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Decreased Risk-taking and Loss chasing after Subthalamic Nucleus Lesion in Rats

Emmanuel Breysse, PhD 1, Julie Meffre PhD 1,2, Yann Pelloux PhD 1,3, Catharine A. Winstanley PhD 4, Christelle Baunez PhD 1*

1: Institut de Neurosciences de la Timone, UMR7289 CNRS and Aix-Marseille Université, Marseille, France
2: present address : Laboratoire de Neurosciences Cognitives, UMR7292 CNRS and Aix-Marseille Université, Marseille, France
3: present address: IIT, Genoa, Italy
4: University of British Columbia, Vancouver, Canada

* :corresponding author :Christelle Baunez
INT, UMR7289 CNRS & AMU
Campus Santé Timone
27 boulevard Jean Moulin
13385 Marseille cedex 05, France

Tel. +33 491324062
Fax +33 491324056

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ABSTRACT (250 words)

The subthalamic nucleus (STN) is known to play a role in the control of impulsivity of action and in impulsivity of choice under certain conditions. In order to assess its influence on decision-making under uncertainty, we have tested here the effects of bilateral STN lesions in rats performing a probability discounting task (PDT) and a "loss-chasing" task, both tasks assessing risky decision under uncertainty, but one in a positive context (probability to obtain a larger reward), the other in a negative context (risk for a larger loss). The PDT measures the choice between a small certain and a large uncertain reward. Conversely, in the "loss-chasing" task, animals choose between accepting a small certain loss versus risking a larger but uncertain penalty. The results show that STN lesions reduce risk-taking in both the PDT and the loss-chasing task, suggesting that STN inactivation could decrease risky decision-making whatever the nature of the outcome in an ambiguous context. Interestingly, opposite results were found in a small number of animals for which the lesions extended to the area dorsal to the STN (in the zona incerta), such that these animals increased choice of the uncertain option in the PDT. These results confirm the specificity of STN involvement in these processes and may provide explanations for some side-effects reported in patients when STN manipulations extend to the Zona Incerta. They also support the choice of the STN as a target for the treatment of impulse control disorders in Parkinson's Disease and in obsessive compulsive disorders.

INTRODUCTION

Decision making is important in many aspects of everyday life, from choosing a restaurant for dinner, to deciding on how to invest for the future. Numerous processes are involved in decision making. It starts with the necessity to value the options, while holding a potential response and then decide on which option to choose depending of what is on board. Sometimes failures occur that can be linked to a loss of inhibitory control, and these may lead to impulse control disorders (ICDs). ICDs are characterized by the DSM-V as a "failure to resist impulses to engage in harmful, disturbing or distressing behaviours which could lead to uncontrollable and excessive risk-taking propensity and compulsivity" (e.g: intermittent explosive disorder, kleptomania, pyromania, trichotillomania, compulsive shopping, punding, binge eating and hypersexuality).

Both animal and human studies show that the subthalamic nucleus (STN) is involved in all aspects of decision-making, starting by the valuation of options. Electrophysiological recordings of STN have shown in rats, monkeys and parkinsonian patients that STN encodes the value of the reward, but also the cost-benefit (Lardeux et al 2009; 2013; Breysse et al 2015; Espinosa-Parilla et al 2013; Zenon et al 2016). Studies using STN manipulations (lesions or deep brain stimulation (DBS)) have confirmed these observations (Baunez et al 2005; Rouaud et al 2010; Frank et al 2007; Atkinson-Clement et al 2019). The STN is also involved in the control of inhibition. Indeed, STN lesions increase impulsivity of action as measured by elevated premature responding on reaction time tasks in rats (Baunez *et al.*, 1995, 2001; Baunez & Robbins, 1997, 1999; Phillips & Brown, 2000); for review (Eagle & Baunez, 2010). Functional imaging study has shown that STN is involved during performance of a stop-signal reaction time task in human

(Aron & Poldrack 2006) and animal data have confirmed it by showing that STN lesions impair response inhibition in the stop signal reaction-time task (Eagle *et al.*, 2008). Various clinical reports have described increased impulsivity after STN DBS in parkinsonian patients (Halbig et al 2009; Cavanagh et al 2011), notably in a go/no-go task (Ballanger *et al.*, 2009) and discussed these results as a functional role of STN itself.

When considering impulsivity of choice, there are several aspects to take into accounts. The level of conflict seems important in human literature as STN manipulation affects high conflict decisions (Frank, 2006; Frank et al., 2007; Thobois et al., 2007; Cavanagh et al., 2011). However, several conditions in terms of 'certainty vs uncertainty' of the outcome and 'positive vs negative' or 'positive vs positive and negative outcomes' in the task can be critical within the concept of 'impulsivity of choice'.

One of the common tasks used to assess impulsive choice is the delay-discounting task that requires the subject to make a choice between two certain options: small immediate and large delayed gratification. In this task, decision making occurs thus in a positive context (only rewards) and certainty of the options. Under these circumstances, STN lesions in rats reduces the choice for the certain immediate reward when the delay increases for the large reward (Winstanley *et al.*, 2005; Uslaner and Robinson, 2006).

Other tasks place the subject in conditions where the outcome is uncertain and can be either a reward or a punishment (or loss). This is the case in the gambling tasks such as Iowa Gambling Task or the Rat Gambling Task. Using this latter, we have shown that risky choices were significantly reduced under STN DBS in risk-preferring rats (Adams *et al.*, 2017). Interestingly, human data, although obtained in pathological patients, also provide evidence for reduced risky decision-making such as reduces risky choices under intermittent STN DBS during performance of an economical decision-making task (Patel *et al.*, 2018) or conservative choice in an ambiguous risk situation (Brandt et al 2015).

