of activity that could emphasize  
6 the importance of individual traits, as demonstrated for the expression or severity of impulse  
7 control disorder in PD<sup>103-105</sup> or compulsive drug taking.<sup>106</sup> Thus, depending on complex  
8 interactions with dopaminergic treatments and according to pre-existing individual traits,  
9 STN-DBS could also lead to the development of hyperdopaminergic states reminiscent of  
10 hypomanic behaviors also observed in PD patients under STN-DBS.<sup>62, 74, 107, 108</sup>

11 Altogether, these data bring coherence to clinical observations that seemed  
12 contradictory until today: apathy in PD patients, at least its motivational dimension, could be  
13 induced by STN-DBS itself and attenuated by activation of D<sub>2</sub>R/D<sub>3</sub>R, regardless of (or in  
14 addition to) DRT reduction and the DA-mediated hypofunction. More detailed molecular  
15 analysis or techniques such as optogenetics could enable us to clarify the structures or sub-  
16 territories involved in this STN-DBS induced DA-driven loss of motivation. While it is beyond  
17 the scope of the present study, it would be also of interest to further investigate the effect of  
18 STN-DBS on the emotional and affective component of apathy, as STN has been proposed  
19 to be involved in such processes<sup>109</sup>.

20 STN-DBS has been shown to prevent cocaine or heroin re-escalation intake in rats<sup>40</sup>,  
21<sup>44</sup> and to reduce dopamine dysregulation syndrome or addictive behavior such as  
22 pathological gambling.<sup>110-114</sup> Thus, STN-DBS is currently explored as an effective treatment  
23 for addiction.<sup>45, 115</sup> However, our results suggest that this apparent beneficial effect could be  
24 underlain by a general motivational deficit. In rats, inhibiting the STN can abolish affective  
25 responses for salient reward<sup>109</sup> and STN-DBS can induce depression-like behaviors.<sup>49, 67, 116</sup>  
26 Furthermore, PD patients for whom addictive behavior was reduced under STN-DBS can  
27 also co-express apathy.<sup>14, 110</sup> These convergent facts are raising the question of the nature of  
28 this apparent "anti-addictive" effect of STN-DBS. This neurosurgical treatment could rather

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1  
2  
3 1 induce a state of negative affect, comparable to a certain extent to the blunted dopaminergic  
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5 2 transmission observed during prolonged drug consumption<sup>117-119</sup> , increasing the risk of  
6  
7 3 addictive behavior resurgence in the same way as drugs of abuse withdrawal syndrome  
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9 4 promotes relapse.<sup>120</sup>  
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11 5 Thus, this new insight calls for reconsideration of the role of STN-DBS on mood in PD  
12  
13 6 to improve patient care and quality of life, and more broadly, to rethink the use of STN-DBS  
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15 7 in psychiatry.  
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For Peer Review

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**12 Author contributions**

13 YV, SB, SC and MS were responsible for the conception and the design of the study. YV,  
14 SB, CC and RM carried out the stereotaxic surgeries and the post-surgery monitoring of the  
15 animals. YV, CC and SB performed the neuroanatomical analysis of electrode implantation  
16 and lesions. YV and SB carried out the behavioral experiments and analysis. LKLG and PS  
17 provided micro-stimulators as well as training and advice for their use. YV and SB wrote the  
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20  
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## STN-DBS and Apathy in Parkinson's Disease

## References

1. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol* 2009;8(1):67-81.
2. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 2009;8(5):464-474.
3. Castrioto A, Lhommee E, Moro E, Krack P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. *Lancet Neurol* 2014;13(3):287-305.
4. Marin RS. Apathy: Concept, Syndrome, Neural Mechanisms, and Treatment. *Semin Clin Neuropsychiatry* 1996;1(4):304-314.
5. Martinez-Fernandez R, Pelissier P, Quesada JL, et al. Postoperative apathy can neutralise benefits in quality of life after subthalamic stimulation for Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry* 2016;87(3):311-318.
6. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex* 2006;16(7):916-928.
7. Chagraoui A, Boukharz L, Thibaut F, Anouar Y, Maltete D. The pathophysiological mechanisms of motivational deficits in Parkinson's disease. *Progress in neuro-psychopharmacology & biological psychiatry* 2018;81:138-152.
8. Chaudhuri KR, Odin P. The challenge of non-motor symptoms in Parkinson's disease. *Prog Brain Res* 2010;184:325-341.
9. Pagonabarraga J, Kulisevsky J, Strafella AP, Krack P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *Lancet Neurol* 2015;14(5):518-531.
10. Sierra M, Carnicella S, Strafella AP, et al. Apathy and Impulse Control Disorders: Yin & Yang of Dopamine Dependent Behaviors. *Journal of Parkinson's disease* 2015;5(3):625-636.
11. Maier F, Lewis CJ, Horstkoetter N, et al. Subjective perceived outcome of subthalamic deep brain stimulation in Parkinson's disease one year after surgery. *Parkinsonism & related disorders* 2016;24:41-47.
12. Maier F, Lewis CJ, Horstkoetter N, et al. Patients' expectations of deep brain stimulation, and subjective perceived outcome related to clinical measures in Parkinson's disease: a mixed-method approach. *Journal of neurology, neurosurgery, and psychiatry* 2013;84(11):1273-1281.
13. Aarsland D, Bronnick K, Alves G, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry* 2009;80(8):928-930.
14. Abbes M, Lhommee E, Thobois S, et al. Subthalamic stimulation and neuropsychiatric symptoms in Parkinson's disease: results from a long-term follow-up cohort study. *Journal of neurology, neurosurgery, and psychiatry* 2018;89(8):836-843.
15. Drapier D, Peron J, Leray E, et al. Emotion recognition impairment and apathy after subthalamic nucleus stimulation in Parkinson's disease have separate neural substrates. *Neuropsychologia* 2008;46(11):2796-2801.
16. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol* 2008;7(7):605-614.
17. Thobois S, Ardouin C, Lhommee E, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain : a journal of neurology* 2010;133(Pt 4):1111-1127.



