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Basal Ganglia and Related Disorders: From Cellular and Circuit Dysfunctions to Therapy

Unilateral and Bilateral Subthalamic Deep Brain Stimulation Differently Favour Apathy in Parkinson's Disease

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ABSTRACT

The link between subthalamic nucleus deep brain stimulation (STN-DBS) and apathy in patients with Parkinson's disease (PD) remains a controversial topic. The literature is mixed and the most supported explanation is the reduction of dopaminergic treatment. Yet a body of clinical and experimental evidences suggest that STN-DBS itself can also promote apathy in certain patients. However, the parameters accounting for apathy heterogeneity in stimulated patients along with the mechanisms underlying apathy induced by STN-DBS remain to be investigated. Whether bilateral and unilateral STN-DBS have the same influence on apathy is for instance unknown. We previously and separately showed in patients and rodents that bilateral STN-DBS can promote apathy per se. Here, we compare the effect of bilateral *versus* unilateral STN-DBS both in patients and in rodents. We conducted a clinical follow-up of patients with Parkinson's disease undergoing unilateral or bilateral STN-DBS and assessing apathy 3 months before and after STN-DBS. In parallel, we applied chronic and uninterrupted unilateral or bilateral DBS in rodents and extract longitudinal motivational changes with a battery of behavioural tests. While bilateral STN-DBS promotes apathy in patients and induces a loss of motivation in rodents, we found that unilateral STN-DBS did not exert such an effect both in patients and in rats. These data show that bilateral but not unilateral STN-DBS promotes apathy. This not only substantiate the induction of neuropsychiatric effects by STN-DBS but also suggest that this might be circumvented if STN-DBS is applied unilaterally instead of bilaterally.

Abbreviations: AMDP-AS, Anxiety Scale of Association for Methodology and Documentation in Psychiatry; C-AES, Clinical Apathy Evaluation Scale; CAPIT, Core Assessment Program for Intracerebral Transplantation; DBS, deep brain stimulation; LEDD, levodopa-equivalent daily dose; MADRS, Montgomery–Åsberg Depression Rating Scale; PD, Parkinson's disease; SD, standard deviation; SEM, standard error of the mean; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

Yvan M. Vachez and Marie Bahout have equal contribution.

Marc Vérin and Sabrina Boulet are co-senior authors.

1 | Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) is a well-established alternative treatment for patients with Parkinson's disease (PD) for whom classical pharmacological treatments have become ineffective or lead to intolerable side-effects (Benabid et al. 2009). Despite its manifest therapeutic benefits for motor symptoms, STN-DBS effects on PD nonmotor symptoms still represent a grey area. Apathy is certainly the symptom for which STN-DBS impact has been the most controversial (Czernecki et al. 2005; Drapier et al. 2006), and the debate is still ongoing (Martínez-Fernández 2020; Vachez et al. 2020a; Zoon et al. 2021, 2024; Béreau et al. 2023). This syndrome is characterized by a loss of motivation accompanied by loss of emotions and flattening of affect (Marin 1996; Aarsland et al. 2009; Chaudhuri and Odin 2010). Apathy induction or aggravation following STN-DBS is frequently reported, reducing the quality of life improvement obtained with DBS (Maier et al. 2013, 2016; Castrioto et al. 2014; Martinez-Fernandez et al. 2016).

To explain this phenomenon, the main hypothesis was the resurgence of pre-existing apathy revealed by the reduction of dopatherapy following STN-DBS (Thobois et al. 2010). However, several studies reported cohorts of patients undergoing STN-DBS for whom apathy was not correlated with the reduction of the pharmacotherapy (Drapier et al. 2006; Le Jeune et al. 2009; Ricciardi et al. 2014; Zoon et al. 2019, 2023; Boon et al. 2021), suggesting that STN-DBS itself could be a factor for apathy aggravation in certain patients.

Today, this link between STN-DBS and apathy is getting more and more acknowledged. A recent meta-analysis showed that overall, apathy following STN-DBS poorly correlates with reduction of the pharmacotherapy (Zoon et al. 2020). However, apathy incidence in clinical centres across the world is still mixed, and factors favouring apathy induced by STN-DBS remain to be elucidated.

To better understand the impact of STN-DBS on motivation, experimental approaches have been undertaken on rodents, allowing a better control of experimental parameters present in patients, as the extent of the degeneration or the pharmacotherapy. These studies tend to show a decrease in motivation-related behaviour in the majority of experiments, as revealed by a meta-analysis (Vachez and Creed 2020), which also pointed out that certain DBS parameters or modalities, as the chronicity, or the electrodes polarity, can influence the magnitude of motivation decreases. However, while STN-DBS can be applied in both or in only one hemisphere depending the individual clinical picture (Benabid et al. 2000, 2009), the effect of unilateral *versus* bilateral STN-DBS on apathy or motivation has never been directly compared in the same physical clinical or research centre.

Today, STN-DBS is most commonly applied bilaterally in PD patients. Consequently, the vast majority of the literature concerning the link between STN-DBS and apathy comes from studies using bilateral STN-DBS. Whether or not the bilateralism of the stimulation is critical for apathy induction has therefore to be investigated.

Here, we have compared a cohort of patients who underwent unilateral STN-DBS with a cohort that underwent bilateral STN-DBS in our clinical centre, in the exact same conditions. To support our observations, we compared bilateral *versus* unilateral STN-DBS effects on apathetic-like behaviours in rodents, assessing motivation with a combination of behavioural tests.

2 | Materials and Methods

2.1 | Clinical Study

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

2.1.1 | Patients

The group of subjects used in this study was composed of 23 adult patients who suffered Parkinson's disease according to clinical criteria of the UK Parkinson's Disease Society Brain Bank for Idiopathic Parkinson's Disease, refractory to medical treatment, at the stage of severe ON/OFF fluctuations and dyskinesias. Among the hundred of patients who underwent STN-DBS in the Neurosurgery Department at Rennes University Hospital Center (France), between September 2006 and March 2016, a subset of patients agreed to participate to a research protocol including a psychiatric follow-up. After exclusion of patients following the criteria described below, 17 men and 6 women were included. All patients fulfilled selective criteria for this surgery, with unilateral STN-DBS proposed for patients with unilateral or very asymmetric bilateral motor symptoms. No neuropsychological disorders and no brain atrophy or vascular lesions were detected preoperatively. Exclusion criteria for STN-DBS were axial motor signs such as gait disorders or postural instability, psychiatric trouble, depression on the Montgomery–Åsberg Depression Rating Scale (MADRS), cognitive impairment on Mattis Dementia Rating Scale, executive functions trouble, which were not found for all patients. All psychiatric assessment at inclusion were realized in ON-dopa condition, accordingly to our previous studies.