Recording of STN activity in PD patients also support these findings, in that very low-frequency local field potentials (2-8 Hz) are increased during conflicting decision in PD patients with Gambling Disorder (Rosa *et al.*, 2013). Recording of STN during performance of a financial decision-making task under uncertainty confirms its involvement in these processes and further shows that STN intermittent stimulation reduces risky choices, increasing risk-aversion (Patel *et al.*, 2018). Gambling Disorder (GD) is one of the main Impulse Control Disorder (ICDs) reported in Parkinson's Disease. Interestingly, the effects of STN DBS on pathological gambling and related behaviour can be both beneficial (Ardouin et al., 2006; Lim et al., 2009; Lhommée et al., 2012; Eusebio et al., 2013; Boller et al., 2014; Castrioto et al., 2014; Brandt et al 2015) and detrimental (Smeding et al., 2007; Ballanger et al., 2009; Hershey et al., 2010; Oyama et al., 2011; Rogers et al., 2011). These effects are mostly discussed as a contribution of STN in these processes, although the mechanisms of DBS imply that not only STN is affected by the high frequency stimulation, but also the network of passing fibers.

"Loss-chasing" is considered as one of the most salient features of GD (Lesieur, 1979). Indeed, frequent gambling often leads to large losses, and this accumulating debt can increase the willingness to continue play in order to clear this balance, even though continued gambling can be problematic. Thus, such loss-chasing is strongly associated with impaired control over gambling behaviour and can lead to a dangerous spiral of accelerating gambling activities, increasing financial liabilities and ultimately, serious adverse family and social consequences (Corless and Dickerson, 1989). Little is known regarding the neurobiological basis of loss-chasing. An fMRI study has shown that decision to chase or quit involves two different cortical and sub-cortical systems (Campbell-Meiklejohn et al., 2008). Another study reported that STN DBS in PD patients

decreases loss-chasing behaviour first and then increases it on a second game (Rogers et al., 2011).

Clarification of the putative role of the STN in various features of GD and ICDs is thus urgently needed. It is important to assess its functions in intact animals to maybe further anticipate and then reduce the possible side-effects induced by manipulations of the STN in patients in the future.

The aim of this study was thus to investigate the role of the STN in decision-making under uncertainty in both positive and negative context. Since the mechanism of DBS is still under debate, we have chosen to inactivate selectively the STN with excitotoxic lesions, not affecting the passing fibers. We therefore assessed the impact of STN lesions on two dissociable behaviours. The first task, a probabilistic discounting task, allows to assess preference for smaller-certain versus larger-uncertain rewards without obvious negative outcome. In contrast, the second task, an animal model of loss-chasing behaviour inspired by Rogers et al., (2013) offers the choice of smaller-certain versus larger-uncertain penalties placing the animal in a negative ambiguous context. Given the fact that STN has been shown to be involved in reward-related processes and valuation, it is important to use tasks that are different in their framing with one (the PDT) using a positive outcome (sweet pellets) and the other (the loss chasing task) using a negative outcome (punishment).

MATERIAL AND METHODS

ANIMALS

A total of 10 male Long Evans (Janvier, Le Genest St Isle, France) and 10 male Lister Hooded rats (Charles River, Cologne, Germany) were used in the probability discounting experiment and 20 male Lister Hooded rats (Charles River, Cologne, Germany) were used in the loss chasing experiment. Our laboratory has switched to Lister Hooded rats, as they seem to require less food restriction to maintain motivation to work for food reward. All animals were housed in pairs in Plexiglas cages (42 x 26.5 x 18.5 cm) in the animal holding room illuminated by cycles of 12 hours (8h-20h). All animals were handled upon arrival to habituate them to contact with the experimenter. The rats had access to water without restriction while their food was limited (12g-15g/day per rat) during all the training and testing sessions. Each day, rats were weighted. At the time of surgery, rats weighed around 380-420g. All procedures, animal handling and surgery, were conducted in accordance with and approved by the local ethical committee and the French Agriculture and Forestry Ministry (Saisine (#3129.01).

APPARATUS & BEHAVIOURAL PROCEDURE

Probability Discounting Task (PDT) (Figure 1A)**:**

Apparatus: during training and experimental phases, animals were placed in two operant boxes equipped with three levers, three lights, one magazine composed of two cups in which the different rewards were delivered, one buzzer and one houselight, that was switched ON to indicate the beginning of a session and OFF during the time outs after an error made by the animals.

Procedure: Animals learned to choose between two levers, one of which was associated either with delivery of a large reward (0.1 mL of 32% sucrose solution), the other with a

small reward (0.05 mL of 32% sucrose solution). The location of these levers was kept constant for each rat throughout testing, but was counter-balanced across the cohort. Over the course of the session (120 trials or 30 min) the probability to obtain the large reward changed in a step-wise fashion between blocks of 40 trials in the following sequence: 100%, 50% and 0%. At the beginning of each trial, the animals had to press the central lever and hold it for 1 s. During this holding period, 400 ms after the lever press, a combination of two lights was switched ON for 100 ms to indicate the probability to obtain the large reward in the present trial (e.g: left and central lights announced 0%; central and right lights announced 50% and left and right lights announced 100%). Then, the rats had to maintain their central lever press for 500 ms until a trigger tone occurred to announce the central lever could be withdrawn. Then, the lateral levers were extended for the animal to make its choice between the small certain reward and the large uncertain reward (0, 50 or 100% probability). Once the rat pressed one of the levers, the associated reward was delivered into the magazine depending on the reinforcement contingency in play. The choice of the probabilities was made in order to have two control situations validating the discrimination of the cue lights and acquisition of the task: 0% should lead the animals to systematically choose the other lever, while 100% should lead the animals to choose mostly the large reward over the small since they are both certain in this condition. The third probability: 50% allows to only assess risk preference without any bias caused by differential reinforcement since the size of the 2 rewards (0.1 vs 0.05 mL) was chosen so that consistent choice of either lever during the 40 trial-block at 50% probability would result in the same volume of 32% sucrose solution delivered.