## STN-DBS and Apathy in Parkinson's Disease

18. Thobois S, Lhomme E, Klinger H, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain : a journal of neurology* 2013;136(Pt 5):1568-1577.
19. Czernecki V, Schupbach M, Yaici S, et al. Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom. *Movement disorders : official journal of the Movement Disorder Society* 2008;23(7):964-969.
20. Magnard R, Vachez Y, Carcenac C, et al. What can rodent models tell us about apathy and associated neuropsychiatric symptoms in Parkinson's disease? *Transl Psychiatry* 2016;6:e753.
21. Drapier D, Drapier S, Sauleau P, et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? *Journal of neurology* 2006;253(8):1083-1091.
22. Le Jeune F, Drapier D, Bourguignon A, et al. Subthalamic nucleus stimulation in Parkinson disease induces apathy: a PET study. *Neurology* 2009;73(21):1746-1751.
23. Zoon TJ, de Bie RM, Schuurman PR, van den Munckhof P, Denys D, Figeet M. Resolution of apathy after dorsal instead of ventral subthalamic deep brain stimulation for Parkinson's disease. *Journal of neurology* 2019.
24. Breyse E, Pelloux Y, Baunez C. The Good and Bad Differentially Encoded within the Subthalamic Nucleus in Rats(1,2,3). *eNeuro* 2015;2(5).
25. Darbaky Y, Baunez C, Arecchi P, Legallet E, Apicella P. Reward-related neuronal activity in the subthalamic nucleus of the monkey. *Neuroreport* 2005;16(11):1241-1244.
26. Espinosa-Parrilla JF, Baunez C, Apicella P. Modulation of neuronal activity by reward identity in the monkey subthalamic nucleus. *The European journal of neuroscience* 2015;42(1):1705-1717.
27. Lardeux S, Pernaud R, Paleressompoulle D, Baunez C. Beyond the reward pathway: coding reward magnitude and error in the rat subthalamic nucleus. *J Neurophysiol* 2009;102(4):2526-2537.
28. Montanari C, Giorla E, Pelloux Y, Baunez C. Subthalamic nucleus mediates the modulation on cocaine self-administration induced by ultrasonic vocalization playback in rats. *Addiction biology* 2018.
29. Lardeux S, Paleressompoulle D, Pernaud R, Cador M, Baunez C. Different populations of subthalamic neurons encode cocaine vs. sucrose reward and predict future error. *J Neurophysiol* 2013;110(7):1497-1510.
30. Justin Rossi P, Peden C, Castellanos O, Foote KD, Gunduz A, Okun MS. The human subthalamic nucleus and globus pallidus internus differentially encode reward during action control. *Human brain mapping* 2017;38(4):1952-1964.
31. Zenon A, Duclos Y, Carron R, et al. The human subthalamic nucleus encodes the subjective value of reward and the cost of effort during decision-making. *Brain : a journal of neurology* 2016;139(Pt 6):1830-1843.
32. Baunez C, Amalric M, Robbins TW. Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2002;22(2):562-568.
33. Baunez C, Dias C, Cador M, Amalric M. The subthalamic nucleus exerts opposite control on cocaine and 'natural' rewards. *Nat Neurosci* 2005;8(4):484-489.
34. Bezzina G, Boon FS, Hampson CL, et al. Effect of quinolinic acid-induced lesions of the subthalamic nucleus on performance on a progressive-ratio schedule of reinforcement: a quantitative analysis. *Behavioural brain research* 2008;195(2):223-230.
35. Uslaner JM, Dell'Orco JM, Pevzner A, Robinson TE. The influence of subthalamic nucleus lesions on sign-tracking to stimuli paired with food and drug rewards: facilitation of incentive salience attribution? *Neuropsychopharmacology* 2008;33(10):2352-2361.

## STN-DBS and Apathy in Parkinson's Disease

- 1 36. Maillard CA, Edwards DA. [Subthalamic lesions eliminate sexual behavior in the  
2 male rat]. *Journal de physiologie* 1988;83(1):50-55.
- 3 37. Pratt WE, Choi E, Guy EG. An examination of the effects of subthalamic nucleus  
4 inhibition or mu-opioid receptor stimulation on food-directed motivation in the non-deprived  
5 rat. *Behavioural brain research* 2012;230(2):365-373.
- 6 38. Eusebio A, Witjas T, Cohen J, et al. Subthalamic nucleus stimulation and compulsive  
7 use of dopaminergic medication in Parkinson's disease. *Journal of neurology, neurosurgery,  
8 and psychiatry* 2013;84(8):868-874.
- 9 39. Lhomme E, Klinger H, Thobois S, et al. Subthalamic stimulation in Parkinson's  
10 disease: restoring the balance of motivated behaviours. *Brain : a journal of neurology*  
11 2012;135(Pt 5):1463-1477.
- 12 40. Pelloux Y, Degoulet M, Tiran-Cappello A, et al. Subthalamic nucleus high frequency  
13 stimulation prevents and reverses escalated cocaine use. *Molecular psychiatry*  
14 2018;23(12):2266-2276.
- 15 41. Rouaud T, Lardeux S, Panayotis N, Paleressompouille D, Cador M, Baunez C.  
16 Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. *Proceedings*  
17 *of the National Academy of Sciences of the United States of America* 2010;107(3):1196-  
18 1200.
- 19 42. Adams WK, Vonder Haar C, Tremblay M, et al. Deep-Brain Stimulation of the  
20 Subthalamic Nucleus Selectively Decreases Risky Choice in Risk-Preferring Rats. *eNeuro*  
21 2017;4(4).
- 22 43. Hachem-Delaunay S, Fournier ML, Cohen C, et al. Subthalamic nucleus high-  
23 frequency stimulation modulates neuronal reactivity to cocaine within the reward circuit.  
24 *Neurobiol Dis* 2015;80:54-62.
- 25 44. Wade CL, Kallupi M, Hernandez DO, et al. High-Frequency Stimulation of the  
26 Subthalamic Nucleus Blocks Compulsive-Like Re-Escalation of Heroin Taking in Rats.  
27 *Neuropsychopharmacology* 2017;42(9):1850-1859.
- 28 45. Creed M. Current and emerging neuromodulation therapies for addiction: insight from  
29 pre-clinical studies. *Curr Opin Neurobiol* 2018;49:168-174.
- 30 46. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: A multicenter  
31 assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease.  
32 *Movement disorders : official journal of the Movement Disorder Society* 2009;24(11):1641-  
33 1649.
- 34 47. Pagonabarraga J, Kulisevsky J. Apathy in Parkinson's Disease. *International review of*  
35 *neurobiology* 2017;133:657-678.
- 36 48. Castelli L, Perozzo P, Zibetti M, et al. Chronic deep brain stimulation of the  
37 subthalamic nucleus for Parkinson's disease: effects on cognition, mood, anxiety and  
38 personality traits. *European neurology* 2006;55(3):136-144.
- 39 49. Temel Y, Boothman LJ, Blokland A, et al. Inhibition of 5-HT neuron activity and  
40 induction of depressive-like behavior by high-frequency stimulation of the subthalamic  
41 nucleus. *Proc Natl Acad Sci U S A* 2007;104(43):17087-17092.
- 42 50. Temel Y, Tan S, Vlamings R, et al. Cognitive and limbic effects of deep brain  
43 stimulation in preclinical studies. *Front Biosci* 2009;14:1891-1901.
- 44 51. Czernecki V, Pillon B, Houeto JL, et al. Does bilateral stimulation of the subthalamic  
45 nucleus aggravate apathy in Parkinson's disease? *Journal of neurology, neurosurgery, and*  
46 *psychiatry* 2005;76(6):775-779.
- 47 52. Robert GH, Le Jeune F, Lozachmeur C, et al. Preoperative factors of apathy in  
48 subthalamic stimulated Parkinson disease: a PET study. *Neurology* 2014;83(18):1620-1626.

