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Research report

Deep brain stimulation of the subthalamic nucleus increases premature responding in a rat gambling task

Lily R. Aleksandrova[a,d], Meaghan C. Creed[a,d], Paul J. Fletcher[b,c,e], Daniela S.S. Lobo[b,f,g], Clement Hamani[d,h], José N. Nobrega[a,b,c,d,*]

[a] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada
[b] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[c] Department of Psychology, University of Toronto, Toronto, ON, Canada
[d] Behavioural Neurobiology Laboratory and Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
[e] Biopsychology Research Section and Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
[f] Neurogenetics Research Section, Neuroscience Department, Centre for Addiction and Mental Health, Toronto, ON, Canada
[g] Problem Gambling Service, Addictions Program, Centre for Addiction and Mental Health, Toronto, ON, Canada
[h] Division of Neurosurgery, Toronto Western Hospital, Toronto, ON, Canada

HIGHLIGHTS

- Bilateral STN-DBS was tested for effects on rat impulsivity.
- Stimulation did not affect gambling-like behaviour.
- However, it significantly increased premature responding in the gambling task.
- Effect developed over several sessions and persisted acutely when no stimulation given.
- Results support association of STN-DBS with impulsivity in absence of parkinsonism.

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ABSTRACT

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a treatment option for the motor symptoms of Parkinson's disease (PD). However, several recent studies have found an association between STN-DBS and increased impulsivity. Currently, it is not clear whether the observed increase in impulsivity results from STN-DBS per se, or whether it involves an interaction with the underlying PD neuropathology and/or intake of dopaminergic drugs. We investigated the effects of STN-DBS on performance of intact rats on two tasks measuring impulsive responding: a novel rat gambling task (rGT) and a differential reinforcement of low rate responding (DRL20s) schedule. Following initial behavioural training, animals received electrode implantation into the STN ($n = 24$) or sham surgery ($n = 24$), and were re-tested on their assigned behavioural task, with or without STN-DBS. Bilateral STN-DBS administered for two hours immediately prior to testing, had no effects on rGT choice behaviour or on DRL response inhibition ($p > 0.05$). However, STN-DBS significantly increased premature responding in the rGT task ($p = 0.0004$), an effect that took several sessions to develop and persisted in subsequent trials when no stimulation was given. Consistent with the notion of distinct facets of impulsivity with unique neurochemical underpinnings, we observed differential effects of STN-DBS in the two tasks employed. These results suggest that STN-DBS in the absence of parkinsonism may not lead to a general loss of inhibitory control, but may instead affect impulsivity under specific conditions.

1. Introduction

Deep brain stimulation (DBS) is a neurosurgical procedure whereby electric current is passed through electrodes implanted within specific brain targets [1,2]. DBS of the subthalamic nucleus (STN-DBS) has been used to treat over 100,000 patients with movement disorders, particularly Parkinson's disease (PD), and is also

* Corresponding author at: Behavioural Neurobiology Laboratory, Centre for Addiction and Mental Health, 250 College Street, M5T 1R8, Toronto, ON, Canada. Tel.: +1 416 535 8501x6259; fax: +1 416 979 4739.
E-mail address: jose.nobrega@camh.ca (J.N. Nobrega).

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Table 1
Reward/punishment contingencies in the rat gambling task.[a]

rGT Choice	Reward		Punishment		Maximum number of
	Probability	Amount	Probability	Duration	pellets per session
P1	0.9	1 pellet	0.1	5 s	295
P2	0.8	2 pellets	0.2	10 s	411
P3	0.5	3 pellets	0.5	30 s	135
P4	0.4	4 pellets	0.6	40 s	99

[a] Four options (P1–P4) are available in the rat gambling task (rGT), each associated with a fixed amount of reward (number of pellets) and a punishing time-out with defined probability (p) and duration (s). The maximum number of pellets that could be earned if a single option is chosen exclusively within a 30-min session is indicated. Within these constraints, the two-pellet option, P2, is the most advantageous, whereas P4 is the highest risk option [18].

an emerging procedure for the treatment of psychiatric conditions, such as depression and obsessive compulsive disorder (OCD) [3,4]. In PD patients, STN-DBS can provide stable symptomatic relief and improve quality of life, while reducing treatment-induced dyskinesias [5,6]. Moreover, adding DBS to the treatment regimen has been shown to reduce the mean dose of dopaminergic drugs required to improve motor symptoms by half, with a consequent reduction in motor side effects [6]. However, several recent clinical trials and case studies of PD patients have found an association between STN-DBS treatment and increases in other side effects, in particular, with increased impulsivity, independent of the drug status [7–12]. For example, subjects undergoing subthalamic stimulation were found to experience a much higher incidence of post-operative impulse control disorders, such as pathological gambling, compulsive shopping or eating, and hypersexuality, compared to those that received medication only (19% vs. 8%, respectively) [8,13].

Currently, it is not clear whether the observed effect on impulsivity results from STN-DBS per se, or whether it involves an interaction with the underlying PD neuropathology. Several previous studies have applied DBS to rats carrying dopaminergic lesions to model Parkinson's disease, and measured the effects on different tests of impulsivity, but results have been inconsistent [14–17]. Moreover, despite the growing application of DBS for other conditions, such as depression [3,4], few studies assessing the impulse-control effects of stimulation on intact, non-parkinsonian rats have been conducted, again with somewhat contrasting results [16,17]. Here we addressed the hypothesis that DBS of the subthalamic nucleus can alter impulsive behaviour when administered to intact rats. To this end, we investigated the effects of STN-DBS on two tasks: a novel rat gambling task [18] and a differential reinforcement of low rate responding (DRL20s) schedule, which were used to model distinct facets of impulsivity. We hypothesized that STN-DBS applied immediately prior to testing, would alter performance on behavioural tasks measuring impulsive behaviour.