The task was considered acquired when the animals had reached stable patterns of choice during the last 10 sessions. 120 trials completed and less than 10% variability in the choice was taken as the criteria.

Loss-chasing (Figure 1B)**:**

Apparatus: Training and test sessions took place in 10 operant boxes (Med Associates, St Albans, GA). Each box was equipped with a five-hole response array with nose-poke detectors at the mouth of each hole, and one magazine in which the pellets were delivered. One tone generator (3.5 kHz) provided a non-lateralized auditory stimulus. A houselight was switched ON at the beginning of the session and turned OFF at the end of the session or during errors. Each operant box was controlled via an interface (MedPC) and a computer.

Procedure: The rats were trained to perform a "Loss Chasing" task inspired by Rogers et al. (2013). In this task, the rats had to nose-poke in the magazine to earn pellets (45 mg, saccharose). In 70% of cases, the pellet was delivered, whereas in 30% of cases it was not. On these "loss" trials, the magazine light flashed and holes 2 and 4 were illuminated, indicating that the rats had then the choice to chase their loss by nose-poking in hole 2 or to quit by nose-poking in hole 4. Nose-poking in hole 4 (i.e. "Quit 1" response) lead to a 4sec time-out and the rat had to wait the entire time-out period before getting the possibility to re-start a trial (i.e. try and earn a pellet by nose-poking in the magazine). In contrast, nose-poking in hole 2 ("Chase 1" response) lead in 50% of cases to restart the trial immediately or in 50% of cases to an 8sec time-out. If the rat had chosen to chase and had an 8sec time-out, it was offered a second choice between quit and chase. The light in hole 2 flashed and holes 1 and 3 were illuminated giving the possibility to the rat to nose-poke in one of them. Nose-poking in hole 3 ("Quit 2" response) lead then to an 8sec time-out period, while nose-poking in hole 1 ("Chase 2" response) lead in 50% of cases to restart a trial immediately or in 50% of cases to a 16sec time-out. Between each trial, rats had to wait for 1sec outside the magazine, and any response made at the magazine prior

to the end of this waiting period was considered a premature response, and the rat had to wait an additional 5sec before the start of a new trial. As such, this loss-chasing task is true to previous human and rat versions, in that the penalties for chasing at each decision point follow a "double or nothing" rule, and the potential losses also double with each successive chase. The task was considered acquired when a stable total "chase over quit" response ratio of 0.6 in average was observed during the ten last sessions.

SURGERY

Once the rats were trained on either behavioural task, they underwent surgery. For two days before surgery, they received antibiotic injection Amoxicilline (Duphamox®, 150mg/mL, s.c.). Then, they were anesthetized with a mixture of Ketamine (Imalgène 1000; 100 mg/kg, s.c.) and Medetomidine (Domitor ®, 250 mg / kg, s.c.). Two bilateral injectors were stereotaxically positioned into the STN in order to inject either ibotenic acid (9.4 µg/µL (53 mM): STN-lesioned rats) or phosphate buffer (0.1M: sham rats) at the following coordinates taken in millimeters: AP = -3.7; L = + / -2.4 from the Bregma; DV = -8.35 relative to the surface of the skull above the target point (Paxinos and Watson, 2005). 0.5 µL of the solutions were injected during 3 min (0.167 µL / min) using Hamilton® syringes, and once the injection was completed, the injectors were left in place for 3 additional minutes to allow for diffusion. The scalp was then sutured. After the surgery, a dose of Atipemazole (Antisédan®, 75mg/kg, s.c.) was administered to cancel the anaesthetic effects of Medetomidine. The animals were then given one-week recovery before testing was performed again.

BEHAVIOURAL & STATISTICAL ANALYSIS

Probabilistic-Discounting Task**:** the mean difference (Post-Pre mean) between post-surgery and pre-surgery for the number of lever presses for each condition, for the risk-taking index and for the premature lever release were calculated and analysed as well as reaction time (RT: time between the trigger tone and the central lever release) and movement time (MT: time between the lateral lever release and the magazine entry). A "risk-taking index" (RTI) was also calculated. To do this, it has been postulated that in the 100% condition for delivery of the large reward, optimal behaviour would correspond to 100% choice for large reward (A), while the opposite for the 0% condition (B) (i.e. A=40 presses and B=0 presses for a given animal). In the case of the 50% condition, since the quantity of reward obtained was the same whatever the choice (i.e. indifference point), there should be no preferential choice for one option over the other, following a linear curve (neutral risk sensitivity) over the various conditions. The RTI has thus been calculated for each individual as the mean number of large reward choices in the 100% condition (A) and the number of large reward choices in the 0% condition (B). This set the theoretical level (C) of large reward choices in the 50% condition ($C=\frac{A+B}{2}$) (e.g. $C=\frac{35+5}{2}=20$; here if the animal is neutral for the risk, it will press the lever for the large reward 20 times in the 50% condition). If the real number (e.g. 28 lever presses) of large reward choices was above the theoretical level of large reward choices in the 50% condition (i.e. 28>20; RTI=28-20=8), it was considered that this animal was risk-prone, but in case of a number of choices below the theoretical level, the animal was considered as risk-aversive (see Figure 3C). For all these data, ANOVA were done using Statview® and in case of interaction effect ($p<0.05$), a post-hoc t-test analysis has been done.