## STN-DBS and Apathy in Parkinson's Disease

- 1 53. Wang Y, Li Y, Zhang X, Xie A. Apathy following Bilateral Deep Brain Stimulation of  
2 Subthalamic Nucleus in Parkinson's Disease: A Meta-Analysis. *Parkinsons Dis*  
3 2018;2018:9756468.
- 4 54. Forni C, Mainard O, Melon C, Goguenheim D, Kerkerian-Le Goff L, Salin P. Portable  
5 microstimulator for chronic deep brain stimulation in freely moving rats. *Journal of*  
6 *neuroscience methods* 2012;209(1):50-57.
- 7 55. Drui G, Carnicella S, Carcenac C, et al. Loss of dopaminergic nigrostriatal neurons  
8 accounts for the motivational and affective deficits in Parkinson's disease. *Mol Psychiatry*  
9 2014;19(3):358-367.
- 10 56. Leentjens AF, Koester J, Fruh B, Shephard DT, Barone P, Houben JJ. The effect of  
11 pramipexole on mood and motivational symptoms in Parkinson's disease: a meta-analysis of  
12 placebo-controlled studies. *Clin Ther* 2009;31(1):89-98.
- 13 57. Favier M, Duran T, Carcenac C, Drui G, Savasta M, Carnicella S. Pramipexole  
14 reverses Parkinson's disease-related motivational deficits in rats. *Movement disorders :*  
15 *official journal of the Movement Disorder Society* 2014;29(7):912-920.
- 16 58. Carcenac C, Favier M, Vachez Y, et al. Subthalamic deep brain stimulation differently  
17 alters striatal dopaminergic receptor levels in rats. *Movement disorders : official journal of the*  
18 *Movement Disorder Society* 2015;30(13):1739-1749.
- 19 59. Tokunaga N, Choudhury ME, Nishikawa N, et al. Pramipexole upregulates dopamine  
20 receptor D(2) and D(3) expression in rat striatum. *J Pharmacol Sci* 2012;120(2):133-137.
- 21 60. Micallef J, Rey M, Eusebio A, et al. Antiparkinsonian drug-induced sleepiness: a  
22 double-blind placebo-controlled study of L-dopa, bromocriptine and pramipexole in healthy  
23 subjects. *Br J Clin Pharmacol* 2009;67(3):333-340.
- 24 61. Castelli L, Lanotte M, Zibetti M, et al. Apathy and verbal fluency in STN-stimulated  
25 PD patients. An observational follow-up study. *Journal of neurology* 2007;254(9):1238-1243.
- 26 62. Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic  
27 nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease.  
28 *Journal of neurology, neurosurgery, and psychiatry* 2004;75(6):834-839.
- 29 63. Gervais-Bernard H, Xie-Brustolin J, Mertens P, et al. Bilateral subthalamic nucleus  
30 stimulation in advanced Parkinson's disease: five year follow-up. *Journal of neurology*  
31 2009;256(2):225-233.
- 32 64. Schupbach WM, Chastan N, Welter ML, et al. Stimulation of the subthalamic nucleus  
33 in Parkinson's disease: a 5 year follow up. *Journal of neurology, neurosurgery, and psychiatry*  
34 2005;76(12):1640-1644.
- 35 65. Temel Y, Visser-Vandewalle V, van der Wolf M, et al. Monopolar versus bipolar high  
36 frequency stimulation in the rat subthalamic nucleus: differences in histological damage.  
37 *Neuroscience letters* 2004;367(1):92-96.
- 38 66. Chaturvedi A, Lujan JL, McIntyre CC. Artificial neural network based  
39 characterization of the volume of tissue activated during deep brain stimulation. *Journal of*  
40 *neural engineering* 2013;10(5):056023.
- 41 67. Creed MC, Hamani C, Nobrega JN. Effects of repeated deep brain stimulation on  
42 depressive- and anxiety-like behavior in rats: comparing entopeduncular and subthalamic  
43 nuclei. *Brain Stimul* 2013;6(4):506-514.
- 44 68. Aleksandrova LR, Creed MC, Fletcher PJ, Lobo DS, Hamani C, Nobrega JN. Deep  
45 brain stimulation of the subthalamic nucleus increases premature responding in a rat gambling  
46 task. *Behavioural brain research* 2013;245:76-82.
- 47 69. Darbaky Y, Forni C, Amalric M, Baunez C. High frequency stimulation of the  
48 subthalamic nucleus has beneficial antiparkinsonian effects on motor functions in rats, but  
49 less efficiency in a choice reaction time task. *Eur J Neurosci* 2003;18(4):951-956.

## STN-DBS and Apathy in Parkinson's Disease

- 1 70. Abulseoud OA, Kasasbeh A, Min HK, et al. Stimulation-Induced Transient Nonmotor  
2 Psychiatric Symptoms following Subthalamic Deep Brain Stimulation in Patients with  
3 Parkinson's Disease: Association with Clinical Outcomes and Neuroanatomical Correlates.  
4 *Stereotactic and functional neurosurgery* 2016;94(2):93-101.
- 5 71. Simmons DB, Dashtipour K. The Quantitative Measurement of Reversible Acute  
6 Depression after Subthalamic Deep Brain Stimulation in a Patient with Parkinson Disease.  
7 *Case reports in neurological medicine* 2015;2015:165846.
- 8 72. Alkemade A, Schnitzler A, Forstmann BU. Topographic organization of the human  
9 and non-human primate subthalamic nucleus. *Brain Struct Funct* 2015;220(6):3075-3086.
- 10 73. Lambert C, Zrinzo L, Nagy Z, et al. Confirmation of functional zones within the  
11 human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion  
12 weighted imaging. *NeuroImage* 2012;60(1):83-94.
- 13 74. Mallet L, Schupbach M, N'Diaye K, et al. Stimulation of subterritories of the  
14 subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of  
15 behavior. *Proc Natl Acad Sci U S A* 2007;104(25):10661-10666.
- 16 75. Stefurak T, Mikulis D, Mayberg H, et al. Deep brain stimulation for Parkinson's  
17 disease dissociates mood and motor circuits: a functional MRI case study. *Movement  
18 disorders : official journal of the Movement Disorder Society* 2003;18(12):1508-1516.
- 19 76. Roji R, Centeno C. The use of methylphenidate to relieve fatigue. *Current opinion in  
20 supportive and palliative care* 2017;11(4):299-305.
- 21 77. Skorvanek M, Gdovinova Z, Rosenberger J, et al. The associations between fatigue,  
22 apathy, and depression in Parkinson's disease. *Acta Neurol Scand* 2015;131(2):80-87.
- 23 78. Benazzouz A, Gao D, Ni Z, Benabid AL. High frequency stimulation of the STN  
24 influences the activity of dopamine neurons in the rat. *Neuroreport* 2000;11(7):1593-1596.
- 25 79. Min HK, Ross EK, Jo HJ, et al. Dopamine Release in the Nonhuman Primate Caudate  
26 and Putamen Depends upon Site of Stimulation in the Subthalamic Nucleus. *The Journal of  
27 neuroscience : the official journal of the Society for Neuroscience* 2016;36(22):6022-6029.
- 28 80. Bruet N, Windels F, Bertrand A, Feuerstein C, Poupard A, Savasta M. High frequency  
29 stimulation of the subthalamic nucleus increases the extracellular contents of striatal  
30 dopamine in normal and partially dopaminergic denervated rats. *J Neuropathol Exp Neurol*  
31 2001;60(1):15-24.
- 32 81. Kocabicak E, Jahanshahi A, Schonfeld L, Heschem SA, Temel Y, Tan S. Deep Brain  
33 Stimulation of the Rat Subthalamic Nucleus Induced Inhibition of Median Raphe  
34 Serotonergic and Dopaminergic Neurotransmission. *Turk Neurosurg* 2015;25(5):721-727.
- 35 82. Zhao XD, Cao YQ, Liu HH, Li FQ, You BM, Zhou XP. Long term high frequency  
36 stimulation of STN increases dopamine in the corpus striatum of hemiparkinsonian rhesus  
37 monkey. *Brain Res* 2009;1286:230-238.
- 38 83. Belin D, Everitt BJ. Cocaine seeking habits depend upon dopamine-dependent serial  
39 connectivity linking the ventral with the dorsal striatum. *Neuron* 2008;57(3):432-441.
- 40 84. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human  
41 imaging. *Neuropsychopharmacology : official publication of the American College of  
42 Neuropsychopharmacology* 2010;35(1):4-26.
- 43 85. Bjorklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. *Trends  
44 in neurosciences* 2007;30(5):194-202.
- 45 86. Gittis AH, Kreitzer AC. Striatal microcircuitry and movement disorders. *Trends in  
46 neurosciences* 2012;35(9):557-564.
- 47 87. Sesack SR, Grace AA. Cortico-Basal Ganglia reward network: microcircuitry.  
48 *Neuropsychopharmacology : official publication of the American College of  
49 Neuropsychopharmacology* 2010;35(1):27-47.