Bilateral STN-DBS (12 patients): At time of surgery, mean age (± SD) of patients was 57.4 (±8.0) years. The mean disease duration (± SD) was 11.2 (±2.4) years. All patients were right-handed, accordingly to the Edinburgh Handedness Inventory criteria.

Unilateral STN-DBS (11 patients): Six patients underwent a left STN-DBS while five patients underwent a right STN-DBS. Single electrode was implanted in contralateral STN to affected hemibody; patients with right motor symptoms were implanted in left STN and patients with left symptoms in the right side. At time of surgery, mean age (± SD) of patients was 49.2 (±9.0) years. The mean disease duration (± SD) was 7.3 (±1.4) years. One patient was left-handed and 10 were right-handed. Oral and written informed consent was obtained for all subjects of this study, which was consistent with ethical guidelines of the Declaration of Helsinki.

2.1.2 | Neurosurgery and DBS

Surgery procedure has been previously described (Le Jeune et al. 2009).

Unilateral STN-DBS, mean (± SD)*:* impulse duration: 62.7 μs (± 9.0); frequency: 145 Hz (± 25.8); voltage: 2.6 V (± 0.6). The mean coordinates of the selected contact were 11.80 ± 1.25 mm lateral to the anterior commissure–posterior commissure line, 0.90 ± 1.60 mm below the anterior commissure–posterior commissure and 1.44 ± 1.30 mm posterior to the middle anterior commissure–posterior commissure.

Bilateral STN-DBS, mean (± SD)*:* impulse duration: 63.4 μs (± 10.0); frequency: 138.6 Hz (± 18.3); voltage: 2.4 V (± 0.5). The mean coordinates of the selected contact were 12.41 ± 1.40 mm lateral to the anterior commissure–posterior commissure line, 1.05 ± 2.10 mm below the anterior commissure–posterior commissure and 2.43 ± 1.60 mm posterior to the middle anterior commissure–posterior commissure.

2.1.3 | Clinical Evaluation

Twenty-three patients were evaluated before surgery of DBS (3 months before) and after surgery (3 months after) using psychiatric and motor scales. Motor evaluations were realized in OFF- and ON-dopa conditions, while psychiatric evaluations were realized in ON-dopa and on stimulation conditions.

2.1.3.1 | Psychiatric Assessment. Patients were subjected to a psychiatric evaluation with the clinician version of Apathy Evaluation Scale (C-AES) (Marin, Biedrzycki, and Firinciogullari 1991), the MADRS and the Anxiety Scale of Association for Methodology and Documentation in Psychiatry (AMDP-AT) during on-drug condition, 3 months before and after neurosurgery.

The AMPDT AT was specifically chosen because of the little power of the somatic items.

2.1.3.2 | Motor Evaluation. All patients were evaluated according to the guidelines of the Core Assessment Program for Intracerebral Transplantation (CAPIT). They were assessed before and after surgery by motor scores with the Unified Parkinson's Disease Rating Scale (UPDRS) Part I to IV, the Hoehn and Yahr scale and the Schwab and England scale. These scores were evaluated in OFF-dopa (at least 12 h without any dopa medication) and ON-dopa conditions with a dopamine challenge (with a dose equal to 50 mg of levodopa added to morning dose). The total levodopa-equivalent daily dose (LEDD) of each patient was calculated before surgery and at the post-operative evaluation, accordingly to the basis method.

2.2 | Preclinical Study

2.2.1 | Animals

Experiments were performed on 80 adult male Sprague–Dawley rats (Janvier, Le Genest-Saint-Isle, France) weighing approximately 350 g (8 weeks old) at the time of surgery. Animals were housed under standard laboratory conditions (12 h light/dark cycle, with lights on at 7 AM) with food and water available *ad libitum*. Protocols used complied with the European Union 2010 Animal Welfare Act and the French directive 2010/63.

2.2.2 | Implantation of Electrodes and STN-DBS

Both sham (control) and DBS groups underwent the surgical procedure. A total of 50 rats were bilaterally implanted and 30 unilaterally implanted (15 left and 15 right) with monopolar electrodes consisting of platinum–iridium wire insulated with Teflon with a 400 μm exposed end (wire diameter, 110 μm insulated, 76 μm bare, PT-IR Teflon, Phymep, Paris, France). Stereotaxic coordinates (relative to bregma, according to the stereotaxic atlas of Paxinos and Watson, 1998) were AP, −3.8 mm; L, ± 2.4 mm, and DV, −7.8 mm; with the incisor bar at +3.2 mm below the interaural plane. The exposed end of the electrode, located in the STN, corresponded to the negative stimulation pole. A screw (Phymep, Paris, France, 0-80x1/16) fixed on the skull was used as the positive pole. Electrodes were soldered to corresponding contacts of the microstimulator support (ISENUSTIMV7, ISEN, Toulon, France), which was permanently fixed to the rat skull with dental cement (Superbond, Phymep, Paris, France). After recovery from anaesthesia, animals were returned to the facility for 1 week, to allow recovery before the beginning of the behavioural experiments.

Chronic long-lasting STN-DBS was performed only for the DBS groups using an electrical portable microstimulator system already validated in freely moving rats (Forni et al. 2012). This system has the advantages of leaving the animals free to move during behavioural 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 anaesthesia (Figure S1A). Monopolar rather than bipolar electrodes were utilized because the former is the most widely applied in PD patients (Benabid et al. 2009) as well as in studies describing apathy under STN-DBS (Funkiewiez et al. 2004; Schupbach et al. 2005; Castelli et al. 2006, 2007; Drapier et al. 2006; Gervais-Bernard et al. 2009; Thobois et al. 2010). Furthermore, monopolar stimulation reduces tissue damage compared with bipolar stimulation (Temel et al. 2004).