Loss-chasing: The ratio of chase over quit responses were analysed for the first and the second level of chase ($\frac{chase\ 1\ or\ 2}{chase\ 1\ or\ 2+\ quit\ 1\ or\ 2}$). The premature magazine entries have been

also measured. For all these data, ANOVA were done using Statview® and in case of interaction effect ($p<0.05$), a post-hoc t-test analysis was performed.

HISTOLOGY

Both experiments: At the end of the experiment, all rats were sacrificed, and the brains were removed, frozen and cut in coronal sections with a cryostat. Frontal 30-µm-thick sections of the STN and ZI were stained with cresyl violet for assessment of the lesions.

RESULTS

PROBABILITY-DISCOUNTING TASK

HISTOLOGY

After histological verification, out of the 20 rats that underwent surgery, 8 sham rats, 9 satisfactory, although partial, STN lesions were observed, but 3 of these 9 had also extended towards the dorsal territory above the STN (the zona incerta). These 3 rats (STN + ZI; Figure 2B) were thus grouped apart from the others (STN lesion, n=6; Figure 2A left) and kept in the analyses as an interesting control group, while 3 rats without bilateral lesion of the STN were discarded. The STN lesioned animals used for the PDT and the Loss-chasing experiment have been separated in Fig. 2A (left for PDT and right for Loss chasing) to illustrate the homogeneity of the lesion across experiments. It is interesting to note that although the variability in extent of the lesion seems large, the behavioural effects were consistent within the STN lesion animals and contrasted to those affecting the ZI as well. No difference between the Long-Evans and the Lister-Hooded animals were found.

BEHAVIOUR

Acquisition of the task: Before and after the surgery, all animals exhibited probability discounting, in that choice of the large reward declined with the probability of its delivery (probability effect: $F(2,12)=225.832$; $p<0.0001$). Moreover, all rats were faster to make any choice when the probability of getting large reward was higher (probability effect: $F(2,12)=6,778$; $p=0.004$; $p<0.05$) (data not shown). These results suggest that, regardless of any lesion effects on choice, animals' behaviour was sensitive to the specific contingencies in play, namely the association between the combination of lights and the probability that the large reward would be delivered. However, the animals took the same time to reach the magazine (movement time: MT) whatever the reward (reward effect: $F(2,12)=0.999$, $p=0.337$; $p>0.05$) although there was a trend for faster movement at the highest probability of large reward delivery (probability effect: $F(2,12)=3.325$; $p=0.053$) (data not shown).

Lesion effects: After surgery, STN-lesioned rats made more premature lever releases, before the light onset, than the sham rats (Post-Pre mean: 6.147 ± 2.418 *vs* -0.195 ± 0.581 for the STN-lesioned and the sham rats respectively) (t-test: $t=-2.918$, $p=0.0129$ $p<0.05$ compared to the sham rats) (Figure 3A), confirming past studies suggesting that STN lesions increase motor impulsivity (Baunez et al., 1995; Baunez and Robbins, 1997; Eagle and Baunez, 2010).

In the 0% condition after surgery, all the rats pressed the large-reward lever the same number of times (Figure 3B). In the 50% condition, the STN-lesioned rats were less risk-prone than the sham rats since after surgery, they pressed the large-reward lever much less than the sham rats (Post-Pre mean: -10 ± 4.95 *vs* 0.875 ± 2.295) (interaction probability x group effect: $F(2,12)=4.151$, $p=0.0107$; post-hoc t-test: $t=2.314$, $p=0.0432$).

In contrast, in the group of STN lesions affecting also the ZI, the rats increased their number of presses on the large-reward lever compared to the sham rats (Post-Pre mean: 13 ± 1.732 *vs* 0.875 ± 2.295) (group effect: $F(2,12)=7.877$, $p=0.0065$; post-hoc t-test: $t=-3.038$, $p=0.0141$) (Figure 3B), suggesting that the STN+ZI-lesioned rats increase their risk-taking. In the 100% condition, the sham and the STN+ZI-lesioned rats increased their lever presses for the large reward in the same way (Post-Pre mean: 6.25 ± 2.617 *vs* 10.33 ± 0.667 respectively) (post-hoc t-test: $t=-0.921$; $p=0.3812$; $p>0.05$) while the STN-lesioned rats decreased it (Post-Pre mean: -4 ± 1.826)(post-hoc t-test: $t=2.572$ and $t=-6.424$; $p=0.0278$ and $p=0.0014$; $p<0.05$, compared to the sham and STN+ZI-lesioned rats respectively) (Figure 3B).

Risk-taking index: In order to better understand the behavioural response to STN and ZI lesions, a "risk-taking index" (RTI) has been calculated, as described in the methods section. This analysis confirmed that rats of the STN + ZI partial lesion group increased their risk-taking (Post-Pre mean: 7.667 ± 1.453) (t-test: $t=-4.45$ and $t=-2.589$; $p=0.0016$ and $p=0.036$; $p<0.05$ compared to the sham and STN only-lesioned rats respectively) whereas both sham rats and STN-lesioned rats decreased their risk-taking in the same manner (Post-Pre mean: -2 ± 1.195 *vs* -5.5 ± 3.413 for the sham and STN-lesioned rats respectively) (t-test: $t=1.083$; $p=0.3$; $p>0.05$), even if the STN-lesioned rats tend to decrease their risk-taking more than the sham rats (Figure 3C).

All the data from this task suggest that **the STN-lesioned rats tended to be more risk-averse, while the STN+ZI-lesioned rats were more risk-taking in a task where there is an uncertainty in a positive context**.

LOSS-CHASING

HISTOLOGY

12 out of the 20 rats used for the Loss-Chasing task were kept in the analysis (n=6 sham and n=6 STN lesion)(Figure 2A right). Neither STN or mislocated lesions affected the ZI in this experiment.

