Bilateral but not unilateral subthalamic stimulation promotes apathy: a translational study in rodents and Parkinson's disease patients

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Conflict of interest statement

The authors have declared that no conflict of interest exists

ABSTRACT

Apathy is frequently reported in Parkinson's disease (PD) patients under subthalamic nucleus deep brain stimulation (STN-DBS). The prevailing clinical view for apathy following STN-DBS is the reduction of dopaminergic medication. However, few clinical reports and recent experimental data suggested the pathogenicity of bilateral STN-DBS on motivation, challenging the leading opinion. Here, we investigate whether bilateralism of STN-DBS influences apathy outcome after STN-DBS, combining pre-clinical and clinical approaches. We assess the motivational effects of chronic unilateral STN-DBS in rats in the exact same conditions having highlighted a loss of motivation under bilateral STN-DBS. Clinical data are obtained by the follow-up of a cohort of parkinsonian patients undergoing unilateral STN-DBS and coming from the clinical center that described apathy related to bilateral STN-DBS itself. Despite an acute effect, which fades rapidly, unilateral STN-DBS did not induce a loss of motivation reminiscent to apathy in rats. In patients, apathy did not increase between the preoperative and the post-operative assessment. Together, those data demonstrate that bilateral but not unilateral STN-DBS can induce a loss of motivation in both rats and patients. This constitutes another evidence of the role of STN-DBS itself for apathy in PD.

Introduction

Subthalamic nucleus (STN) deep brain stimulation (DBS) is a well-established alternative treatment for Parkinson's disease (PD) patients for whom classical pharmacological treatments became ineffective(1). According to the gravity of the disease and the presence, or not, of symptoms in both hemi bodies, STN-DBS is applied in an unilateral or bilateral fashion and permits to efficiently alleviate motor disturbances(1, 2). Despite its manifest therapeutic benefits, STN-DBS effects on PD non-motor symptoms still represent a grey area(3, 4). Numerous emotional, behavioral and cognitive side-effects are frequently reported(5-8), but in most cases, it is complicated to dissociate effects originating from STN-DBS, pharmacological treatments or the progression of the disease itself(5). Among those symptoms, apathy is certainly the one for which STN-DBS impact has been the most controversial. With depression and anxiety, apathy represents the core neuropsychiatric symptoms of PD(9) and is often present in *de novo* patient(10-12). This symptom is characterized by a loss of motivation or a reduction in goal-directed behaviors, not attributable to diminished level of consciousness, cognitive impairment, or emotional distress(9, 13, 14). Inducement or aggravation of apathy is one of the most reported non-motor side effect of STN-DBS, with a dramatic reduction in daily activities, and it can completely neutralize the quality of life improvement permitted by this neurosurgical treatment(5, 15-20).

Parkinsonian apathy, following STN-DBS or not, can be alleviated by dopaminergic pharmacotherapies(12, 21, 22). Furthermore, functional imaging studies suggest the implication of the dopaminergic degenerative process for apathy apparition in non-stimulated patient(23). In line with this assumption, we demonstrated in experimental approaches in rodents(24) the implication of the loss of substantia nigra pars compacta dopaminergic neurons for this loss of motivation in a rodent model of neuropsychiatric symptoms of PD (25), as well as the therapeutic contribution of dopaminergic agonists, especially those targeting the D_2R and D_3R(26, 27). Thus, because STN-DBS classically permits to reduce the dopaminergic treatments(28), apathy following STN-DBS apathy was commonly attributed to the resurgence of pre-existing apathy revealed by the reduction or withdrawal of dopatherapy rather than to

an effect of STN-DBS itself (29, 30).