The frequency and pulse width used, 130 Hz and 60 μs, respectively, were similar to those applied in humans. For each animal of the DBS groups, the intensity was gradually increased until dyskinetic movement appeared as previously described (Boulet et al. 2006) and then adjusted just below this pro-dyskinetic threshold. This value was conserved throughout the study. The stimulation intensity was 176 ± 11 μA on average and ranged between 100 and 225 μA. These parameters were determined the day before the beginning of stimulation. STN-DBS was uninterrupted until rat euthanasia.

2.2.3 | Behavioural Procedures

Rats were not food or water deprived during the experimental procedures. Behavioural procedures were started 7 days after the surgery.

2.2.3.1 | Sucrose Self-Administration. Rats were trained to work for a 2.5% sucrose reinforcer, chosen for its relatively moderate rewarding outcome, in a self-administration task in operant chambers (Med Associates, St Albans, VT, USA) under a fixed ratio 1 reinforcement schedule. Rats were given the choice between two levers: an active and reinforced one, delivering 0.2 mL sucrose solution in a receptacle when pressed, and an inactive, nonreinforced lever, producing nothing (Drui et al. 2014).

Conditions were counter-balanced among the different tests. Trainings occurred before and after electrodes implantation. Once performances were stable during the second training (less than 20% performance variation over three consecutive sessions), STN-DBS was turned ON and uninterrupted until animal euthanasia.

2.2.3.2 | Two Bottle Choice. In their home cage, rats were given 24 h concurrent access to two graduated 250 mL plastic bottles (Techniplast, Lyon, France), for 3 days. One bottle contained tap water, whereas the other contained 2.5% sucrose (Sigma) in tap water. Rats and bottles were weighed daily, with the position of the bottles (left or right) alternated to control for side preference. The first day was used as an acclimation period. The volumes of sucrose solution and water consumed on the second and third days were averaged to determine preference for sucrose over water (sucrose intake/total intake, expressed as a percentage).

2.2.3.3 | Stepping Test. Animals were moved sideways along a smooth-surfaced table over 90 cm and the number of forelimb adjusting steps measured (Drui et al. 2014). The test was carried out three times for each paw.

2.2.3.4 | Open Area. Rats were placed in a dimly lit white Perspex open arena (50 × 25 × 40 cm) and horizontal distances travelled were recorded with a video-tracking system to assess locomotor and basal activity (Viewpoint S.A., Champagne au Mont d'Or, France), over a 1 h period.

2.2.4 | Euthanasia and Histology

Briefly, rats were sacrificed under chloral hydrate anaesthesia at the end of the behavioural experiments, intracardially perfused with NaCl (0.9%) and their brains frozen in cooled isopentane (−40°C) and stored at −30°C. Serial coronal sections (14-μm thick) of STN were cut with a cryostat (Microm HM 500, Microm, Francheville, France) and collected on slides.

Sections were stained with Cresyl violet and analysed under a light microscope (Nikon, Eclipse 80i, TRIBVN, Châtillon, France) coupled to the ICS FrameWork computerized image analysis system (TRIBVN, 2.9.2 version, Châtillon, France) in order to check the positions of electrodes (Figure S1B,C) Animals with incorrect electrode locations (around 50%) were excluded from the study.

2.3 | Statistics

Statistics were performed in GraphPad Prism version 8. Normality and homogeneity of variances were verified beforehand. A P value of 0.05 was considered significant. Data are shown as

TABLE 1 | Clinical and motor scores (mean ± SEM) of Parkinson's disease patients 3 months before (M − 3) and after (M + 3) bilateral or unilateral subthalamic nucleus stimulation.

	OFF-dopa				ON-dopa			
	Pre–STN-DBS (M-3, preoperative)		STN-DBS (M + 3, postoperative)		Pre–STN-DBS (M-3, preoperative)		STN-DBS (M + 3, postoperative)	
	Bilateral STN-DBS	Unilateral STN-DBS	Bilateral STN-DBS	Unilateral STN-DBS	Bilateral STN-DBS	Unilateral STN-DBS	Bilateral STN-DBS	Unilateral STN-DBS
UPDRS III	31.1 ± 3.7	26.0 ± 3.6	**14.3 ± 2.6****	**11.1 ± 2.6****	7.5 ± 1.4	7.6 ± 2.3	5.5 ± 1.0	**2.9 ± 0.8***
Schwab and England	70.0 ± 6.8	73.6 ± 6.2	74.5 ± 6.6	**84.5 ± 4.9***	93.0 ± 1.9	90.9 ± 2.5	90.9 ± 2,7	**96.4 ± 2.0***
Hoehn and Yahr	2.2 ± 0.3	1.4 ± 0.1	1.6 ± 0.3	1.1 ± 0.1	1.1 ± 0.2	0.954 ± 0.2	0.9 ± 0.3	**0.2 ± 0.1***
LEDD (mg)	—	—	—	—	1200 ± 123.1	1162.0 ± 160.9	**796.66 ± 179.0***	**589.0 ± 91.2****

Note: Data shown as means ± SEM. Unilateral, $n = 11$, bilateral, $n = 12$.
Abbreviations: LEDD, levodopa equivalent daily dose; UPDRS, United PD Rating Scale.
*$p < 0.05$, **$p < 0.01$.

means ± SEM. For the clinical study, the Wilcoxon signed rank sum test was used to realize intragroup analyses. For the experimental study, Student's *t*-test was used for two-group analysis; otherwise, repeated measure or two-way ANOVA was performed.

3 | Results

3.1 | Bilateral but Not Unilateral Subthalamic Stimulation Promotes Apathy in Parkinson's Disease Patients

Since 2006, our clinical centre followed-up a cohort of patients who suffered of Parkinson's disease and fulfilled selective criteria for STN-DBS surgery, with unilateral STN-DBS proposed for patients with unilateral or very asymmetric bilateral motor symptoms, and bilateral for the others.

Except the symptoms asymmetry consideration, preoperative motor states were similar in both cohorts of patients, as highlighted by the UPDRS, Schwab and England, and Hoehn and Yahr scores evaluated 3 months before the surgery (Table 1). Moreover, the LEDD were identical (Table 1), suggesting a similar disease's stage. Finally, psychiatric status was also equivalent since apathy (AES), depression (MADRS) and anxiety (AMDP-AT) measurements did not differ between patients (Table 2).