BEHAVIOUR

Before surgery all the rats had a mean of total chase over quit of 0.55 ± 0.06, near to 0.6, suggesting that they tended to be chasers as defined by Rogers et al. (2013). After surgery, for the first chase level, the STN-lesioned rats chased less than the sham rats (mean: 0.27 ± 0.6 *vs* 0.66 ± 0.1 respectively) (group effect: $F(1,10)=6.033$; $p=0.034$; interaction surgery (pre-post) x group (sham-STN) effect: $F(1,10)=6.252$; $p=0.0314$; post-hoc t-test: $t=3.408$; $p=0.007$; $p<0.05$) (Figure 4), suggesting that the STN-lesioned rats were less likely to loss-chase, i.e. to gamble in order to evade an otherwise-guaranteed loss. For the second chase level, the STN-lesioned rats still chased less than the sham rats (mean: 0.36 ± 0.05 *vs* 0.65 ± 0.8 respectively) (group effect: $F(1,10)=4.961$; $p=0.05$) (Figure 5), suggesting that the STN-lesioned rats were less likely to chase their losses repeatedly. STN-lesioned rats also made more premature responses (interaction surgery x group effect: $F(1\text{-}10)=6.903$, $p=0.0253$; $p<0.05$) (Figure 6). These results suggest that, even though STN-lesioned rats showed higher levels of motor impulsivity, they were also less loss-sensitive than the sham rats in that a potential loss did not trigger the urge to gamble.

DISCUSSION

This study shows that STN lesions reduce risky choice for uncertain outcomes, either positive (rewards) or negative (potential losses or punishment), while larger

lesions affecting both the STN and the ZI, although in small number, seem to indicate an opposite effect.

Before discussing our results, it is important that we mention we are aware that most of the published data in human subjects have been obtained using DBS in patients with pathologies affecting their brain. DBS is not the equivalent of a lesion since it is considered to be inactivating the cell bodies in the target area, but also activating the passing fibers. Lesions in intact animals is therefore not comparable. However, most studies using DBS in patients draw conclusions regarding the involvement of the target structure (or at least its network) in the studied processes. Bearing this in mind, we will refer to these studies cautiously. Previous studies using STN DBS in PD patients argued that STN was involved in decision making (Frank, 2007; Brandt et al 2015) and loss-chasing behaviour (Rogers et al., 2011), but all the results are not in line with the present study carried out with lesions in non-DA depleted animals. The discrepancy can be due to the integrity of the DA system here. Indeed DA is well known to be involved in decision-making processes and risky choices, especially via D2/3 receptors (Zeeb et al., 2009; Zeeb et al., 2013 ; Cocker et al 2017 ; Tremblay et al 2017). The reduced risk-taking and maladaptive behaviour observed here after STN lesions in intact animals is in line with clinical data from patients with obsessive compulsive disorders who show improvement of their compulsions under STN DBS (Mallet et al 2008) or reduced risk taking (Voon et al., 2018), although these patients have cerebral dysfunctions before STN manipulation that our rats subjected to STN lesions do not share.

Our results showing reduction in both risk-taking and impulsive-related loss-chasing may seem surprising in regard of the influence of the STN lesion on impulsivity of

action and perseverative behaviour in the 5-choice serial reaction time task (Baunez and Robbins, 1997; Eagle and Baunez 2010). Interestingly, in both experiments presented here, the STN-lesioned rats showed higher levels of impulsive action (premature responses) in keeping with previous reports (Baunez et al 1995, Baunez and Robbins 1997; Baunez et al 2001), while concurrently reducing choice of the risky or uncertain outcomes in the loss-chasing task and PDT respectively, in line with the STN DBS effect in risk-prefering rats in the gambling task (Adams et al 2017) and the decrease in impulsive choice of smaller-sooner over larger-later rewards in delay-discounting tasks (Winstanley et al 2005). As such, our findings that STN lesions increase motor impulsivity while reducing risky or impulsive decisions matches well with the literature (for review Eagle and Baunez, 2010). This reduced choice for risky options fits also well with the reduced addiction-risky-related behaviour towards cocaine and heroin after STN lesions or DBS (Pelloux et al 2018, Wade et al 2017; Degoulet et al 2019).

STN lesions have been shown to increase motivation for sweet reward (Baunez et al 2002, 2005), ruling out the possibility to interpret the lack of choice for the larger reward in the STN lesioned animals as a decreased sensitivity to reward. An increased motivation for the large reward could thus overcome a possible impulsivity and result in the choice for the larger reward in any task. It was the case in a delay-discounting task (Winstanley et al., 2005). In the present choice task (the PDT), probably due to the uncertainty to obtain the reward, it is not the case. Indeed, choosing the large reward lever may lead to the risk of not getting any. A high level of motivation may therefore not necessarily lead to choose the larger uncertain reward, as observed here in STN rats. This result confirms the role of STN in dealing with conflict and uncertainty. This role has been suggested by computational models which proposed that the STN acts by increasing the decision threshold during situations in which several choices are possible, slowing down

responses, and thereby preventing impulsive decisions (Frank, 2006; Bogacz, 2007).