Yet, we reported clinical cases of apathy after bilateral STN-DBS which were not correlated with the reduction of the pharmacotherapy, strongly suggesting the pro-apathetic effect of STN-DBS(15-17, 31). To confirm those clinical observations, we combined bilateral stimulation with a wireless micro-stimulator(32) and appropriate behavioral approaches to assess STN-DBS effects on motivation in rats, and overcome the bias of the dopatherapy reduction or the progression of the disease. We showed that chronic bilateral STN-DBS negatively affect reward seeking and induce behavioral hypoactivity(33). We also demonstrated that this loss of motivation reminiscent to apathy was reversed by a D_2 and D_3 dopaminergic receptors agonist, as it can be the case in patients(21, 22). Thus, after years of debate, the combination of these clinical and fundamental data finally reconciles both hypothesis concerning post-STN-DBS apathy: in addition to the reduction of the dopaminergic treatments that reveals the impact of the DA denervation, the STN-DBS by itself can be causal for apathy apparition(33, 34).

Although we demonstrated the deleterious effect of STN-DBS applied bilaterally, those of unilateral STN-DBS remains to be investigated either in the clinic or in preclinical approaches. Bilateral STN-DBS permits strongest motor improvements(35-37), but might also induce more non motor sides-effects than unilateral STN-DBS (35, 38, 39). Thus, one can hypothesize that unilateral STN-DBS effects on apathy could be weaker. Discrepancies concerning STN-DBS neuropsychiatric effects are due to a lack of reproducibility of clinical or experimental conditions between the different studies coming from multiple centers. We, clinicians and scientists having previously described STN-DBS-induced apathy in PD patients(15-17, 31) and in rodents(33) respectively, associate in the present study to investigate if unilateral STN-DBS is sufficient or not to promote apathy. We test whether unilateral STN-DBS induces a sustainable reward seeking deficit in rats, and we confirm those results with a longitudinal follow-up of apathy in unilaterally stimulated patients. We provide a direct comparison of those results obtained with unilateral STN-DBS with the counterparts preclinical (33) and clinical (17) studies we previously achieved using bilateral STN-DBS.

Those investigations were made in the exact same conditions that the present study, in same centers and by the same clinician and scientist groups.

Results and Discussion

Experimental study

Because apathy particularly affects activity of daily living and simple tasks, motivation in rats was assessed with a sucrose fixed ratio 1 self-administration task. We previously showed that bilateral STN-DBS induces a persistent deficit in this task **(Figure 1A)**(33). Unilateral STN-DBS acutely induces from the first day a strong decrease of reward seeking, as bilateral STN-DBS(33) (**Figure 1B and C**). However, this deficit does not last and is only transient and progressively disappears with the chronicity of unilateral STN-DBS. The reward seeking deficit become non-significant from the second day and is completely absent the sixth day of stimulation. From there, control and STN-DBS rats obtain similar amount of reward throughout the rest of days. (**Figure 1B and C**). At day 10, rats under bilateral STN-DBS still exhibits a loss of motivation but not those under unilateral STN-DBS. Stimulation parameters cannot account for this difference since we used similar current amplitude (Bilateral STN-DBS: 183 ± 13 μA; unilateral: 176 ± 11 μA). The time course of the unilateral STN-DBS induced reward seeking deficit intriguingly resembles to the transient deleterious effect of unilateral STN-DBS previously observed in a choice reaction time task(40). Such ephemeral effects could indicate the progressive implementation of compensation mechanisms equilibrating the neurobiological effect of bilateral STN-DBS responsible for the sustained reward seeking deficit.

Because self-administration engages preparatory and consummatory components of motivated behavior, we next isolate the consummatory components (*i.e.* liking) by evaluating rats sensitivity to the motivational properties of sucrose in a two-bottle choice procedure. The preference for sucrose is not altered by unilateral STN-DBS, meaning that both preparatory and consummatory components are preserved **(Figure 1D)**.

In addition to cause a deficit in reward seeking deficit, bilateral STN-DBS also induces behavioral hypoactivity, highlighted in an open area task(33). Here, unilateral STN-DBS does not induce such an effect, with both control and stimulated groups travelling the same distance during the task **(Figure 2A)**. The unilateralism of STN-DBS does not induce contralateral

abnormal movement of rotation, since pattern of activity is the same for both groups **(Figure 2B)**. Furthermore, left and right limbs fine motor skills during a stepping test right after the first session of sucrose self-administration are not altered by unilateral STN-DBS. It means that the transient operant deficit cannot be attributed to a motor impairment or potential dyskinesias induced by STN-DBS **(Figure 2C)**.