## STN-DBS and Apathy in Parkinson's Disease

- 1 88. Simon MJ, Higuera-Matas A, Roura-Martinez D, et al. Changes in D1 but not D2  
2 dopamine or mu-opioid receptor expression in limbic and motor structures after lateral  
3 hypothalamus electrical self-stimulation: A quantitative autoradiographic study. *Neurobiology*  
4 *of learning and memory* 2016;127:17-26.
- 5 89. Le Foll B, Goldberg SR, Sokoloff P. The dopamine D3 receptor and drug dependence:  
6 effects on reward or beyond? *Neuropharmacology* 2005;49(4):525-541.
- 7 90. Simpson EH, Winiger V, Biezonski DK, Haq I, Kandel ER, Kellendonk C. Selective  
8 overexpression of dopamine D3 receptors in the striatum disrupts motivation but not  
9 cognition. *Biol Psychiatry* 2014;76(10):823-831.
- 10 91. Drew MR, Simpson EH, Kellendonk C, et al. Transient overexpression of striatal D2  
11 receptors impairs operant motivation and interval timing. *The Journal of neuroscience : the*  
12 *official journal of the Society for Neuroscience* 2007;27(29):7731-7739.
- 13 92. Trifilieff P, Feng B, Urizar E, et al. Increasing dopamine D2 receptor expression in the  
14 adult nucleus accumbens enhances motivation. *Mol Psychiatry* 2013;18(9):1025-1033.
- 15 93. Ishibashi K, Ishii K, Oda K, Mizusawa H, Ishiwata K. Binding of pramipexole to  
16 extrastriatal dopamine D2/D3 receptors in the human brain: a positron emission tomography  
17 study using 11C-FLB 457. *PloS one* 2011;6(3):e17723.
- 18 94. Knight EJ, Testini P, Min HK, et al. Motor and Nonmotor Circuitry Activation  
19 Induced by Subthalamic Nucleus Deep Brain Stimulation in Patients With Parkinson Disease:  
20 Intraoperative Functional Magnetic Resonance Imaging for Deep Brain Stimulation. *Mayo*  
21 *Clinic proceedings* 2015;90(6):773-785.
- 22 95. Carriere N, Besson P, Dujardin K, et al. Apathy in Parkinson's disease is associated  
23 with nucleus accumbens atrophy: a magnetic resonance imaging shape analysis. *Movement*  
24 *disorders : official journal of the Movement Disorder Society* 2014;29(7):897-903.
- 25 96. Reijnders JS, Scholtissen B, Weber WE, Aalten P, Verhey FR, Leentjens AF.  
26 Neuroanatomical correlates of apathy in Parkinson's disease: A magnetic resonance imaging  
27 study using voxel-based morphometry. *Movement disorders : official journal of the*  
28 *Movement Disorder Society* 2010;25(14):2318-2325.
- 29 97. Maillet A, Krack P, Lhommee E, et al. The prominent role of serotonergic  
30 degeneration in apathy, anxiety and depression in de novo Parkinson's disease. *Brain : a*  
31 *journal of neurology* 2016;139(Pt 9):2486-2502.
- 32 98. Creed MC, Hamani C, Bridgman A, Fletcher PJ, Nobrega JN. Contribution of  
33 decreased serotonin release to the antidyskinetic effects of deep brain stimulation in a rodent  
34 model of tardive dyskinesia: comparison of the subthalamic and entopeduncular nuclei. *The*  
35 *Journal of neuroscience : the official journal of the Society for Neuroscience*  
36 2012;32(28):9574-9581.
- 37 99. Chang WL, Breier MR, Yang A, Swerdlow NR. Disparate effects of pramipexole on  
38 locomotor activity and sensorimotor gating in Sprague-Dawley rats. *Pharmacol Biochem*  
39 *Behav* 2011;99(4):634-638.
- 40 100. Riddle JL, Rokosik SL, Napier TC. Pramipexole- and methamphetamine-induced  
41 reward-mediated behavior in a rodent model of Parkinson's disease and controls. *Behavioural*  
42 *brain research* 2012;233(1):15-23.
- 43 101. Favier M, Carcenac C, Drui G, et al. Implication of dorsostriatal D3 receptors in  
44 motivational processes: a potential target for neuropsychiatric symptoms in Parkinson's  
45 disease. *Sci Rep* 2017;7:41589.
- 46 102. Hurley MJ, Jenner P. What has been learnt from study of dopamine receptors in  
47 Parkinson's disease? *Pharmacol Ther* 2006;111(3):715-728.
- 48 103. Marin-Lahoz J, Pagonabarraga J, Martinez-Horta S, et al. Parkinson's Disease:  
49 Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. *Frontiers*  
50 *in psychiatry* 2018;9:465.