A large body of evidence supports these models of STN function, by showing that STN high frequency stimulation leads to impaired conflict resolution and impulsive responses (Frank et al., 2007; Cavanagh et al., 2011; Green et al., 2013). Choice can be guided by the cost/benefit evaluation for the outcome, but also of its level of uncertainty, contributing to the conflict between the available options. STN contribution to decision making has been hypothesized to be critical via the processing of conflict information (Frank et al 2007). In Frank's study, the high frequency stimulation of STN, supposed to mimic an inactivation, diminishes the reaction time to make a choice, but only in high conflict situations when "holding your horses" is the most required for the appropriate choice (Frank et al 2007). This facilitatory effect can be compared to impulsivity of choice described in other tasks and we could have expected similar trends in our study. The results observed here are opposite to a "disinhibition" effect, since STN lesioned rats chose the "safe" option and did not show decreased reaction time in the high-conflict situation. One possible explanation can be that the level of conflict used here is different. Although we could consider that the 50% situation is the "high conflict" situation and the 0 and 100% are "low-conflict" situations in the PDT, the outcome between the options is different. Frank et al. used a win/win situation, while in the present study we offered the choice between a secure reward versus uncertainty to obtain a larger reward that may have lead to the choice for the secure reward. This difference may explain the discrepancy of the results. It is also important to note that we have shown however that STN activity, assessed by measure of LFPs in PD patients, seems to be more related to the encoding of the reward value and the cost value (effort required), thus a cost/benefit value, than conflict in the process of decision-making (Zenon et al 2016).

In case of certainty, such as the 100% condition, one might have thus expected to see an increase of choices for the large reward in the STN rats compared to the controls, like in the delay discounting task (Winstanley et al 2005). It was not the case. The 2 other groups exhibited a higher choice for the large reward, suggesting that they had acquired the visual discrimination properly and further improved their performance over time. Although they seem to diminish in their choice for the large reward, the STN lesioned rats did not show any sign of impaired motivation either, since they did not exhibit a longer RT or time to reach the magazine. Their motivation for the food reward was thus not decreased. This rules out the possibility that the lack of increased choice for the large reward results from a change in motivational state. Indeed, it has been shown that STN lesion could lead to a deficit in working memory (El Massioui et al., 2007). Thus, the decreased lever presses for the large-reward lever in the 100% condition could be due to a deficit in working memory., but such a deficit should increase loss chasing, which is not the case, making this hypothesis less likely. A third hypothesis is that the STN is involved in automatic and habitual behaviour (Banca et al., 2015). Indeed, setting an automatic behaviour leads to process it faster than a behaviour requiring continuous online control. Thus, lesion of the STN could block the installation of this automatic behaviour and block the improvement of the behaviour, leading to a lower performance. This is however unlikely since it has never been observed in former experiments.

One way to understand the risk aversion exhibited by the STN-lesioned rats could be that the STN lesion increases the sensibility to the reward omission. This hypothesis has already been raised by Winstanley et al. (2005) using the autoshaping paradigm. Indeed, in this paradigm, the animals have to associate a conditioned stimulus (CS) with a reward. When the CS is no longer associated with the reward, sham animals show perseverative responses for the CS. The authors found that the STN lesion decreased the animals'

perseverative responses for the CS when it was no longer associated with the reward, suggesting that this effect could be due to an increased sensitivity for the omitted reward. However, it is important to note that in another procedure, STN lesioned rats pressed more than sham animals on a lever leading to presentation of a CS formerly associated with a reward (Conditioned reinforcement task, Baunez et al 2002). Omission of a positive reward can be seen as a negative outcome, but it was also important to assess the effects of STN lesions in a risky task involving a negative outcome such as the loss chasing task in order to generalize, or not, the conservative behaviour observed in STN lesioned animals. The present results confirm that STN lesions leads to the choice for certain limited loss/penalty over risky option.

In line with this, it has been reported that STN DBS increases risk-averse tendency in ambiguous risky task, especially when the framing is negative (risk to loose more money) vs positive (risk to gain less money) (Brandt et al 2015). This particular sensitivity to uncertainty is of particular interest if we consider that STN lesions have been shown to reduce affective responses (Pelloux et al 2014) and that STN DBS in OCD patients impairs discrimination of loss magnitude (Voon et al 2018).

One fMRI study carried out during loss chasing performance revealed that the ventral medial prefrontal cortex (vmPFC) and the subgenual cingulate cortex (sgACC), associated with the anticipation of positive outcomes and appetitive states, show activity when deciding to chase as compared to deciding to quit (Campbell-Meiklejohn et al. 2008). Interestingly, STN is involved in reward expectation (Baunez et al 2002 ; Lardeux et al 2009, 2013 ; Breysse et al 2015). If the circuit of reward expectation is involved, therefore, preventing STN activation with lesion should reduce the anticipation of positive outcome and favour decision to quit. This may seem paradoxical regarding the increased motivation for sweet food observed after STN lesions discussed above, but our further

studies suggest that enhanced motivation after STN lesions might be the consequence of an urge for calories with a loss of hedonic responses (Pelloux et al 2014).

Although they rely on a very small number of animals, the opposite effects found between the lesion affecting both part of the STN and part of the zona incerta (ZI) (n=3) are homogeneous and serve as a good control to compare with lesions made in the STN only (even partially), as they are surprising. However, a former study has shown that bicuculline could induce motor effects when injected into the ZI but not in the STN (Périer et al 2002), highlighting the fact that these two areas do not contribute exactly in the same manner to motor behaviour. Studies in PD patients have reported that ZI DBS could have similar to better effects than STN DBS to treat the motor symptoms (Nandi et al., 2002; Benazzouz et al., 2004; Plaha et al,. 2006; Blomstedt et al., 2011; 2012). However, only few of these studies investigated non-motors effects of the ZI DBS and the differences shown here can be important when considering the possible side effects of DBS applied in the STN but also often affecting the ZI. It is not clear whether or not DBS improves or worsens ICDs in PD patients as explained in the introduction. While some authors suggest that PG behaviour results from a combination of bilateral STN DBS and treatment with dopamine agonists and not only from STN DBS itself (Smeding et al., 2007), it is possible that it results from DBS affecting the ZI. The effects of STN and ZI DBS have been poorly documented to date. One report has shown that ZI DBS could improve anxiety and depression in PD patients (Burrows et al., 2012), while another has reported that either STN or ZI DBS could lead to psychiatric complications like irritability, psychomotor agitation and severe progressive insomnia (Merello et al., 2009). Our results suggest that this area should be taken into accounts carefully.