2. Experimental procedures

All procedures were approved by the Animal Care Committee at the Centre for Addiction and Mental Health and complied with Canadian Council on Animal Care (CCAC) and NIH standards and guidelines.

2.1. Subjects

Male Sprague-Dawley rats (n = 48) (Charles River, Quebec), initially weighting 250–300 g, were housed individually on a 12 h light–dark cycle (lights on at 8:00 a.m.), with all training occurring during the light period. Upon arrival, a week of acclimatization to the facility was allowed. Starting at day 5 after arrival, animals were food-restricted and fed 18–20 g once a day, always after training. Under this schedule rats have been previously shown to remain healthy, increase their body weight steadily and maintain stable levels of behavioural performance [19]. Water was available ad libitum in the home cages. One week after arrival, all rats began training on their assigned behavioural task in two distinct cohorts: DRL (n = 24) and rGT (n = 24). Testing took place 5 days a week, between 10 a.m. and 3 p.m.

2.2. Differential reinforcement of low rates of responding (DRL20s)

DRL testing took place in standard operant conditioning chambers (Med Associates, St Albans, VT), equipped with a response lever and food pellet dispenser as previously described [19]. Animals (n = 24) were initially trained to press a lever for food reward on a fixed ratio 1 (FR1) schedule of reinforcement, in three daily 40 min sessions. Thereafter, they were switched to a DRL20s schedule, in which bar presses were reinforced only if at least 20 s had elapsed since the previous response. Any responses occurring less than 20 s since the last response were not rewarded, and reset the 20 s requirement. Each session began with illumination of the house light, and insertion of the lever into the chamber, and the first response of each session was always reinforced. DRL testing was carried out for 33 sessions prior to surgery, until stable responding was established on the group level in the last three DRL sessions immediately prior to surgery (pre-op phase), based on mean inter-response time (mIRT, s) and efficiency (reinforcers/responses × 100, %) (p > 0.05). Subjects were then divided in two matched surgery groups based on their pre-op mIRT and efficiency, to receive either implantation of STN electrodes (n = 12) or sham surgery (n = 12). The mIRT was calculated as the average of all inter-response times per session, excluding those that lie in the 0–4 s bin, which eliminates the burst responding peak that is often observed after a pellet is obtained [19].

2.3. Rat gambling task (rGT)

rGT testing took place in commercial five-choice chambers (Med Associates, St. Albans, VT), equipped with response holes (middle hole omitted) and food pellet dispenser as described previously [18]. In this task, each option (P1, P2, P3, P4) is associated with the delivery of a fixed amount of food pellets, but also with a specific probability and duration of punishing time-out periods, during which reward cannot be earned (Table 1) [18]. Initially, rats learned the rGT reinforcement schedules corresponding to each of the holes in a forced choice paradigm (rGT-FC), where only one of the four options was available on each trial. After 7 sessions on the rGT-FC, testing began on the actual rGT, where rats were free to choose among the four holes. Each session was 30 min long, thus creating pressure to adopt the optimal choice strategy to earn as much food as possible in a limited time. An individual's choice profile is thought to reflect the ability to identify the most advantageous, and avoid the high-risk options. Upon analysis of the data, each rGT option was calculated as a percent of total trials per session. The task also measures the level of premature responding, or the number of responses made during the 5 s inter-trial-time, which is a distinct measure of impulse control, reflecting the ability to delay a response. rGT animals were randomly divided in two groups, each presented with the four options in a different order (version 1, n = 12: P1, P4, P2, P3; version 2, n = 12: P4, P1, P3, P2), so that the test design was counterbalanced [18]. Training on the rGT took place over 26 sessions prior to surgery, until stable responding was established on the group level in the last three rGT sessions immediately prior to surgery (pre-op phase), based on rGT choice profile (P1–P4) and level of premature responding (p > 0.05). Subjects were then divided in two matched surgery groups based on their pre-op P1–P4 distribution and premature responses, to receive either implantation of STN electrodes (n = 12) or sham surgery (n = 12).

2.4. Surgical procedure

Animals assigned to the DBS group (DRL: n = 12; rGT: n = 12) were anesthetized with isoflurane (3–5% inhalation) and placed in a stereotaxic frame. Polymide-insulated stainless steel monopolar electrodes (250 μm in diameter with 0.5 mm of surface exposed) were bilaterally implanted into the STN (AP −3.8 mm; ML +2.5 mm; DV −8.0) [20–22]. Anodes were connected to a bone screw in the skull. Control animals (DRL: n = 12; rGT: n = 12) were anesthetized and had holes drilled into the skull, but were not implanted with electrodes. After surgery, animals were allowed to recover for one week prior to resuming behavioural testing, with food freely available for the first 5 days.

2.5. Deep brain stimulation (DBS) protocol

DBS was applied using a portable stimulator (St Jude Medical, Model 6510, Plano, Texas) set to deliver 12.5 μA of current (90 μs pulse width, 130 Hz). Considering the electrode diameter and exposed surface these parameters were estimated to generate a charge density similar to that used clinically in human patients, and were below the threshold for induction of dyskinesias [20,23]. Following a week-long post-surgical recovery period, all animals were re-tested on the behavioural