However, apathy scores significantly differ between the two cohorts after 3 months of stimulation. While bilateral STN-DBS strongly increased apathy (Figure 1A and Table 2), unilateral STN-DBS did not exert such an effect, and apathy score remained stable (Figure 1B and Table 2).

This absence of post–STN-DBS apathy cannot be attributed to an ineffective stimulation or electrodes misleading, because all patients present a significant postoperative motor improvement in OFF- and ON-dopa conditions, shown by UPDRS, the Hoehn and Yahr, and the Schwab and England scores (Figure 1 and Table 1). In addition, stimulation parameters between unilateral STN-DBS (impulse duration: 62.7 μs ± 9.0; frequency: 145 Hz ± 25.8; voltage: 2.6 V ± 0.6) and bilateral STN-DBS (impulse duration: 63.4 μs ± 10.0; frequency: 138.6 Hz ± 18.3; voltage: 2.4 V ± 0.5) were equivalent. Furthermore, the pre-STN-DBS LEDD are similar between the two cohorts, and both bilateral and unilateral STN-DBS permitted to significantly decrease the medication dosage, and this reduction even tends to be greater in the unilateral cohort (Figure 1 and Table 1). Finally, as depression and anxiety increase can also be the consequence of dopaminergic medication reduction, neither bilateral nor unilateral STN-DBS significantly modified these two symptoms (Table 2). Thus, the dopaminergic withdrawal hypothesis cannot be supported for the differential apathy incidence.

Altogether, while both unilateral and bilateral STN-DBS permitted a significant and equivalent motor improvement, bilateral but not unilateral STN-DBS promoted apathy in spite of the greatest reduction of dopaminergic medication in the unilateral cohort.

3.2 | Bilateral but Not Unilateral Subthalamic Stimulation Decreases Motivation in Rats

We operationalized apathy in rodent models as previously validated (Carnicella et al. 2014; Drui et al. 2014; Favier et al. 2014; Favier et al. 2017), with a low-cost sucrose fixed ratio 1 self-administration task rather than effortful and high demanding tasks less relevant in regard to apathy that affects activity of daily living and simple tasks that patients used to routinely achieve (Chaudhuri and Odin 2010). Because our previous study had also shown a similar motivational deficit in both naïve and PD rats subjected to bilateral STN-DBS (Vachez et al. 2020b), we used here naïve rats, to focus on the effect of DBS, without the risk of potential bias caused by the dopaminergic degeneration.

Rats were trained every day to press on a lever to induce the delivery of a rewarding sucrose solution. Once performances were stable for multiple days in a row, we applied bilateral or unilateral STN-DBS with a portable microstimulator allowing stimulation 24 h a day during several days (Figure 2A,C). Bilateral STN-DBS induced a persistent deficit in this task decreasing performances from 50%, consistent with what we already observed (Figure 2A). Strikingly, unilateral STN-DBS did not exert such a loss of motivation, as control and STN-DBS rats obtain similar amount of reward (Figure 2C). We also tested the effect of STN-DBS on the consummatory dimension of motivation with a two-bottle choice test between sucrose and water (Liu et al. 2018), but neither bilateral (Figure 2B) or unilateral (Figure 2D) STN-DBS modified the preference for sucrose.

TABLE 2 | Psychiatric scores (mean ± SEM) of Parkinson's disease patients 3 months before (M − 3) and after (M + 3) bilateral or unilateral subthalamic nucleus stimulation.

	Pre–STN-DBS (M − 3, preoperative)		STN-DBS (M + 3, postoperative)	
	Bilateral STN-DBS	**Unilateral STN-DBS**	**Bilateral STN-DBS**	**Unilateral STN-DBS**
AES	30.9 ± 1.2	27.4 ± 2.1	**39.2 ± 1.8****	27.1 ± 2.0
MADRS	4.8 ± 1.7	3.4 ± 1.0	6.2 ± 2.4	2.8 ± 0.6
AMDP-AT	6.5 ± 1.8	6.5 ± 1.1	11.1 ± 2.8	6.1 ± 1.8

Note: Unilateral, $n = 11$, bilateral, $n = 12$. Data shown as means ± SEM.
Abbreviations: AES, Apathy Evaluation Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; AMDP-AT, Anxiety Scale of Association for Methodology and Documentation in Psychiatry.
**$p < 0.01$.