## STN-DBS and Apathy in Parkinson's Disease

104. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 2010;67(5):589-595.
105. Houeto JL, Magnard R, Dalley JW, Belin D, Carnicella S. Trait Impulsivity and Anhedonia: Two Gateways for the Development of Impulse Control Disorders in Parkinson's Disease? *Front Psychiatry* 2016;7:91.
106. Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ. High impulsivity predicts the switch to compulsive cocaine-taking. *Science (New York, NY)* 2008;320(5881):1352-1355.
107. Scangos KW, Shahlaie K. Acute Frequency-Dependent Hypomania Induced by Ventral Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: A Case Report. *Biological psychiatry* 2017;82(5):e39-e41.
108. Welter ML, Schupbach M, Czernecki V, et al. Optimal target localization for subthalamic stimulation in patients with Parkinson disease. *Neurology* 2014;82(15):1352-1361.
109. Pelloux Y, Meffre J, Giorla E, Baunez C. The subthalamic nucleus keeps you high on emotion: behavioral consequences of its inactivation. *Frontiers in behavioral neuroscience* 2014;8:414.
110. Ardouin C, Voon V, Worbe Y, et al. Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. *Movement disorders : official journal of the Movement Disorder Society* 2006;21(11):1941-1946.
111. Bandini F, Primavera A, Pizzorno M, Cocito L. Using STN DBS and medication reduction as a strategy to treat pathological gambling in Parkinson's disease. *Parkinsonism & related disorders* 2007;13(6):369-371.
112. Knobel D, Aybek S, Pollo C, Vingerhoets FJ, Berney A. Rapid resolution of dopamine dysregulation syndrome (DDS) after subthalamic DBS for Parkinson disease (PD): a case report. *Cognitive and behavioral neurology : official journal of the Society for Behavioral and Cognitive Neurology* 2008;21(3):187-189.
113. Witjas T, Baunez C, Henry JM, et al. Addiction in Parkinson's disease: impact of subthalamic nucleus deep brain stimulation. *Movement disorders : official journal of the Movement Disorder Society* 2005;20(8):1052-1055.
114. Castrioto A, Carnicella S, Fraix V, Chabardes S, Moro E, Krack P. Reversing dopaminergic sensitization. *Movement disorders : official journal of the Movement Disorder Society* 2017;32(12):1679-1683.
115. Pelloux Y, Baunez C. Deep brain stimulation for addiction: why the subthalamic nucleus should be favored. *Curr Opin Neurobiol* 2013;23(4):713-720.
116. Tan SK, Janssen ML, Jahanshahi A, et al. High frequency stimulation of the subthalamic nucleus increases c-fos immunoreactivity in the dorsal raphe nucleus and afferent brain regions. *J Psychiatr Res* 2011;45(10):1307-1315.
117. Martinez D, Gil R, Slifstein M, et al. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biological psychiatry* 2005;58(10):779-786.
118. Barak S, Carnicella S, Yowell QV, Ron D. Glial cell line-derived neurotrophic factor reverses alcohol-induced allostasis of the mesolimbic dopaminergic system: implications for alcohol reward and seeking. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2011;31(27):9885-9894.
119. Martinez D, Greene K, Broft A, et al. Lower level of endogenous dopamine in patients with cocaine dependence: findings from PET imaging of D(2)/D(3) receptors following acute dopamine depletion. *The American journal of psychiatry* 2009;166(10):1170-1177.
120. Le Moal M, Koob GF. Drug addiction: pathways to the disease and pathophysiological perspectives. *Eur Neuropsychopharmacol* 2007;17(6-7):377-393.
121. Paxinos G WC. *The rat brain in stereotaxic coordinates*. 1998.

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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.<sup>121</sup> Each bar represents the placement of one electrode. **(C)** and **(D)** Example of electrode trace within the left STN stimulated at 100  $\mu$ A **(C)** or 225  $\mu$ 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.<sup>121</sup> 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



## STN-DBS and Apathy in Parkinson's Disease

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

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

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

## STN-DBS and Apathy in Parkinson's Disease

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2  
3 1 **FIGURE 4:** STN-DBS exacerbates the deficit of preparatory behaviors of the existing  
4 motivational deficit in a rodent model of the neuropsychiatric symptoms of PD. **(A)** Time  
5 2 course of the sucrose self-administration experiment. STN-DBS decreased the number of  
6 3 sucrose deliveries. PPX induced a complete reversion of this deficit. **(B)** Mean sucrose  
7 4 deliveries over the last 5 days of experiment. **(C)** STN-DBS and PPX did not alter the  
8 5 preference for sucrose in 6-OHDA rats. Lesion + Veh: n = 6; Lesion + PPX: n = 4; Lesion +  
9 6 STN-DBS + Veh: n = 5; Lesion + STN-DBS + PPX: n = 5. Data shown as means  $\pm$  SEM.  
10 7 Lesion + Veh versus Lesion + STN-DBS + Veh:  $*p < .05$ ; Lesion + STN-DBS + Veh versus  
11 8 Lesion + STN-DBS + PPX:  $\#p < .05$ .

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24 11 **FIGURE 5:** Subthalamic nucleus deep brain stimulation (STN-DBS) or pramipexole (PPX)  
25 12 individually promote hypoactivity but do not impair motor abilities. **(A)** Total distance traveled  
26 13 during a 1h open area test. STN-DBS induced a non-significant tendency towards decreased  
27 14 basal locomotor activity. In non-stimulated rats, PPX induced a dramatic decrease in the  
28 15 distance traveled. The combination of both treatments increased activity. **(B)** STN-DBS and  
29 16 PPX did not change the mean ambulatory speed during the open area test. **(C)** STN-DBS  
30 17 and/or PPX did not alter the fine motor skills of front limbs as demonstrated by adjusting  
31 18 steps in the course of the stepping test. Lesion + Veh: n = 6; Lesion + PPX: n = 4; Lesion +  
32 19 STN-DBS + Veh: n = 5; Lesion + STN-DBS + PPX: n = 5. Data shown as means  $\pm$  SEM.  
33 20 Lesion + PPX versus Lesion + STN-DBS + PPX:  $*p < .05$ .

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Figure 1

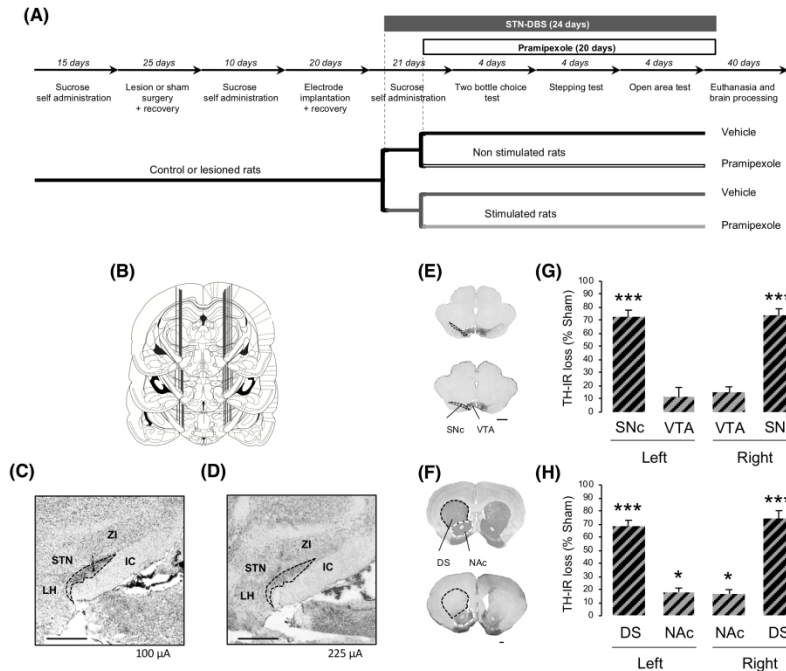


FIGURE 1: Experimental design and electrode implantation.

(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.<sup>119</sup> Each bar represents the placement of one electrode. (C) and (D) Example of electrode trace

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3 within the left STN stimulated at 100  $\mu$ A (C) or 225  $\mu$ A (D), after Cresyl violet staining. Scale bar: 1 mm. IC,  
4 Internal Capsule; LH, Lateral Hypothalamus; ZI, Zona Incerta.

5 (E) and (F) Representative photomicrographs of coronal sections stained for tyrosine hydroxylase (TH) in  
6 striatal (bottom, 1.6 mm to bregma) and mesencephalic (top, -5.6 mm to bregma) regions from naïve (top)  
7 and lesioned (bottom) rats.119 Scale bar = 1 mm. (G, H) Quantification of TH Immuno Reactivity (IR) loss  
8 in the midbrain (G) and the striatum (H), expressed as percentage difference in the mean value obtained for  
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11 Veh: n = 22; Lesion: n = 20. Control + Veh versus Lesion: \*p < .05; \*\*\*p < .001. DS: dorsal striatum;  
12 NAc: nucleus accumbens; SNc: substantia nigra compacta, VTA: ventral tegmental area.