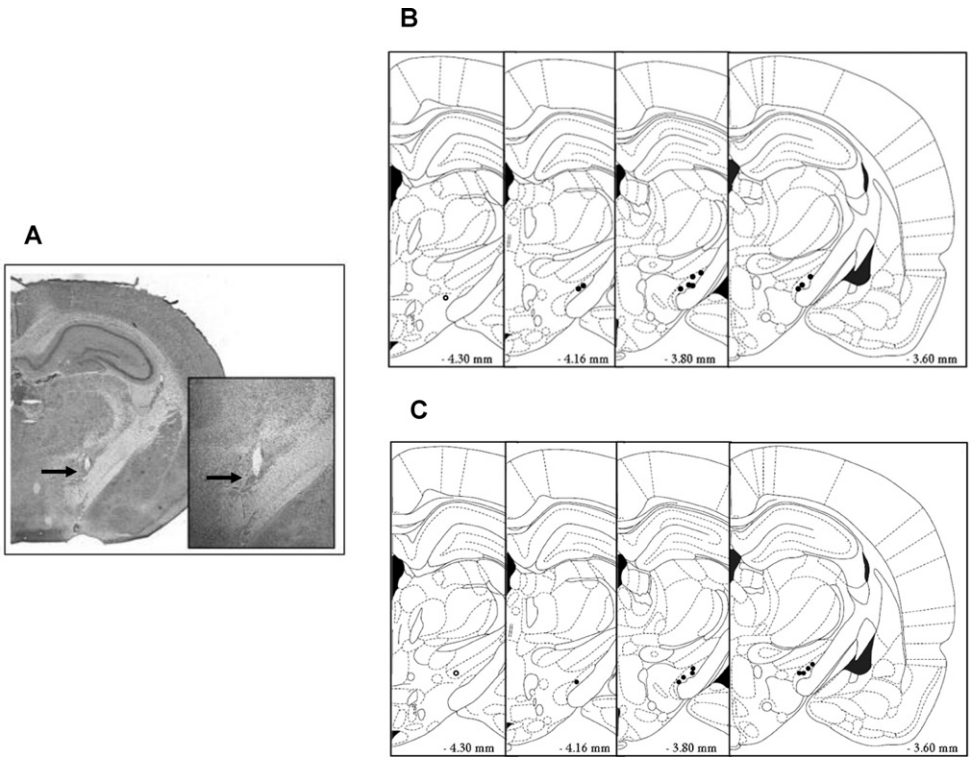

Fig. 1. Electrode localization. A. An example of a cresyl violet stained section through the STN, showing the electrode tracks and location of the electrode tip within the STN. B, C. Electrode placements for all DRL (B) and rGT (C) DBS animals that completed the study ($n = 10$). Filled circles indicate placements within the STN, open circles indicate placements outside the target area. Only animals with both electrodes placed within the STN were included in the final data analyses. The number at the top of each panel corresponds to distance from bregma in mm, according to the Paxinos and Watson [22] atlas (reproduced with permission).

tasks, without any pre-treatment (post-op phase: first three sessions after recovery). Thereafter, electrode-implanted animals (DRL: $n = 12$; rGT: $n = 12$) were tested in two distinct phases (A and B), involving different procedures prior to behavioural testing. On phase A days (DBS ON), electrode-implanted animals received STN-DBS bilaterally for two hours, immediately followed by behavioural testing on the assigned impulsivity task. On phase B days, electrode-implanted animals were connected to the DBS stimulator for two hours, but no current was applied (DBS OFF). We have chosen not stimulate the animals during the task to avoid the possibility of cables interfering with the behaviour; it is established that the effects of stimulation persist well beyond the actual stimulation period [20,23]. In the first two weeks, electrode-implanted animals received subthalamic stimulation on all testing days, thereafter phase A and B testing days were randomized. During phases A and B, sham-operated animals (DRL: $n = 12$; rGT: $n = 12$), which served as surgical cage controls, underwent no pre-treatment, but were tested on the behavioural tasks at the same time as their DBS counterparts.

2.6. Verification of electrode placements

Upon completion of all experiments, rats were deeply anesthetized with sodium pentobarbital, and brains were recovered, sectioned, and then stained with cresyl violet, in order to verify the electrode placements. The locations of the electrode tips were determined and mapped onto standardized sections of the rat brain [22].

2.7. Statistical analyses

The dependent variables, DRL efficiency (%) and mean inter-response time (mIRT), and rGT choice distribution (P1%, P2%, P3% and P4%) and number of premature responses were analyzed using one-way repeated measures ANOVA (Pre-Op, Post-op, Phase A, Phase B). The ANOVAS were performed separately for the DBS and control groups because phase B involved different treatments for the two groups), followed by paired t tests for post hoc comparisons.

3. Results

3.1. Histology

Two animals, one from each cohort (rGT and DRL) were removed from the analysis because of electrode misplacements (Fig. 1). Two electrode-implanted rGT animals died before the end of the experiment (one haemorrhage, one fallen electrode cap), so their data were also excluded from any subsequent analysis. Final results were based on 23 DRL rats (DBS: $n = 11$; control: $n = 12$) and 21 rGT rats (DBS: $n = 9$; control: $n = 12$).

3.2. Baseline DRL performance

Results are shown in Fig. 2. While all animals ($n = 23$) initially exhibited a high level of responding in the task, the number of responses per session dropped dramatically with training, to 158.5 ± 7.4 immediately prior to surgery (versus 375.9 ± 21.0 at day 1) ($p < 0.001$). At the same time, the number of reinforcers earned per session increased significantly to 42.4 ± 4.7 pellets (versus 21.8 ± 0.7 at day 1) ($p < 0.001$). Thus, the mean efficiency increased significantly from 6.3% (±0.5%) to 30.8% (±4.3%) ($p < 0.001$). As expected, the mean inter-response time (mIRT) for the group approached 20 s (18.1 ± 0.7 s) immediately prior to surgery (Fig. 2A–C). Considerable variability in inter-individual performance was observed at this time (efficiency range: 5.9–85.8%; mIRT range: 13.1–28.5 s), reflecting a large spread in terms of impulsive-like behaviour in this population. A total of 33 DRL training sessions were completed, and statistically stable responding on the task was confirmed in the last three sessions prior to surgery (pre-op phase) ($p > 0.05$).