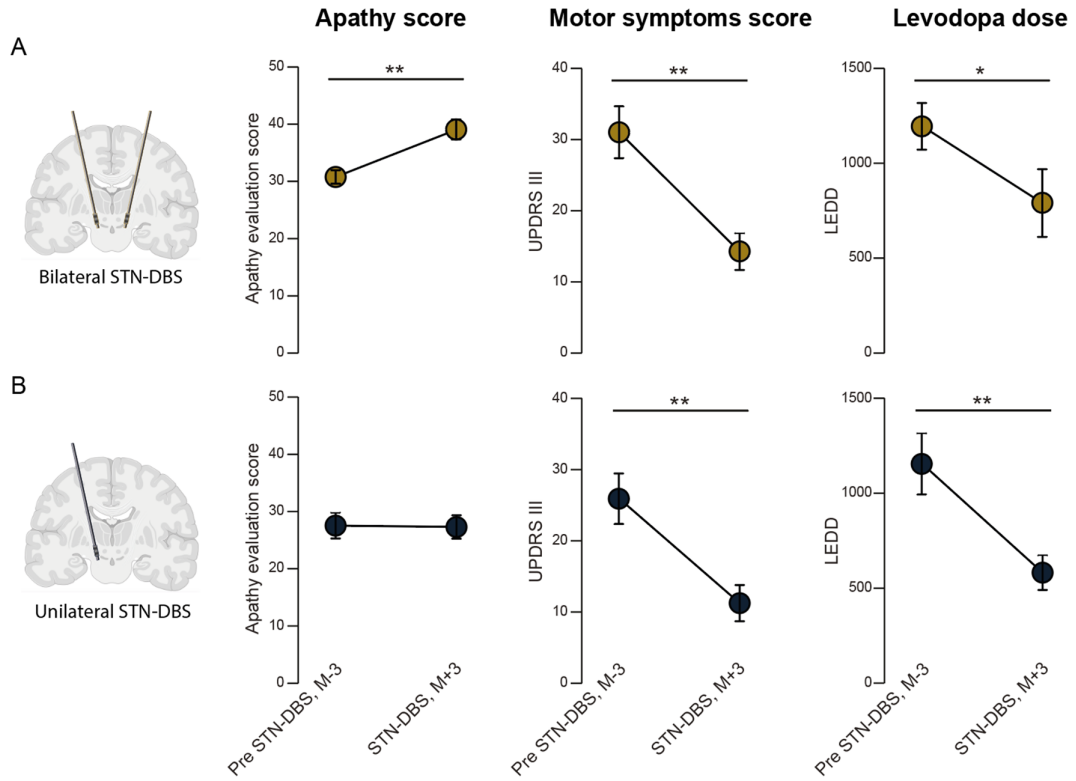

FIGURE 1 | Bilateral but not unilateral STN-DBS promotes apathy in Parkinson's disease patients. (A) Bilateral STN-DBS promotes apathy, highlighted by a significant increase of the Apathy Evaluation Scale (AES) score (pre–STN-DBS: 30.9 ± 1.2, STN-DBS: 39.2 ± 1.8, Wilcoxon signed rank test, $p = 0.002$), and permit a significant Unified Parkinson's Disease Rating Scale III (UPDRS III) score improvement (pre–STN-DBS: 31.1 ± 3.7, STN-DBS: 14.3 ± 2.6, Wilcoxon signed rank test $p = 0.007$), along a significant levodopa-equivalent daily doses (LEDD) reduction (pre–STN-DBS: 1200.0 ± 123.1, STN-DBS: 796.7 ± 179.0, Wilcoxon signed rank test $p = 0.02$). (B) Unilateral STN-DBS does not only promote apathy, as shown by a similar AES score before and after DBS (pre–STN-DBS: 27.4 ± 2.1, STN-DBS: 27.1 ± 2.0, Wilcoxon signed rank test $p = 0.82$), but also permits a significant UPDRS III score improvement (pre–STN-DBS: 26 ± 3.6, STN-DBS: 11.1 ± 2.6, Wilcoxon signed rank test $p = 0.0011$) and LEDD reduction (1162.0 ± 160.9, STN-DBS: 589.0 ± 91.2, Wilcoxon signed rank test, $p = 0.0011$). Unilateral, $n = 11$, bilateral, $n = 12$. Data shown as means ± SEM. $^*p < 0.05$, $^{**}p < 0.01$.

Not only does bilateral STN-DBS decreased the preparatory dimension of reward motivation (Figure 2A), but it also induces a general decrease of behavioural activity, as distance travelled in the open arena test was reduced (Figure 3A). Deficits in both paradigms are reminiscent to the impairment of basal and general activity in apathetic patients but cannot be attributed to motor impairments, as we did not highlight any deficits during the stepping test (Figure 3B). Coherently, with the absence of effect during sucrose self-administration (Figure 2C), unilateral STN-DBS did not promote hypoactivity or any motor impairment during the open arena (Figure 3B) and stepping test (Figure 3C).

Overall, bilateral STN-DBS reduced motivated behaviours in rats, consistent with the hypothesis that STN-DBS can promote apathy in patients with PD. But importantly, when applied in a unilateral way, STN-DBS fails at replicating the same phenotype.

4 | Discussion

Apathy following STN-DBS is an enduring controversial and topical debate (Martínez-Fernández 2020; Vachez et al. 2020a; Zoon et al. 2021). Because this adverse effect is still not well accepted, very few studies have focused on parameters that could influence this outcome, such as the bilateralism of the stimulation. Bilateral STN-DBS is applied in patients suffering from advanced stage PD with bilateral symptoms whereas unilateral STN-DBS is advocated for unilateral or very asymmetrical motor symptoms. Few clinical studies have compared unilateral and bilateral STN-DBS, but those investigations consistently highlight that bilateral STN-DBS seems more effective in alleviating motor disturbances such as gait, tremor and oculomotor control (Huss et al. 2015; Lizarraga, Jagid, and Luca 2016; Goelz et al. 2017). However, bilateral STN-DBS also seems to induce more deleterious side effects, aggravating cognitive processes perturbations, loss of verbal fluidity and weight gain in a greater proportion than unilateral stimulation (Lee et al. 2011; Sjoberg et al. 2012; Goelz et al. 2017). It is yet uncertain if the bilateralism of STN-DBS is also critical for psychiatric side effects, in particular apathy. Some of the few studies considering the effects of unilateral STN-DBS on mood, for instance, report very limited impacts (Okun et al. 2014), or even an improvement of mood ratings, in particular in the case of left STN-DBS (Campbell et al. 2012). Even less studies have addressed the impact of unilateral STN-DBS on apathy.