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Figure 2

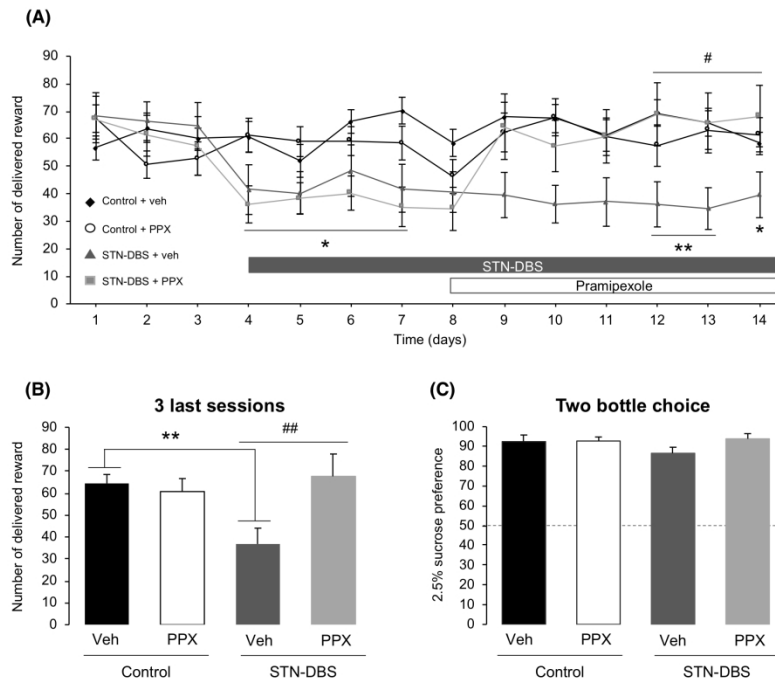


FIGURE 2: Subthalamic nucleus deep brain stimulation (STN-DBS) induces a deficit of preparatory behaviors in 2.5% sucrose self-administration that is rescued by pramipexole (PPX). (A) Time course of the sucrose self-administration experiment. STN-DBS induced a significant decrease of the number of sucrose deliveries. Pramipexole induced a total reversion of this deficit. (B) Mean sucrose deliveries over the last 3 days of experiment. (C) Subthalamic nucleus deep brain stimulation (STN-DBS) and pramipexole (PPX) do 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:  $\#p < .05$ ;  $\#\#p < .01$ .

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Figure 3

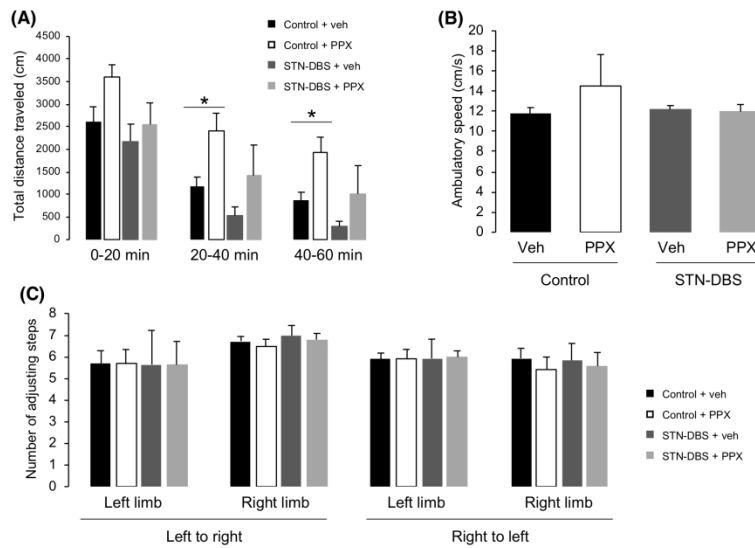


FIGURE 3: Subthalamic nucleus deep brain stimulation (STN-DBS) and pramipexole (PPX) promote hypo and hyper locomotor activity respectively but do not impair motor abilities. (A) Total distance travelled during a 1h open area test. STN-DBS induced a non-significant tendency towards decreased basal locomotor activity that was counteracted by treatment with pramipexole. In control rats, pramipexole induced a dramatic increase in the distance traveled. (B) STN-DBS and pramipexole did not change the mean ambulatory speed during the last 2 periods of the open area test. (C) STN-DBS and/or pramipexole 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

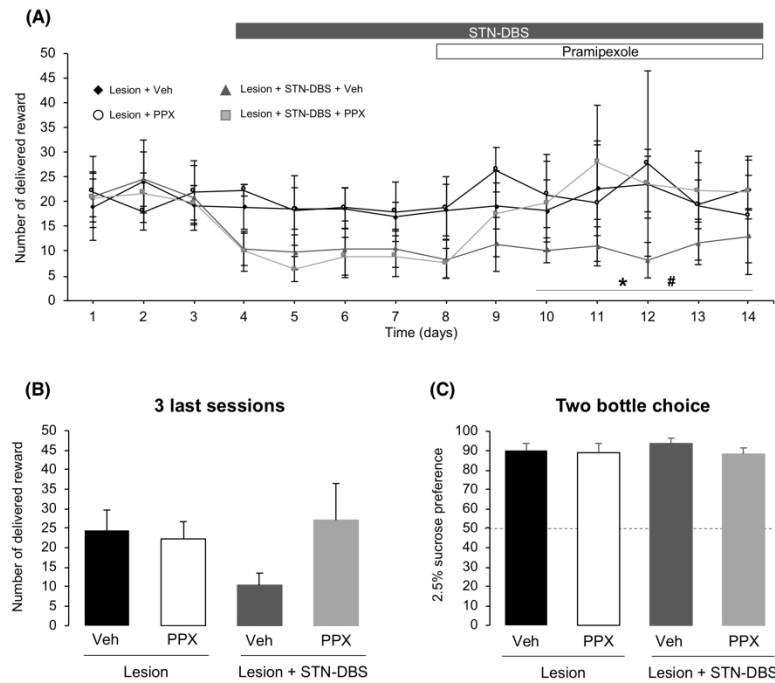


FIGURE 4: STN-DBS exacerbates the deficit of preparatory behaviors of the existing motivational deficit in a rodent model of the neuropsychiatric symptoms of PD. (A) Time course of the sucrose self-administration experiment. STN-DBS induced a decrease of the number of sucrose deliveries. Pramipexole induced a complete reversion of this deficit. (B) Mean sucrose deliveries over the last 5 days of experiment. (C) Subthalamic nucleus deep brain stimulation (STN-DBS) and pramipexole (PPX) do 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:  $\#p < .05$ .