To conclude, our study shows that STN lesion decreases risk-taking, while lesions affecting both STN and the ZI area may increase it. These results confirm the critical role of STN in decision-making processes, but they also may have a high impact for surgical treatment. Indeed, if we consider that DBS affects the functioning of the targeted structure (among other mechanisms), they strongly suggest that it is important to better control the DBS implantation site and better understand the way the DBS current diffuses in the STN vicinity, and especially to the ZI, in order to minimize its possible side-effects. Reducing the activity of STN seems a good option to reduce certain forms of ICDs seen in various pathologies.

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Authors contribution:

Design of the study: YP, CB. Funding of the study: CB, CAW. Experimental work: EB, JM, YP, CB. Histological work: EB. Computer programming of the tasks: JM, EB, YP. Statistical analysis: EB. Writing of the manuscript: EB, CAW, CB

Conflict of interest:

All the authors have no competing financial interests in relation to the work described to declare.

Data Availability:

The entire set of data can be made available under request to the corresponding author

List of abbreviations:

DA: dopamine

STN: subthalamic nucleus

OCD: obsessive compulsive disorders

GD: gambling disorders

ICD: Impulse Control Disorders

rGT: rat Gambling Task

PDT: Probability Discounting Task

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LEGENDS

Figure 1. A: Probability-discounting task. The rats had to press down the central lever for one second. During this one second period, after 400 ms had elapsed, a combination of two cue lights was switched ON (either right and left, or right and central or central and left) for 100 ms, providing information regarding the probability of getting the large reward (e.g: left and right lights=getting the large reward in 100%). The rats had to maintain their paw on the central lever until the end of the one-second period (i.e. an extra 500ms) that was signaled by a tone. Then, the central lever was retracted and the two lateral levers were extended so that the animals could make a choice by pressing either the left or the right lever. Pressing the lateral lever lead to reward delivery in one cup of the magazine (e.g: left lever press= uncertain large reward (0.1 mL of 32% sucrose delivered at the probability announced by the lights) and right lever press= certain small reward (0.05 mL of 32% sucrose delivered systematically)).

B: Loss-chasing task. Start: the rats had to nose-poke in the magazine. In 70% of cases the nose-poke delivered one sucrose pellet (45 mg) in the magazine and the magazine light was switched ON to signal this gain. In 30% of the cases pellet was not delivered and the magazine light was flashed ON to signal this loss. 1st chase level: In the same time, the holes 2 and 4 were switched ON (e.g: hole 2=chase 1 and hole 4=quit 1). Choosing to quit lead in 100% of cases to four seconds time-out period before the animals were allowed to start the next trial. Choosing to chase leads, in 50% of cases, to allowing the animals to immediately start the next trial, while in the 50% other cases, it leads to eight seconds time-out period before the animals were allowed to initiate the next trial. 2nd chase level: The chasing hole was then flashed ON (e.g: hole 2 flashing = 2nd chase level) and the light in the holes 1 and 3 were switched ON (e.g: hole 1=chase2 and hole 3=quit2). Choosing to quit lead in 100% of cases to eight seconds time-out period before the animals were allowed to start the next trial. Choosing to chase leads, in 50% of cases, to allowing the

animals to immediately start the next trial, while in the 50% other cases, it leads to sixteen seconds time-out period before the animals were allowed to initiate the next trial. Each operant box was equipped with five holes with light inside, one houselight, one buzzer and one magazine with one light inside. Choice periods were differentiated from time-out periods thanks to a 1Hz tone.

Figure 2: Schematic reconstruction of the lesions. A. Top: Photograph of one sham STN (left; delimitation materialized by black dashed line) and one STN lesion (right; delimitation materialized by red dashed line). Bottom: Bilateral STN lesions illustrated at the various antero-posterior levels of the Paxinos and Watson atlas (2007) (numbers in mm from Bregma on the right-hand side). The red striped area illustrates the largest lesion observed, while the plain red area represents the smallest of all the animals kept for analysis in the PDT (left, n=6) and the loss chasing experiment (right n= 6). B. Bilateral lesions affecting not only the STN partially, but the zona incerta (ZI) illustrated at the various antero-posterior levels of the Paxinos and Watson atlas (2007) (numbers in mm from Bregma on the right-hand side). The green striped area illustrates the largest lesion observed, while the plain green area represents the smallest (n=3).

Figure 3. Behavioural data for each group in the probabilistic-delivery task. A: Mean difference (Post-Pre) between post and pre-surgery for the number of premature lever release before the lights onset for all groups: Sham rats (n=8; blue individual dots), STN-lesioned rats (n=6; red individual dots) and STN+ZI-lesioned rats (n=3; green individual dots). *: significantly different from the sham rats ($p<0.05$); a: significantly different from the STN-lesioned rats before surgery. **B:** Mean difference between post and pre-surgery for the number of large-reward lever presses depending on the probability of getting the

large reward (left=100%; middle=50%; right=0%) for all groups: Sham rats (blue individual dots), STN-lesioned rats (red individual dots) and STN+ZI-lesioned rats (green individual dots). *: significantly different from the sham rats ($p<0.05$); #: significantly different from the STN-lesioned rats ($p<0.05$); b: significantly different from the STN+ZI-lesioned rats before surgery. **C:** Mean difference between post and pre-surgery for the risk-taking index for all groups: Sham rats (blue individual dots, n=8), STN-lesioned rats (red individual dots, n=6) and STN+ZI-lesioned rats (green individual dots, n=3). *: significantly different from the sham rats ($p<0.05$) ; b: significantly different from the STN+ZI-lesioned rats before surgery.