3.3. Effect of STN-DBS on DRL performance

Following a week of recovery, all DRL animals completed 8 phase A (DBS ON) sessions and 3 phase B (No DBS) sessions over 3 weeks. Although DRL behaviour had appeared stable pre-operatively, it continued to improve post-operatively in both DBS and control animals (mIRT $F_{3,69} = 9.56$, $p < 0.001$, efficiency $F_{3,69} = 9.56$, $p < 0.001$; DBS group, $p = 0.02$; control group, $p = 0.014$, compared to their

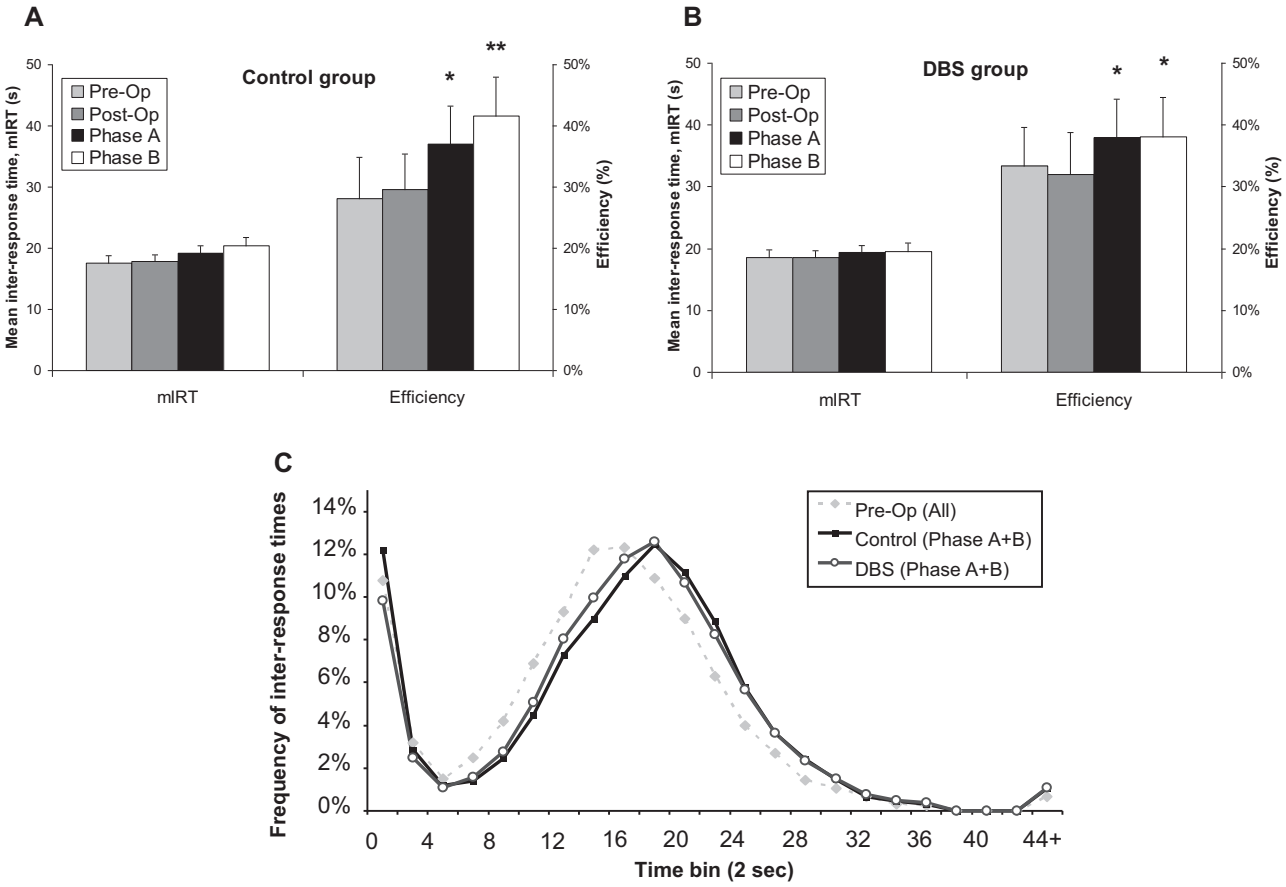

Fig. 2. Effects of STN-DBS on DRL20 responding. A, B. Mean inter-response time (mIRT) and efficiency (%) for the control (panel A) and DBS (panel B) groups during different phases of the experiment: pre-op (last three sessions immediately prior to surgery), post-op (first three sessions after post-surgical recovery, with no pre-treatment for either group). In phase A, each DRL session was preceded by 2 h of STN-DBS for the DBS group, and no pre-treatment for the control group. In phase B, each DRL session was preceded by 2 h of being connected to the DBS stimulator with no current for the DBS group, and no pre-treatment for the control group. All comparisons were made to the corresponding post-op value. $^{*}p < 0.05$, $^{**}p < 0.02$, paired t tests. C. Frequency distributions of DRL20 inter-trial-responses (IRTs) per session in 2-sec time bins (0–44+ s), during different phases of the experiment: pre-op for all animals (control and DBS group, $n = 24$), post-op for control animals (phases A + B, $n = 12$), and post-op for DBS group (phases A + B, $n = 12$). Data for phases A and B were combined since no differences were noted in the two IRT distribution curves for both groups ($p > 0.05$). The mIRT excludes any responses that fell in the 0–2 and 2–4 s time bins.

respective post-op baselines) (Fig. 2A, B), with maximal efficiency of 37.5% (±4.1%) ($n = 24$) being reached at the end of the experiment (session 47). This was also evident in the slight rightward shifts in mIRT distribution curves for both groups (Fig. 2C).