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Figure 5

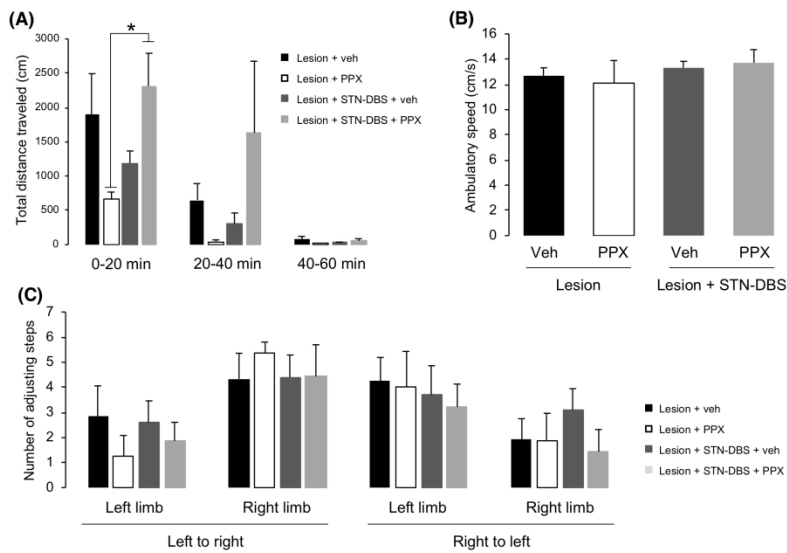


FIGURE 5: Subthalamic nucleus deep brain stimulation (STN-DBS) and pramipexole (PPX) individually promotes hypoactivity but do not impair motor abilities. (A) Total distance travelled during a 1h open area test. STN-DBS induced a non-significant tendency towards decreased basal locomotor activity. In non-stimulated rats, pramipexole induced a dramatic decrease in the distance traveled. The combination of both treatments increased activity. (B) STN-DBS and pramipexole did not change the mean ambulatory speed during the open area test. (C) STN-DBS and/or pramipexole 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 ± SEM. Lesion + PPX versus Lesion + STN-DBS + PPX: \*p < .05.

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# 1 Subthalamic nucleus stimulation impairs motivation: implication for apathy in 2 Parkinson's disease

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9 4 Yvan Vachez, PhD<sup>1,2</sup>, Carole Carcenac, PhD<sup>1,2</sup>, Robin Magnard, PhD<sup>1,2</sup>, Lydia Kerkerian -Le Goff,  
10 5 PhD<sup>3</sup>, Pascal Salin, PhD<sup>3</sup>, Marc Savasta, PhD<sup>1,2</sup>, Sebastien Carnicella, PhD<sup>1,2</sup> and Sabrina Boulet,  
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## 23 Supplemental Material and Methods

### 24 *Bilateral 6-OHDA lesions*

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26 16 As previously described,<sup>1-4</sup> rats were first treated with desipramine hydrochloride (25 mg.kg<sup>-1</sup>  
27 17 in 0.9% NaCl, subcutaneously; Sigma; St Quentin-Fallavier, France) to protect noradrenergic  
28 18 neurons 30 min before 6-OHDA injection.<sup>5</sup> They were then anesthetized with a mixture of  
29 19 xylazine (15 mg.kg<sup>-1</sup>, i.p) and ketamine (100 mg.kg<sup>-1</sup>, i.p) and secured in a Kopf stereotaxic  
30 20 apparatus (Phymep, Paris, France). As previously described<sup>2</sup>, 6 µg of 6-OHDA dissolved in  
31 21 2.3 µl sterile 0.9% NaCl with 0.2% ascorbic acid (Sigma), or 2.3 µl of vehicle (0.9% NaCl,  
32 22 0.02% ascorbic acid) were injected bilaterally, at a flow rate of 0.5 µl min<sup>-1</sup>. The stereotaxic  
33 23 coordinates of the injection site relative to bregma according to the stereotaxic atlas of  
34 24 Paxinos and Watson<sup>6</sup> were as follows: anteroposterior (AP), -5.4 mm; mediolateral (L), ±1.8  
35 25 mm, and dorsoventral (DV), -8.1 mm; with the incisor bar at +3.2 mm below the interaural  
36 26 plane. The cannulae were left in position for 5 min after each injection to allow absorption of  
37 27 the solution without spreading. After recovery from anesthesia, the animals were returned to  
38 28 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  $\mu\text{m}$  exposed end (wire diameter, 110  $\mu\text{m}$  insulated, 76  $\mu\text{m}$  bare, PT-IR Teflon, Phymep, Paris, France). Stereotaxic coordinates (relative to bregma, according to the stereotaxic atlas of Paxinos and Watson<sup>6</sup>) were: AP, -3.8 mm; L,  $\pm 2.4$  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.<sup>7</sup> 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 patients<sup>8</sup> as well as in studies describing apathy under STN-DBS.<sup>9-15</sup> Furthermore, a preclinical study in rat has clearly demonstrated that it reduces tissue damage compared to bipolar stimulation.<sup>16</sup> 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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3 1 The frequency and pulse width used, 130 Hz and 60  $\mu$ s respectively, were similar to those  
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5 2 applied in humans. For each animal, the intensity was gradually increased until dyskinetic  
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7 3 movement of the contralateral forelimb appeared as previously described<sup>17</sup> and then  
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9 4 adjusted just below this pro-dyskinetic threshold. This value was conserved throughout the  
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11 5 study. The stimulation intensity was 183  $\pm$  13  $\mu$ A on average and ranged between 100 and  
12  
13  
14 6 225  $\mu$ A.  
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16 7

### 8 ***Behavioral procedures***

9 Rats were not food or water deprived during the experimental procedures.

#### 10 *Sucrose self-administration*

11 Rats were trained to work for 2.5% sucrose reward, chosen for its relatively moderate  
12  
13 rewarding outcome, in a self-administration task in operant chambers (Med Associates, St  
14  
15 Albans, VT, USA) under a fixed ratio 1 reinforcement schedule. Rats were given the choice  
16  
17 between two levers: an active and reinforced one, delivering 0.2 ml sucrose solution in a  
18  
19 receptacle when pressed, and an inactive, non-reinforced lever, producing nothing<sup>1-4</sup>.

#### 20 *Two bottle choice*

21 In their home cage, rats were given continuous access to two graduated 250 ml plastic  
22  
23 bottles (Techniplast, Lyon, France), for 3 days. One bottle contained tap water, whereas the  
24  
25 other contained 2.5% sucrose (Sigma) in tap water. Rats and bottles were weighed daily,  
26  
27 with the position of the bottles (left or right) alternated to control for side preference. The first  
28  
29 day was for acclimatation. The volumes of sucrose solution and water consumed on the  
30  
31 second and third days were averaged to determine preference for sucrose over water  
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33 (sucrose intake/total intake, expressed as a percentage).  
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3 1 *Stepping test*  
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5 2 Animals were moved sideways along a smooth-surfaced table over 90 cm and the number of  
6  
7 3 forelimb adjusting steps measured. The test was carried out three times for each paw.  
8

9 4  
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11 5 *Open area*  
12

13 6 Rats were placed in a dimly lit white Perspex (Castorama, Saint Martin d'Hères, France)  
14  
15 7 open arena (50 x 25 x 40cm) and horizontal distances traveled were recorded with a video-  
16  
17 8 tracking system to assess locomotor and basal activity (Viewpoint S.A., Champagne au Mont  
18  
19 9 d'Or, France), over a 1h period.  
20  
21