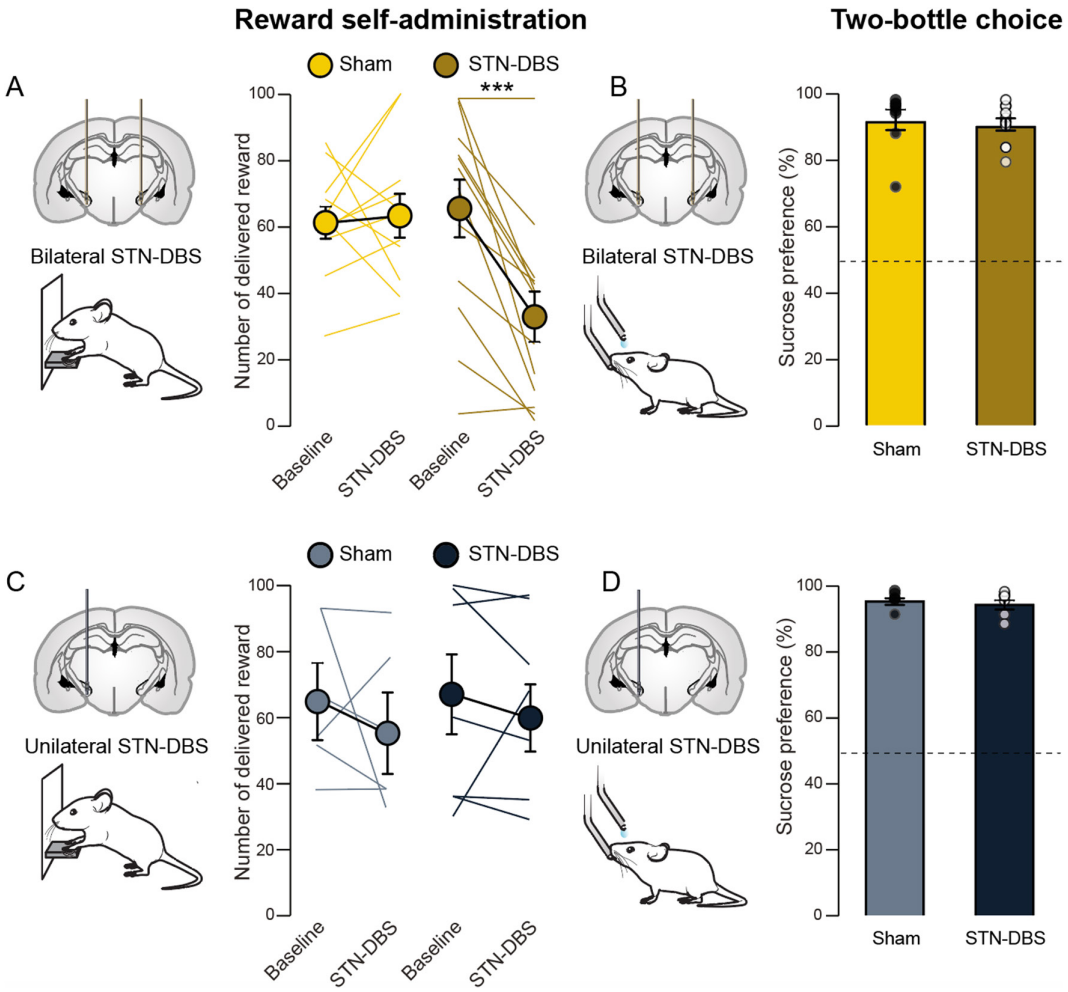

FIGURE 2 | Bilateral but not unilateral STN-DBS reduces reward motivation. (A) Bilateral STN-DBS decreases reward seeking, highlighted by a decrease of the number of delivered reward (sham, baseline: 61.5 ± 4.9 rewards, STN-DBS: 63.6 ± 6.6 rewards; paired *t* test, sham: $t_{10} = 0.2964$, $p = 0.7730$; STN-DBS, baseline: 67.2 ± 8.6 rewards; STN-DBS: 34.6 ± 7.6 rewards; paired *t* test, STN-DBS: $t_{12} = 4.876$, $p = 0.0004$). (B) Bilateral STN-DBS do not alter preference for sucrose over water in a two-bottle choice test (sham: 91.9% ± 3.0, bilateral STN-DBS: 90.4% ± 1.8; *t* test: $t_{17} = 0.4120$, $p = 0.6855$). (C) Unilateral STN-DBS does not decrease the number of delivered reward in the self-administration task (sham, baseline: 66.0 ± 11.7 rewards, STN-DBS: 54.8 ± 12.4 rewards; paired *t* test: $t_5 = 0.7815$, $p = 0.4699$; STN-DBS, baseline: 65.0 ± 12.1 rewards; STN-DBS: 57.9 ± 10.2 rewards; paired *t* test: $t_6 = 0.02022$, $p = 0.9845$). (D) Unilateral STN-DBS does not alter preference for sucrose over water (sham: 95.9% ± 1.0, STN-DBS: 94.9% ± 1.4; *t* test: $t_{11} = 0.5485$, $p = 0.5943$). Bilateral: sham: $n = 7$–13, STN-DBS: $n = 6$–13; Unilateral: sham: $n = 6$, STN-DBS: $n = 7$. Data shown as means ± SEM. ***$p < 0.001$.

Here, we provide data showing that, if bilateral STN-DBS can promote apathy by itself, it seems not to be the case with a unilateral stimulation. Yet, in a previous study, an increase of apathy with unilateral STN-DBS had been reported (Kirsch-Darrow et al. 2011), but without comparing unilateral and bilateral stimulation. These heterogeneous results, as well as the limited amount of data concerning psychiatric side-effects of unilateral STN-DBS, show that further investigations still have to be conducted, especially given the multifactorial aspect of apathy (Béreau et al. 2023). Comparing unilateral and bilateral STN-DBS patients is particularly delicate, given that these two types of stimulation are generally offered to patients at different stages of Parkinson's disease. Thus, the two cohorts differ in terms of age and disease duration. As apathy is also part of the PD symptomatology and can worsen with age (Béreau et al. 2023), these differences could account for the apathy score after STN-DBS. The motor severity also differs between the two cohorts, and the prevalence of apathy seems to be influenced by the motor phenotype of patients (Voruz et al. 2020, 2022; Lenka, Gazes, and Vanegas-Arroyave 2023). This represents another potential limitation, in addition to the relatively small number of patients we have been able to include. However, the preoperative apathy, motor scores and dopaminergic medication level between both cohorts lie very close. Yet the combination and synergistic effect of these parameters cannot completely be ruled-out. Thus, it remains challenging to disentangle for each patients the origin of apathy following STN-DBS.