When STN-DBS was applied performance was not affected, as the change in efficiency seen in the DBS group was not different from that of the control group, which never received stimulation (Phase A Fig. 2A vs. Phase A Fig. 2B, $p > 0.05$). Moreover, no significant differences were observed between phase A (DBS ON) and phase B (rats connected to the stimulator, but not stimulated) ($p > 0.05$) (Fig. 2A, B). Furthermore, stimulation had no effects on DRL burst responding (ITI 1-4s, which is excluded from the mIRT measure).

3.4. Baseline rGT performance

During rGT training animals learned to associate each hole (P1–P4) with a particular reinforcement schedule, where P2 is the optimal choice and P4 represents the riskiest option (Table 1). In the forced choice version of the task (rGT-FC), all options were chosen equally, as expected ($p > 0.05$). In contrast, after 26 sessions on the free rGT, rats chose P2 > P3 > P1 > P4, with a highly significant preference for option P2, which represented an average of 66% ± 6.2% of all choices made per session ($p < 0.0001$) (Fig. 3). Rats completed an average of 94 ± 4.8 trials per 30-min session. Individuals generally exhibited an extremely stable pattern of behaviour, with small within-subject variability, but considerable variability in the choice distribution between animals (P2 range: 8–100%; P4 range: 0–33% of total choices per session). Interestingly, significant differences in choice profile were observed between the two rGT versions (Version main effect, $F = 6.493$, $p = 0.001$). Animals assigned to perform version 2 of the task consistently performed better than those on version 1 (e.g. P2 average: 82% vs. 50% of total choices per session, respectively, $p = 0.006$; with a corresponding change in P3 choices, $p = 0.0008$). This was not noted in previous reports [18] and suggests some location preference in our experiments. However, since rats performing on each version were evenly distributed between the DBS and control groups, the observed version differences are not likely to affect the validity of our results. Immediately prior to surgery, the average number of premature responses (PRs) per session was 12.2 (±2.0), again with a considerable inter-individual variability (PR range: 0–36), reflecting a large spread in terms of impulsivity in this population (Fig. 4).

3.5. Effect of STN-DBS on rGT choice behaviour

Twenty-three rats completed 15 non-consecutive phase A sessions and 8 non-consecutive phase B sessions over 6 weeks. During the post-op phase, which started a week after surgery and involved no DBS or cable connecting, both control and DBS animals

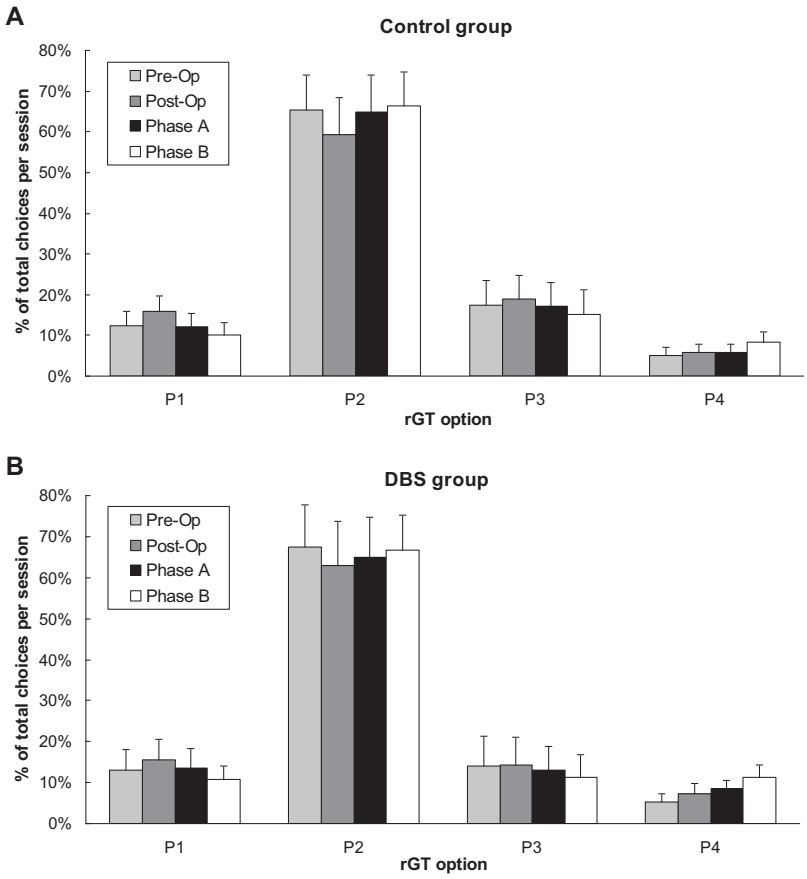

Fig. 3. Effects of STN-DBS on choice behaviour in the rGT. A, B. Rat gambling task (rGT) choice profiles for the control (panel A) and DBS (panel B) groups. Each option (P1–P4) is shown as a percent of total choices per session for different phases of the experiment: pre-op (last 3 rGT sessions immediately prior to surgery), post-op (first 3 rGT sessions after post-surgical recovery with no pre-treatment for either group). In phase A (15 non-consecutive sessions over 6 weeks) each session was preceded by 2 h of STN-DBS for the DBS group, and no pre-treatment for the control group. In phase B (8 non-consecutive sessions over 6 weeks), each session was preceded by 2 h of being connected to the DBS stimulator with no current for the DBS group, and no pre-treatment for the control group.

experienced a slight reduction in optimal performance, as indicated by a significant decrease in the number of trials completed (from 94 pre-op to 79 post-op, $p < 0.0001$) and slight decrease in the percent of P2 choices (Fig. 3A, B). However, the number and distribution of choices quickly returned to its pre-operative levels in both groups ($p > 0.05$ after 3 days of post-op testing). This step served as a within-subject control for the possibility that electrode insertion itself could affect rGT performance, but no evidence for this hypothesis was found. When DBS was applied (phase A) no significant effects of subthalamic stimulation were observed, relative to the post-op phase (P1–P4: $p > 0.05$). Moreover, no significant differences were observed between phase A (DBS ON) and phase B (rats connected to the stimulator, but not stimulated) (P1–P4: $p > 0.05$) (Fig. 3A).