Overall, aside from an acute effect, chronic unilateral STN-DBS does not affect motivated behavior in rats on the contrary to bilateral STN-DBS(33).

Clinical study

To emphasize the clinical implication of that fundamental difference between bilateral and unilateral STN-DBS on reward seeking, we complete this approach with a clinical follow-up.

Bilateral STN-DBS is applied in patients suffering from advanced stage PD or/with symmetrical symptoms whereas unilateral STN-DBS is advocated for asymmetrical and/or mild stage PD(2). Few clinical studies compared unilateral and bilateral STN-DBS in same patients, but consistently, they highlight that bilateral STN-DBS seems more effective to alleviate motor disturbances such as gait, shaking and oculomotor control(35-37, 41). Thus, it is admitted that bilateral STN-DBS induces greater therapeutic effect (2). However, bilateral STN-DBS seems also to induce more deleterious side effects, aggravating cognitive processes, verbal fluidity and weight gain in a greater proportion than unilateral stimulation(35, 38, 39). We previously made the unique description of post-STN-DBS apathy in bilaterally stimulated patients, that was not correlated to dopaminergic reduction **(Figure 3)**(15-17, 31). Here, we are providing the follow-up of patients who are treated in our center in the exact same conditions but with unilateral stimulation.

No statistically significant difference is found between the pre-operative and the postoperative conditions for patients, on the three psychiatric tests assessing apathy (AES), depression (MADRS) and anxiety (AMDP-AT) (Table 1). Individual apathy scores is identical between pre STN-DBS and post STN-DBS assessment, compared to the counterpart study using bilateral

STN-DBS(17) **(Figure 3)**. This absence of post STN-DBS apathy cannot be attributed to an ineffective stimulation or electrodes misleading, since all patients present a significant postoperative motor improvement in OFF and ON-dopa conditions, shown by UPDRS II to IV, the Hoehn and Yahr and the Schwab and England scores, (Supplemental Table 1). Furthermore, the pre-STN-DBS Levodopa-Equivalent Daily Dose (LEDD) (1162.0 ± 533.5 mg) and its reduction following the surgery (589.0 ± 302 mg) match the dose prescribed to the cohort of patients who developed apathy following bilateral STN-DBS (from 1200.0 ± 426.5 mg to 796.66 ± 620.0 mg)(17). Finally, even if the number of patients (n=11) is relatively low, it is unlikely that this prevents us to detect an apathetic effect of unilateral STN-DBS, since we were able to statistically highlight apathy inducement following bilateral STN-DBS in only 12 patients(17).

Although bilateral STN-DBS has quickly become a standard way to apply DBS, this should not be an exclusive approach for all stimulated PD patients. Efficacy and safety of unilateral STN DBS has been established in PD for patients with unilateral (42) or bilateral asymmetric motor symptoms(43), with significant effect on the ipsilateral hemi body(44, 45). In addition to present a significant motor improvement, with strong reduction of LEDD, the cohort of patients under unilateral STN-DBS also exhibit cognitive processes amelioration, whereas bilateral STN-DBS can worsen those executive function (16, 46). Unilateral STN-DBS significantly improve Stroop test performances in the “color-word” condition and in the calculated interference score (Supplemental Table 2), highlighting a strong amelioration of attentional processes. Regarding other non-motor effect, unilateral stimulation is only associated with weight gain and increased body mass index, also described in patients who underwent bilateral STN-DBS(47) and probably linked to a resting energy expenditure reduction, or improvement of gastrointestinal dysfunction(48).

In sum, in the logical continuation of our previous studies(15, 17, 31, 33) which demonstrated that, in association or not with dopaminergic treatment reduction, STN-DBS is another factor that may favor apathy apparition or worsening in PD patients, the present

translational work refines the importance of STN-DBS modality (unilateral versus bilateral) in the apparition of this side effect. Hence, it sheds light on the legitimacy to reconsider the rationale for unilateral versus bilateral STN-DBS use in PD patients regarding unilateral STN-DBS efficiency together with the lower incidence of non-motor side-effect, including apathy.