Experimental approaches in animal models allow a better control of the different confounding parameters. Apathy is a multifaceted symptom and the best way to model it in experimental model is still debated (Magnard et al. 2016; Okitsu et al. 2024). Thus, observations should always be interpreted with caution,

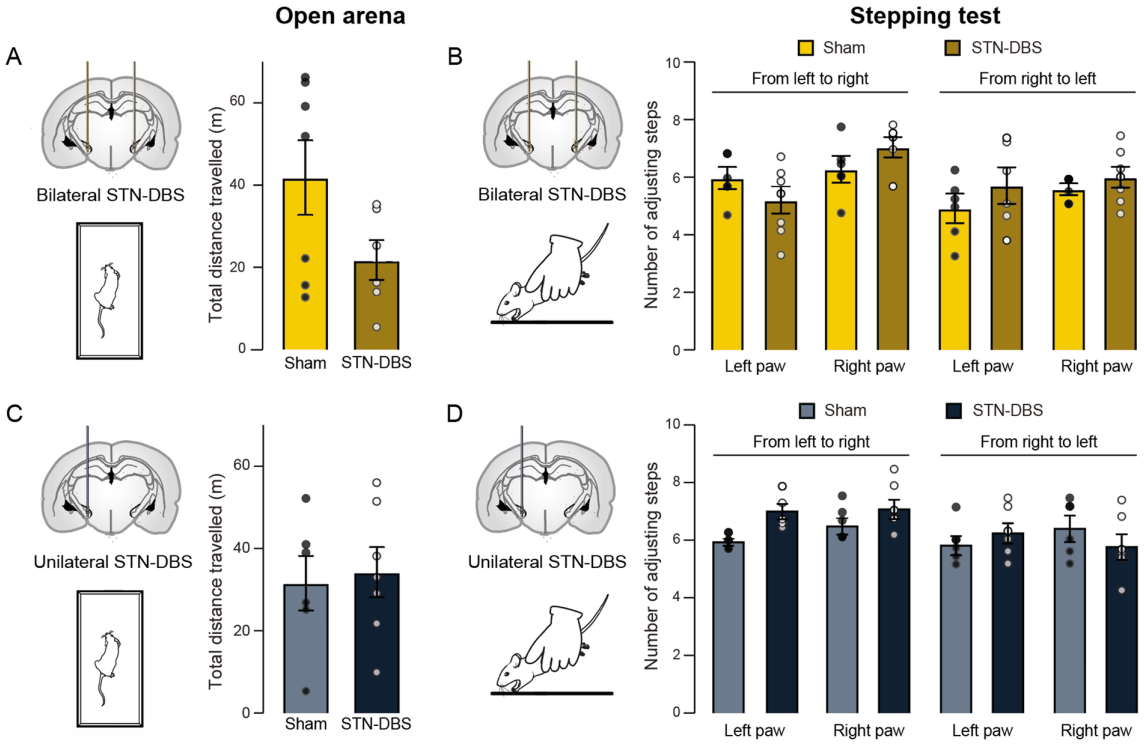

FIGURE 3 | Bilateral but not unilateral STN-DBS reduces basal activity. (A) Bilateral STN-DBS tends to induce hypoactivity in rats during an open area test and decreases the total travelled distance (sham: 4184.4 ± 906.8 cm; STN-DBS: 2179.6 ± 484.9 cm; *t* test: $t_{11} = 1.853$, $p = 0.0908$), (B) but does not alter the fine motor skills of front limbs as demonstrated by adjusting steps in the course of the stepping test (sham: 5.7 ± 0.6 adjusting steps, STN-DBS: 6.1 ± 0.9 adjusting steps; RM 1 way ANOVA, STN-DBS effect: $F_{1,3} = 0.6834$, $p = 0.4690$; trials effect: $F_{1,1} = 2.533$, $p = 0.3571$). (C) Unilateral STN-DBS does not modify behavioural activity in the open area test (sham: 3156.9 ± 663.9 cm; STN-DBS: 3421.0 ± 609.6 cm; *t* test: $t_{11} = 0.2932$, $p = 0.7748$), or (D) the stepping test performances (sham: 6.2 ± 0.2 adjusting steps, STN-DBS: 6.6 ± 0.3 adjusting steps; RM 1 way ANOVA, STN-DBS effect: $F_{1,3} = 0.9981$, $p = 0.3914$; trials effect: $F_{1,1} = 0.9529$, $p = 0.5077$). Bilateral: sham: $n = 7$–8, STN-DBS: $n = 6$–11; Unilateral: sham: $n = 6$, STN-DBS: $n = 7$. Data shown as means ± SEM.

and conclusions should be made carefully. Nevertheless, by using an approach we previously validated to extract the motivational dimension of apathy (Carnicella et al. 2014; Drui et al. 2014; Favier et al. 2014, 2017), we show in that study that bilateral but not unilateral STN-DBS decreases reward motivation and basal activity in rats, without the combined impact of the degenerative processes and the dopaminergic medication. While the definitions and differences between apathy and anhedonia are still discussed (Husain and Roiser 2018), the decrease of self-administration performances without alteration of sucrose preference during the two-bottle choice could be interpreted as an anticipatory or motivational anhedonia, without consummatory anhedonia (Der-Avakian and Markou 2012). The effect of bilateral STN-DBS we highlight in this study is in compliance with a recent meta-analysis showing that, despite few exceptions (Baunez et al. 2007; Rouaud et al. 2010), STN-DBS tends overall to reduce motivated behaviours (Vachez and Creed 2020). While the modality of the stimulation (polarity, chronicity etc.), differences between the tests and the metabolic state of animals are some of the parameters that can explain the variation between these studies, here, we compared bilateral and unilateral STN-DBS in the exact same conditions and applied similar current amplitude (bilateral: 183 ± 13 μA; unilateral: 176 ± 11 μA). The fact that we achieved this comparison in healthy rats only still represents a limitation, but we (Vachez et al. 2020b) and others (Darbaky et al. 2003; Baunez et al. 2007) previously observed the same effect of bilateral STN-DBS on motivation in both control and 'parkinsonian' animals, as reviewed in Vachez and Creed (2020). Overall, combining these two clinical and preclinical approaches permit to compensate their individual limitations and consolidate our conclusion that unilateral STN-DBS is less likely to promote apathy than when applied bilaterally.