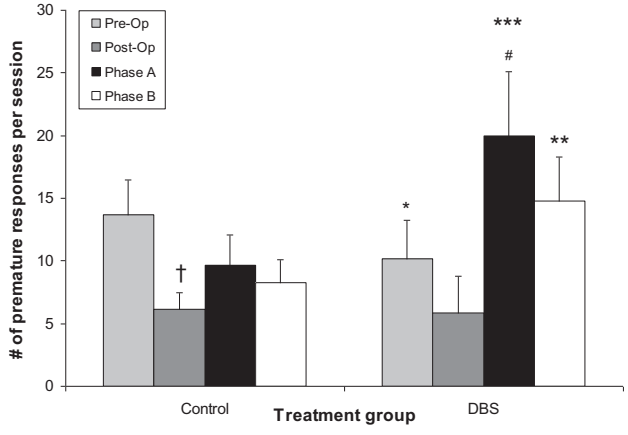

Fig. 4. Effects of STN-DBS on premature responding in the rGT. Number of premature responses per rGT session for DBS and control groups, during different phases of the experiment, as described in the legend to Fig. 3. All comparisons used paired *t* tests after a signficant repeated measures ANOVA. $^{*}p < 0.05$; $^{**}p < 0.02$; $^{***}p < 0.001$ vs. corresponding post-op value; $\dagger p < 0.02$ compared to pre-op baseline; $\#p < 0.05$, compared to post-op phase B.

3.6. *Effect of STN-DBS on rGT premature responding*

During the post-op phase immediately after surgery, both control and DBS groups experienced a slight reduction in the number of premature responses per session ($F_{3,60} = 6.85$, $p < 0.002$; control $p = 0.03$; DBS $p = 0.05$, paired *t* tests vs. pre-op baseline). During phases A and B, control animals maintained a level of premature responding that was still slightly below the pre-surgical baseline (9.7 ± 2.4 vs. 13.7 ± 2.8; $p = 0.05$) (Fig. 4). In contrast, in the DBS group, subthalamic stimulation significantly increased the number of premature responses per session, from 5.9 (± 2.9) prior to stimulation, to an average of 20.0 (± 5.1) during phase A ($p = 0.0004$). It took four consecutive DBS sessions for this effect to be first observed, as the level of premature responding in the first week of stimulation was very similar to the post-operative values (7.7 ± 2.7 vs. 5.9 ± 2.9, respectively, $p > 0.05$). Moreover, this deficit in inhibitory control decreased in magnitude, but was not completely abolished during phase B, when animals were connected to

the DBS stimulator, but no current was passed through (phase A vs. B, p = 0.05; post-op vs. phase B, $p = 0.001$) (Fig. 4). No significant changes were seen in any other dependent variables, such as latencies to respond, omissions and perseverative responses ($p > 0.05$) (data not shown).

4. Discussion

The main finding of this study was that DBS applied to the STN did not affect response inhibition in the DRL or choice behaviour in the rGT, but did induce a significant and lasting increase in premature responding in the latter task. These results suggest that STN-DBS may not lead to a general loss of inhibitory control, but may instead affect impulsivity under specific conditions. Of note, the observed effects of STN-DBS on premature responding were seen in otherwise intact rats, suggesting that STN stimulation may affect aspects of impulsive behaviour in the absence of parkinsonian neuropathology and medications.

In the DRL group, surgery or repeated subthalamic stimulation had no effect on response inhibition on a DRL20s schedule. In the rat gambling task (rGT), animals learned to "play the odds", while choosing between four options based on the expected reward or punishment. Option P2 is the most optimal option, associated with the most food pellets earned per unit time, whereas P4 represents the most maladaptive choice. A bias towards option P4 might thus indicate a preference for immediate gratification over long-term gain, or a pattern of impulsive, high-risk, decision making. Consistent with previous experiments [18], we found a significant preference of animals for option P2 (2/3 of total choices at baseline). Of note, individual behaviour was extremely stable over time and most rats adopted the optimal strategy in the task. The level of "impulsive" P4 responding, on the other hand, remained low for the group (5% of total choices at baseline), with several high impulsivity animals exhibiting a much higher propensity for this disadvantageous option (P4 range: 0–33% of total choices per session). Sham or electrode implantation surgery was found to transiently impair rGT performance in terms of total choices completed, but this effect was abolished by day 3 of post-op testing. We found no evidence that repeated STN-DBS had any significant effects on rGT gambling-like behaviour. In contrast, STN-DBS significantly increased premature responding in the task, an effect that developed over several sessions and was still evident on subsequent trials when no stimulation was given.

As expected, we observed a dissociation between the effects of STN-DBS on decision making and premature responding in the rGT. In the literature, two distinct facets of impulsivity are commonly distinguished, impulsive choice (or the inability to avoid high-risk options, a more cognitive construct) and impulsive action (or the inability to withhold a response, a motor component of impulsivity) [18]. These are modelled separately in the rGT task, are thought to have unique neurochemical underpinnings, and are often differentially affected by different treatments, as this dissociation is consistent with previous pharmacological analyses using the rGT task [18,24]. Here we observed no effects of repeated DBS treatment on impulsive choice behaviour in the gambling task, which may only be affected with chronic, continuous stimulation and/or a higher current amplitude.