Methods

All the experimental(33) and clinical(17) procedures have previously been described and are extensively detailed in the supplementary Methods.

Study approval

Protocols used for the experimental part complied with the European Union 2010 Animal Welfare Act and the French directive 2010/63.

Oral and written informed consent was obtained for all subjects of the clinical study, which was consistent with ethical guidelines of Helsinki's Declaration.

Statistic

Statistics were performed in Graphpad prism version 8. A *P* value of 0.05 was considered significant. Experimental study: data are shown as means ± SEM. Student's t-test was used for 2 groups analysis; otherwise repeated measure or 2-way ANOVA were performed. Clinical study: data are shown as means ± SD. The Wilcoxon signed rank sum test was used to realize intra-group analyses.

Author contributions

YV, SB designed animal experiments with inputs from SC, MS. YV performed animal experiments with help from RM, CC and SB. MB, P-MD, GR, MV performed clinical assessment, clinical data collection and clinical data analysis. YV, MB, MV and SB wrote the manuscripts with inputs from all the authors.

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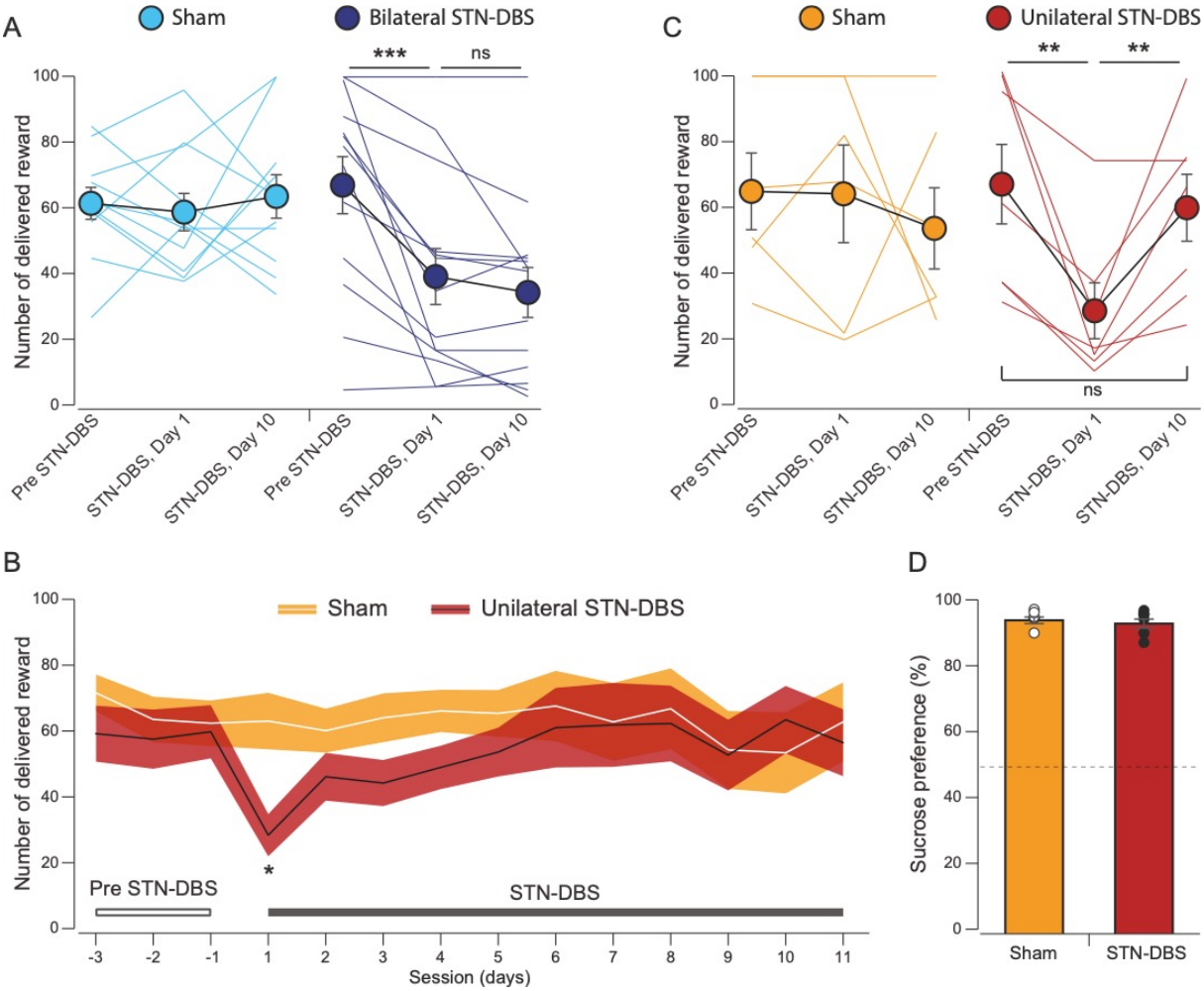