Mechanisms underlying apathy following STN-DBS and explaining the potential difference between unilateral and bilateral stimulation remain to be investigated, but the exact location of electrodes or active contacts seems to be determinant. Case reports from distinct centres highlight that DBS of the more ventral (limbic) or medial (associative) part of the STN and not the dorsal (motor) one can induce apathy (Drapier et al. 2006; Zoon et al. 2019, 2023) or other negative psychiatric outcome (Mallet et al. 2007; Somma et al. 2022). These territories are interconnected to many regions playing pivotal roles in reward processing, as the nucleus accumbens or the ventral pallidum (Vachez et al. 2021; Prasad and Wallén-Mackenzie 2024). Hence, modulation of the activity of the non–motor subthalamic circuits by STN-DBS could drive apathy. However, few studies report opposite results, showing that dorsal STN-DBS drive apathy (Ricciardi et al. 2014), or even claiming that ventral STN-DBS is effective at alleviating preoperative apathy (Petry-Schmelzer

et al. 2019). One possible explanation for these discrepancies could be that current spreading outside the STN in neighbouring structures mediates apathy. For instance, Ricciardi et al. showed unequivocally that switching on and off the most dorsal contact colocalized in the zona incerta acutely induces apathy (Ricciardi et al. 2014). Zoon et al. observed acute apathy in patients receiving DBS in the ventral part of the STN, but this was alleviated when reducing the voltage, which drastically limits the area of the electric field and the volume of tissue activated (Zoon et al. 2019). The STN is surrounded not only by the zona incerta but also by the lateral hypothalamus, and both structures are strongly implicated in motivation (Rossi et al. 2019; Ye, Nunez, and Zhang 2023). Further investigations using advanced techniques to determine the precise location of active contacts and to highlight networks neuromodulation, related to psychiatry outcome, will provide valuable insights to refine implantation and programming strategies as steering techniques (Timmermann et al. 2015) that minimize adverse effects such as apathy.

Nevertheless, apathy following STN-DBS is likely due to the recruitment of limbic circuits connected to or in the vicinity of the STN, especially when this circuit neuromodulation happens in a bilateral way. This unilateral hypothetic off-target effect could also be sufficient to induce apathy. In this scenario, bilateral STN-DBS would be more deleterious by doubling the probability of ectopic stimulation, all the more so as the second electrode implantation in a bilateral surgery is frequently less accurate and associated with a lower threshold for side effect in patients (Sammartino et al. 2016). Finally, the STN is connected to contralateral brain structures (Cavdar et al. 2018) and unilateral STN-DBS changes the activity of the contralateral STN (Walker et al. 2011). Thus, it is also possible that DBS may drive compensatory metabolic or neural circuit changes in the un-stimulated hemisphere that may mitigate the loss of motivation induced by STN-DBS. Of note, the microlesion induced by the implantation could also be one additional factor favouring apathy, as patients and rats receiving unilateral STN-DBS in our study are not implanted with a second electrode. Advanced imaging approaches, neurophysiological techniques and sophisticated circuit dissection will be necessary to test these different hypotheses.

Even if it is subject of controversies, we cannot rule out a potential lateralized effect of STN-DBS (Lin et al. 2021). Hemispheres are specialized for certain cerebral functions, and interventions focused on one or the other hemisphere can likely produce different outcome. The STN seems to support this lateralization, including nonmotor functions (Eitan et al. 2013). Thus, it is legitimate to speculate that left or right STN-DBS could differentially affect motor and nonmotor behaviours, including apathy. However, there is too much discrepancies between the case reports (Walker et al. 2009a; Kirsch-Darrow et al. 2011; Campbell et al. 2012; Schulz et al. 2012; Okun et al. 2014; Black et al. 2022; Béreau et al. 2023; Del Bene et al. 2023) to confidently conclude on specific left or right STN-DBS effects. Furthermore, our results do not support a lateralized effect for apathy following STN-DBS. This lack of consistency could be explained by the existence of a 'dominant STN' in at least 50% of patients (Castrioto et al. 2011). In these patients, DBS of the dominant STN produces similar motor benefits than bilateral DBS (Rizzone et al. 2017). Whether or not apathy outcome could rely on DBS of the dominant STN has never been investigated.

Although the present study emphasizes the deleterious side effects of STN-DBS, especially when applied bilaterally, apathy after STN-DBS is not systematic. In numerous patients, STN-DBS can have a beneficial effect on mood and other nonmotor symptoms (Okun et al. 2014). A longer follow up period, what is more on a bigger cohort, would have been beneficial to highlight any potential delayed compensatory effects that could have mitigate the detrimental effect of STN-DBS. A large number of factors come into play for post-operational apathy, such as the maladaptive reduction of the dopamine replacement, or the motivational and cognitive status of the patient before DBS (Béreau et al. 2023). The overarching goal of this work is to provide new elements to understand the phenomenology of STN-DBS side effects, pointing out the differences between bilateral *versus* unilateral DBS, in order to refine this treatment.

Although bilateral STN-DBS has quickly become a standard way to apply DBS, this should not be an exclusive approach for all PD patient candidates for stimulation. Efficacy and safety of unilateral STN-DBS have been established in PD for patients with unilateral (Kumar et al. 1999) or bilateral asymmetric motor symptoms (Walker et al. 2009b; Gülke et al. 2023), with even significant effects on the ipsilateral hemi body (Tabbal et al. 2008; Shemisa et al. 2011). In practice, a unilateral surgery could be a good option for young patients with prominent asymmetric symptoms in order to protect them from apathy. If necessary, a contralateral surgery could be performed later.

5 | Conclusion

To summarize, the present translational work refines the importance of STN-DBS modality (unilateral *versus* bilateral) in the induction of apathy. Regarding the efficiency of unilateral STN-DBS and the lower incidence of nonmotor side-effect, including apathy, it seems legitimate to reconsider the use of unilateral *versus* bilateral STN-DBS in certain PD patients.

Author Contributions

Yvan M. Vachez: conceptualization, data curation, formal analysis, investigation, visualization, writing – original draft. **Marie Bahout:** data curation, formal analysis, investigation, visualization, writing – original draft. **Robin Magnard:** data curation, investigation, writing – review and editing. **Pierre-Maxime David:** data curation, formal analysis, investigation, writing – review and editing. **Carole Carcenac:** data curation, investigation, methodology, visualization, writing – review and editing. **Mylène Wilt:** data curation, formal analysis, writing – review and editing. **Gabriel Robert:** conceptualization, data curation, investigation, methodology, writing – review and editing. **Marc Savasta:** conceptualization, funding acquisition, methodology, supervision, validation, writing – review and editing. **Sebastien Carnicella:** conceptualization, funding acquisition, methodology, supervision, writing – review and editing. **Marc Vérin:** conceptualization, funding acquisition, investigation, methodology, validation, writing – review and editing. **Sabrina Boulet:** conceptualization, data curation, funding acquisition, investigation, methodology, supervision, validation, visualization, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data presented in this work are available upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.70019.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.