The finding that STN-DBS had no significant effects on DRL performance or on choice behaviour in the rGT, while increasing premature responding in the rGT is intriguing. Even though both DRL and premature responding in the rGT are thought to measure the motor aspect of impulsive behaviour (impulsive action), we observed different effects of DBS on these two outcome measures. It is likely that these two behaviours rely on cognitive and motivational processes to different extents. For example, responding on the DRL schedule largely depends on the ability to accurately perceive the passage of time, as rats are only rewarded if they lever press at greater than 20-second intervals. In the rGT, on the other hand, the start of every trial is signalled by a light stimulus, and therefore, premature responding in this reflects a general inability to inhibit or delay a response in a high conflict situation, where the primary task is to choose between options with different reinforcement schedules. In fact, the ability of STN-DBS to increase impulsive, premature responding in human PD patients performing a reaction time task is thought to be significantly enhanced in high conflict situations [2] and to be mediated by the hyperdirect pathway from the cortex to STN [25]. Therefore, it could be hypothesized that STN-DBS induces premature responding in the rGT task, which represents a high conflict situation; whereas stimulation did not alter performance in the less demanding DRL task. Moreover, in the DRL, a failure to inhibit a response anywhere in the first 20 s results in the immediate loss of reward in the current trial and the return of the clock to zero. In contrast, a premature response in the rGT is punished somewhat less severely, with the start of a new trial after a 5-second time-out. These and other potential differences in the two paradigms reflect different pressures on impulse control, resulting in different susceptibility of the observed behaviours to STN-DBS. It seems possible, therefore, to suggest that in the absence of pathology STN-DBS may not result in a general loss of inhibitory control, but may instead increase impulsivity in a situation-dependent fashion, possibly as a function of situational stress.

Accumulating evidence supports an association between DBS applied to the subthalamic nucleus and increased impulsivity [7–12]. While our results support the clinical link between STN-DBS and higher impulsivity in intact rats, studying this association in laboratory animals in the context of Parkinson's disease has been generally difficult. A major limitation of using fully parkinsonian rats to investigate treatment effects on impulse control is that they experience various motor and cognitive deficits that impair performance on complex operant tasks, such as those assessing impulsive behaviour, and this inability to perform the tasks is often not alleviated by STN-DBS, despite its anti-parkinsonian effects [15,26,27]. Studies report both worsening and reversal of lesion-induced attentional and inhibitory deficits (e.g. in terms of reaction times, premature and perseverative responses) in parkinsonian rats following STN-DBS, depending on the stimulation parameters [16,17,27,28]. To our knowledge, however, none have found a significant association of STN-DBS with increased impulsive, premature responding in either intact or PD animals. Interestingly, physical lesions of the subthalamic nucleus in both intact and parkinsonian rats were previously found to induce a dramatic increase in premature responding in a 5-choice serial reaction time task [29–31] and a stop-signal reaction-time (SSRT) [32]. This deficit in response inhibition after STN lesions is quite consistent with the current findings, as we recently found that STN-DBS is functionally equivalent to transient inactivation of the subthalamic nucleus [33].

An unexpected observation in this study was that the effects of DBS on premature responding persisted to some extent on subsequent trials when no stimulation was given. One possibility is that the cable connecting procedure alone is stressful enough to cause a significant effect in subsequent impulsivity testing. This seems unlikely, however, since the level of premature responding in the first week of stimulation, when the procedure would be thought to be most stressful, was similar to the level observed without any pre-treatment. This suggests that it is the STN-DBS that induces the observed deficit in impulse control, and that this effect may persist after stimulation has been ceased, which could have clinical implications. This issue of reversibility between phase A (DBS ON) and B (DBS OFF) is likely reflective of the mechanisms by which

DBS exerts its effects on the brain. Our results are consistent with a mechanism of DBS action which involves more than just a transient change in excitability of local tissue and extends beyond the actual stimulation period. Previous studies have found various cellular and synaptic changes following repeated DBS, such as alternations in neuronal firing, neurotransmitter release and transcription factor levels [14,23], which could account for the prolonged effects of stimulation long after the current was turned off. Future studies should address the temporal effects of STN-DBS, in order to establish how long the observed deficit in inhibitory control persists for after discontinuation of STN-DBS. Further experiments, such as microdialysis in freely-moving intact and parkinsonian rats during subthalamic stimulation, could also be performed to investigate the molecular mechanisms underlying the effects of this procedure on impulse control.