Figure 1: Unilateral STN-DBS does not reduce reward seeking. (A) Vachez et al., 2020 established that bilateral STN-DBS consistently decreased reward seeking from the first day of stimulation and this effect was stable and sustainable (RM ANOVA: Sessions effect: Sham, $F_{2,20} = 0.2259$, $P = 0.7998$; STN-DBS, $F_{2,24} = 17.34$, $P < 0.0001$). (**B**) Unilateral STN-DBS induced only an acute decrease of the number of sucrose deliveries but this was not sustained throughout days (RM ANOVA: STN-DBS effect: $F_{1,27} = 1.206$, $P = 0.2819$; Sessions effect: $F_{10,179} = 2.466$ $P = 0.0482$; STN-DBS x Session interaction: $F_{10,179} = 2.767$, $P = 0.0034$). **(C)** Unilateral STN-DBS consistently decreased reward seeking the first day of stimulation but this effect was not sustainable (RM ANOVA: Sessions effect: Sham, $F_{2,10} = 0.3613$, $P = 0.7055$; STN-DBS, $F_{2,12} = 12.36$, $P = 0.0012$). **(D)** Unilateral STN-DBS does not alter preference for sucrose over water in a two-bottle choice test ($t_1 = 0.5485$, $P = 0.5943$). Sham: n = 6-11; STN-DBS: n = 7-13. Data shown as means ± SEM. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; ns: not significant.