22 10

23  
24 11 *Histological analysis*  
25

26 12 Briefly, rats were sacrificed under chloral hydrate anesthesia at the end of the behavioral  
27  
28 13 experiments, intracardially perfused with NaCl (0.9%) and their brains frozen in cooled  
29  
30 14 isopentane (-40°C) and stored at -30°C. Serial coronal sections (14 µm-thick) of striatum,  
31  
32 15 mesencephalon and subthalamic nucleus were cut with a cryostat (Microm HM 500, Microm,  
33  
34 16 Francheville, France), collected on slides and stored at -30°C.  
35  
36

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38  
39 18 *Immunohistochemistry:*  
40

41 19 Immunohistochemical analysis was performed as previously described.<sup>2, 17</sup> 14 µm-thick  
42  
43 20 coronal sections from the striatum and the mesencephalon were incubated with an anti-TH  
44  
45 21 antibody, and then with a biotinylated goat anti-mouse IgG antibody. Immunoreactivity was  
46  
47 22 visualized with avidin-peroxidase conjugate.  
48  
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50 23

51 24 *Quantification of the extent of the striatal DA denervation*  
52

53 25 As described previously,<sup>2</sup> TH immunoreactivity (TH-IR) was quantified with the ICS  
54  
55 26 FrameWork computerized image analysis system (TRIBVN, 2.9.2 version, Châtillon, France)  
56  
57 27 coupled to a light microscope (Nikon, Eclipse 80i) and a Pike F-421C camera (ALLIED Vision  
58  
59 28 Technologies, Stadroda, Germany) for digitalization of the DS and the NAc (+ 0.7 to 2.2 mm  
60

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.

#### 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.

#### 17 **Supplemental Figure and Figure Legend:**

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

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

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3 1 Veh: n = 6; Lesion PPX: n = 5. Control Veh versus Lesion Veh:  $###p < .001$ ; Control PPX  
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5 2 versus Lesion PPX:  $##p < .01$ .  
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For Peer Review



1. Carnicella S, Drui G, Boulet S, et al. Implication of dopamine D3 receptor activation in the reversion of Parkinson's disease-related motivational deficits. *Translational psychiatry* 2014;4:e401.
2. Drui G, Carnicella S, Carcenac C, et al. Loss of dopaminergic nigrostriatal neurons accounts for the motivational and affective deficits in Parkinson's disease. *Molecular psychiatry* 2014;19(3):358-367.
3. Favier M, Carcenac C, Drui G, et al. Implication of dorsostriatal D3 receptors in motivational processes: a potential target for neuropsychiatric symptoms in Parkinson's disease. *Scientific reports* 2017;7:41589.
4. Favier M, Duran T, Carcenac C, Drui G, Savasta M, Carnicella S. Pramipexole reverses Parkinson's disease-related motivational deficits in rats. *Movement disorders : official journal of the Movement Disorder Society* 2014;29(7):912-920.
5. Schwarting RK, Huston JP. Unilateral 6-hydroxydopamine lesions of meso-striatal dopamine neurons and their physiological sequelae. *Progress in neurobiology* 1996;49(3):215-266.
6. Paxinos G WC. *The rat brain in stereotaxic coordinates*. 1998.
7. Forni C, Mainard O, Melon C, Goguenheim D, Kerkerian-Le Goff L, Salin P. Portable microstimulator for chronic deep brain stimulation in freely moving rats. *Journal of neuroscience methods* 2012;209(1):50-57.
8. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *The Lancet Neurology* 2009;8(1):67-81.
9. Drapier D, Drapier S, Sauleau P, et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? *Journal of neurology* 2006;253(8):1083-1091.
10. Thobois S, Ardouin C, Lhomme E, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain : a journal of neurology* 2010;133(Pt 4):1111-1127.
11. Castelli L, Lanotte M, Zibetti M, et al. Apathy and verbal fluency in STN-stimulated PD patients. An observational follow-up study. *Journal of neurology* 2007;254(9):1238-1243.
12. Castelli L, Perozzo P, Zibetti M, et al. Chronic deep brain stimulation of the subthalamic nucleus for Parkinson's disease: effects on cognition, mood, anxiety and personality traits. *European neurology* 2006;55(3):136-144.
13. Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry* 2004;75(6):834-839.
14. Gervais-Bernard H, Xie-Brustolin J, Mertens P, et al. Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: five year follow-up. *Journal of neurology* 2009;256(2):225-233.
15. Schupbach WM, Chastan N, Welter ML, et al. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. *Journal of neurology, neurosurgery, and psychiatry* 2005;76(12):1640-1644.
16. Temel Y, Visser-Vandewalle V, van der Wolf M, et al. Monopolar versus bipolar high frequency stimulation in the rat subthalamic nucleus: differences in histological damage. *Neuroscience letters* 2004;367(1):92-96.
17. Boulet S, Lacombe E, Carcenac C, et al. Subthalamic stimulation-induced forelimb dyskinesias are linked to an increase in glutamate levels in the substantia nigra pars reticulata. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2006;26(42):10768-10776.

Supplemental figure 1

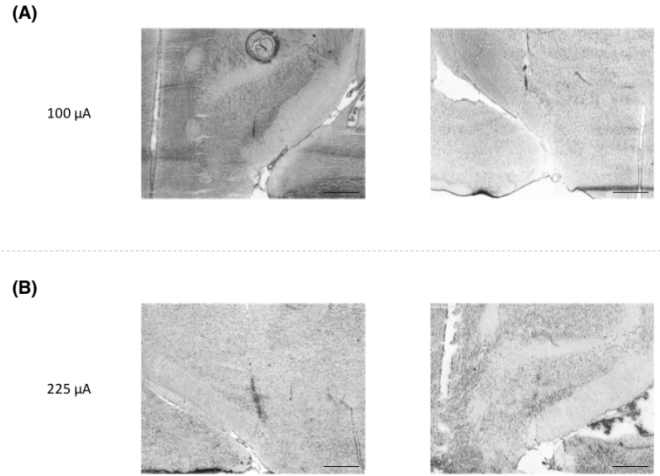


FIGURE S1: Example of electrode trace and tissue state in animals stimulated at 100  $\mu$ A (A) or 225  $\mu$ A (B), after Cresyl violet staining. Scale bar: 1 mm.

190x275mm (150 x 150 DPI)

Supplemental figure 2

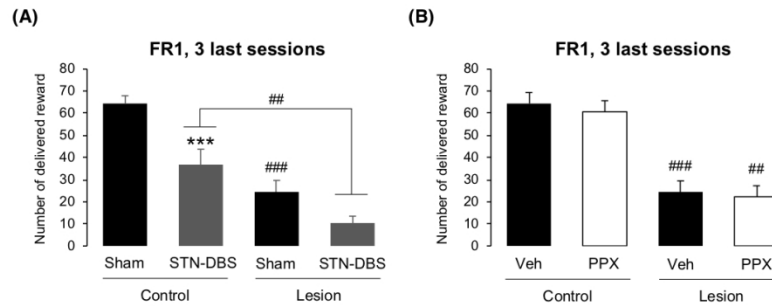


FIGURE S2: Comparison of the effects of STN-DBS (A) or PPX treatment (B) in control and lesioned animals on the mean sucrose deliveries over the last 3 days of sucrose self-administration experiment. Data shown as means  $\pm$  SEM. (A) Control Sham:  $n = 22$ ; Control STN-DBS:  $n = 13$ ; Lesion Sham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