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References

[1] Lyons MK. Deep brain stimulation: current and future clinical applications. Mayo Clinic Proceedings 2011;86:662–72.
[2] Wylie SA, Ridderinkhof KR, Elias WJ, Frysinger RC, Bashore TR, Downs KE, et al. Subthalamic nucleus stimulation influences expression and suppression of impulsive behaviour in Parkinson's disease. Brain 2010;133:3611–24.
[3] Chabardes S, Polosan M, Krack P, Bastin J, Krainik A, David O, et al. Deep brain stimulation for obsessive compulsive disorder: subthalamic nucleus target. World Neurosurgery 2012.
[4] Mohr P, Rodriguez M, Slavickova A, Hanka J. The application of vagus nerve stimulation and deep brain stimulation in depression. Neuropsychobiology 2011;64:170–81.
[5] Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. New England Journal of Medicine 2006;355:896–908.
[6] Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks Jr WJ, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA 2009;301:63–73.
[7] Demetriades P, Rickards H, Cavanna AE. Impulse control disorders following deep brain stimulation of the subthalamic nucleus in Parkinson's disease: clinical aspects. Parkinson's Disease 2011;2011:658415.
[8] Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 2007;318:1309–12.
[9] Robert G, Drapier D, Verin M, Millet B, Azulay JP, Blin O. Cognitive impulsivity in Parkinson's disease patients: assessment and pathophysiology. Movement Disorders 2009;24:2316–27.
[10] Rodriguez-Oroz MC, Lopez-Azcarate J, Garcia-Garcia D, Alegre M, Toledo J, Valencia M, et al. Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. Brain 2011;134: 36–49.
[11] Smeding HM, Goudriaan AE, Foncke EM, Schuurman PR, Speelman JD, Schmand B. Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease. Journal of Neurology Neurosurgery & Psychiatry 2007;78:517–9.
[12] Witt K, Pulkowski U, Herzog J, Lorenz D, Hamel W, Deuschl G, et al. Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. Archives of Neurology 2004;61:697–700.
[13] Halbig TD, Tse W, Frisina PG, Baker BR, Hollander E, Shapiro H, et al. Subthalamic deep brain stimulation and impulse control in Parkinson's disease. European Journal of Neurology 2009;16:493–7.
[14] Baunez C, Gubellini P. Effects of GPi and STN inactivation on physiological, motor, cognitive and motivational processes in animal models of Parkinson's disease. Progress in Brain Research 2010;183:235–58.
[15] Darbaky Y, Forni C, Amalric M, Baunez C. High frequency stimulation of the subthalamic nucleus has beneficial antiparkinsonian effects on motor functions in rats, but less efficiency in a choice reaction time task. European Journal of Neuroscience 2003;18:951–6.
[16] Desbonnet L, Temel Y, Visser-Vandewalle V, Blokland A, Hornikx V, Steinbusch HW. Premature responding following bilateral stimulation of the rat subthalamic nucleus is amplitude and frequency dependent. Brain Research 2004;1008:198–204.
[17] Temel Y, Visser-Vandewalle V, Aendekerk B, Rutten B, Tan S, Scholtissen B, et al. Acute and separate modulation of motor and cognitive performance in parkinsonian rats by bilateral stimulation of the subthalamic nucleus. Experimental Neurology 2005;193:43–52.
[18] Zeeb FD, Robbins TW, Winstanley CA. Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. Neuropsychopharmacology 2009;34:2329–43.
[19] Fletcher PJ, Chambers JW, Rizos Z, Chintoh AF. Effects of 5-HT depletion in the frontal cortex or nucleus accumbens on response inhibition measured in the 5-choice serial reaction time test and on a DRL schedule. Behavioural Brain Research 2009;201:88–98.
[20] Creed M, Hamani C, Nobrega JN. Deep brain stimulation of the subthalamic or entopeduncular nucleus attenuates vacuous chewing movements in a rodent model of tardive dyskinesia. European Neuropsychopharmacology 2011;21:393–400.
[21] Paterson NE, Wetzler C, Hackett A, Hanania T. Impulsive action and impulsive choice are mediated by distinct neuropharmacological substrates in rat. International Journal of Neuropsychopharmacology 2011:1–15.
[22] Paxinos G, Watson C. The Rat Brain in Stereotaxic Coordinates. New York: Academic Press; 1986.
[23] Boulet S, Lacombe E, Carcenac C, Feuerstein C, Sgambato-Faure V, Poupard A, et al. Subthalamic stimulation-induced forelimb dyskinesias are linked to an increase in glutamate levels in the substantia nigra pars reticulata. Journal of Neuroscience 2006;26:10768–76.
[24] Baarendse PJ, Winstanley CA, Vanderschuren LJ. Simultaneous blockade of dopamine and noradrenaline reuptake promotes disadvantageous decision making in a rat gambling task. Psychopharmacology (Berl).225:719-31.
[25] Redgrave P, Rodriguez M, Smith Y, Rodriguez-Oroz MC, Lehericy S, Bergman H, et al. Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nature Reviews Neuroscience 2010;11:760–72.
[26] Avila I, Reilly MP, Sanabria F, Posadas-Sanchez D, Chavez CL, Banerjee N, et al. Modeling operant behavior in the Parkinsonian rat. Behavioural Brain Research 2009;198:298–305.
[27] Henderson JM, Annett LE, Ryan LJ, Chiang W, Hidaka S, Torres EM, et al. Subthalamic nucleus lesions induce deficits as well as benefits in the hemiparkinsonian rat. European Journal of Neuroscience 1999;11:2749–57.
[28] Baunez C, Christakou A, Chudasama Y, Forni C, Robbins TW. Bilateral high-frequency stimulation of the subthalamic nucleus on attentional performance: transient deleterious effects and enhanced motivation in both intact and parkinsonian rats. European Journal of Neuroscience 2007;25:1187–94.
[29] Baunez C, Nieoullon A, Amalric M. In a rat model of parkinsonism, lesions of the subthalamic nucleus reverse increases of reaction time but induce a dramatic premature responding deficit. Journal of Neuroscience 1995;15:6531–41.
[30] Baunez C, Robbins TW. Effects of dopamine depletion of the dorsal striatum and further interaction with subthalamic nucleus lesions in an attentional task in the rat. Neuroscience 1999;92:1343–56.
[31] Baunez C, Robbins TW. Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. European Journal of Neuroscience 1997;9:2086–99.
[32] Eagle DM, Baunez C, Hutcheson DM, Lehmann O, Shah AP, Robbins TW. Stop-signal reaction-time task performance: role of prefrontal cortex and subthalamic nucleus. Cerebral Cortex 2008;18:178–88.
[33] Creed MC, Hamani C, Nobrega JN. Early gene mapping after deep brain stimulation in a rat model of tardive dyskinesia: comparison with transient local inactivation. European Neuropsychopharmacology 2012;22:506–17.