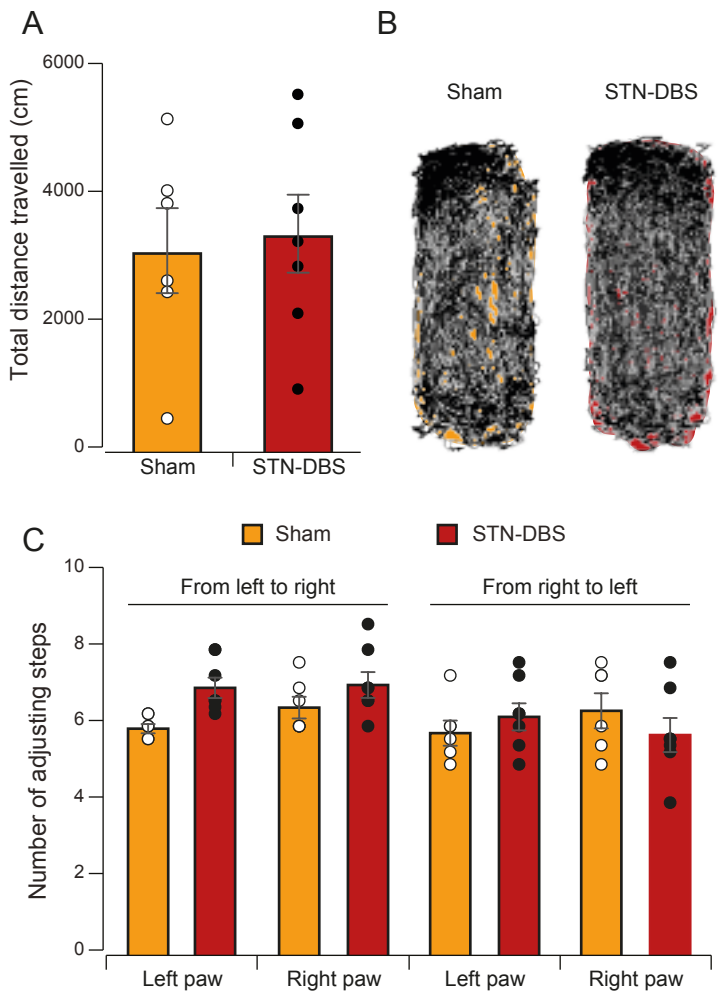

Figure 2: Unilateral STN-DBS does not alter basal locomotor activity or motor skills. Neither **(A)** the travelled distance ($t_1 = 0.2932$, $P = 0.7748$) or **(B)** the pattern of activity in an open area test was modified by unilateral STN-DBS. **(C)** Unilateral STN-DBS does not alter the fine motor skills of front limbs as demonstrated by adjusting steps in the course of the stepping test (2 way ANOVA, STN-DBS effect: $F_{1,44} = 2.1$, $P = 0.1481$; trials effect: $F_{3,44} = 2.1$, $P = 0.1180$; Interaction: $F_{3,44} = 2.1$, $P = 0.1049$). Sham: n = 6; STN-DBS: n = 7. Data shown as means ± SEM.

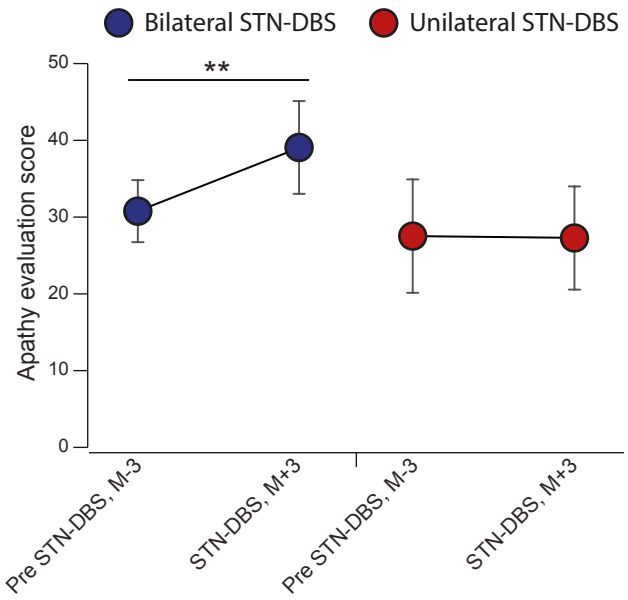

Figure 3: Bilateral but not unilateral STN-DBS induces apathy in Parkinson's disease patients. Apathy Evaluation Scale (AES) was assessed 3 months before (M-3) and after (M+3) STN-DBS was switched-ON. Le Jeune et al., 2009 demonstrated that bilateral STN-DBS promotes apathy, highlighted by a significant increase of the AES (Wilcoxon signed rank test, $P = 0.002$). On the contrary, unilateral STN-DBS does not modify the AES, highlighting an absence of apathy modification (Wilcoxon signed rank test, $P = 0.82$). Bilateral: n = 12; Unilateral: n = 11. Data shown as means ± SD.

Table 1. Psychiatric scores (mean ± SD) of patients, 3 months before (M-3) and 3 months after (M+3) unilateral STN-DBS.

Rating scales	Pre STN-DBS ON-dopa (M-3, preoperative)	STN-DBS ON-dopa (M+3, postoperative)	*p*
AES	27.36 ± 7.45	27.09 ± 6.77	0.82
MADRS	3.36 ± 3.61	2.82 ± 2.23	0.64
AMDP-AT	6.54 ± 3.75	6.09 ± 6.30	0.80

Table 1. Psychiatric rating scales of patients, 3 months before (M-3) and 3 months after (M+3) unilateral STN-DBS.

AES: Apathy Evaluation Scale; MADRS: Montgomery and Asberg Depression Rating Scale; AMDP-AT: Association for Methodology and Documentation in Psychiatry-Anxiety. Statistical significances were calculated with the Wilcoxon signed rank test.