Figure 4. Behavioural data obtained in the loss-chasing task for the first chase level. **A:** animals' distribution depending on the number of time they choose to chase compare to the number of time they quit for the sham rats (blue, n=7) and the STN-lesioned rats (red, n=6). The black dotted (f(x)=y) line represents the limit between animals classified as chaser or quitter. **B:** mean chase over quit ratio for sham (blue, n=7) and the STN-lesioned rats (red, n=6). *: significant effect compared to the sham rats ($p<0.05$).

Figure 5. Behavioural data obtained in the loss-chasing task for the second chase level. A: animals' distribution depending on the number of time they choose to chase again compared to the number of time they quit for the sham rats (blue, n=7) and the STN-lesioned rats (red, n=6). The black dotted (f(x)=y) line represents the limit between animals classified as chaser or quitter. **B:** mean chase over quit ratio for sham (blue, n=7) and the STN-lesioned rats (red, n=6). *: significant effect compared to the sham rats ($p<0.05$).

Figure 6. Mean number of premature magazine entry for the sham (blue, n=7) and STN-lesioned rats (red, n=6) in the loss-chasing task. *: significant effect compared to the sham rats ($p<0.05$).

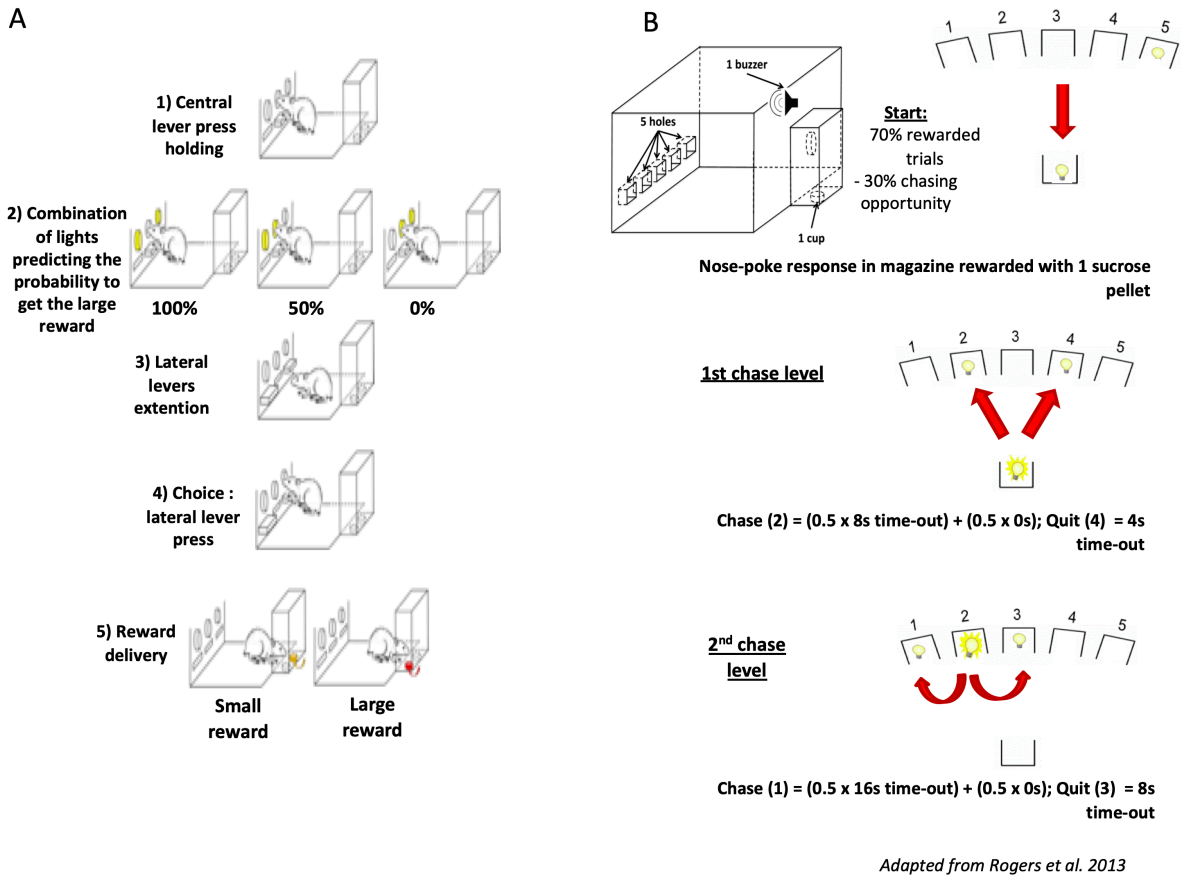

A
1) Central lever press holding
2) Combination of lights predicting the probability to get the large reward
100%
50%
0%
3) Lateral levers extention
4) Choice : lateral lever press
5) Reward delivery
Small reward
Large reward
B
1 buzzer
5 holes
1 cup
Start:
70% rewarded trials
- 30% chasing opportunity
1 2 3 4 5
Nose-poke response in magazine rewarded with 1 sucrose pellet
1st chase level
Chase (2) = (0.5 x 8s time-out) + (0.5 x 0s); Quit (4) = 4s time-out
2nd chase level
Chase (1) = (0.5 x 16s time-out) + (0.5 x 0s); Quit (3) = 8s time-out
Adapted from Rogers et al. 2013

Figure 1

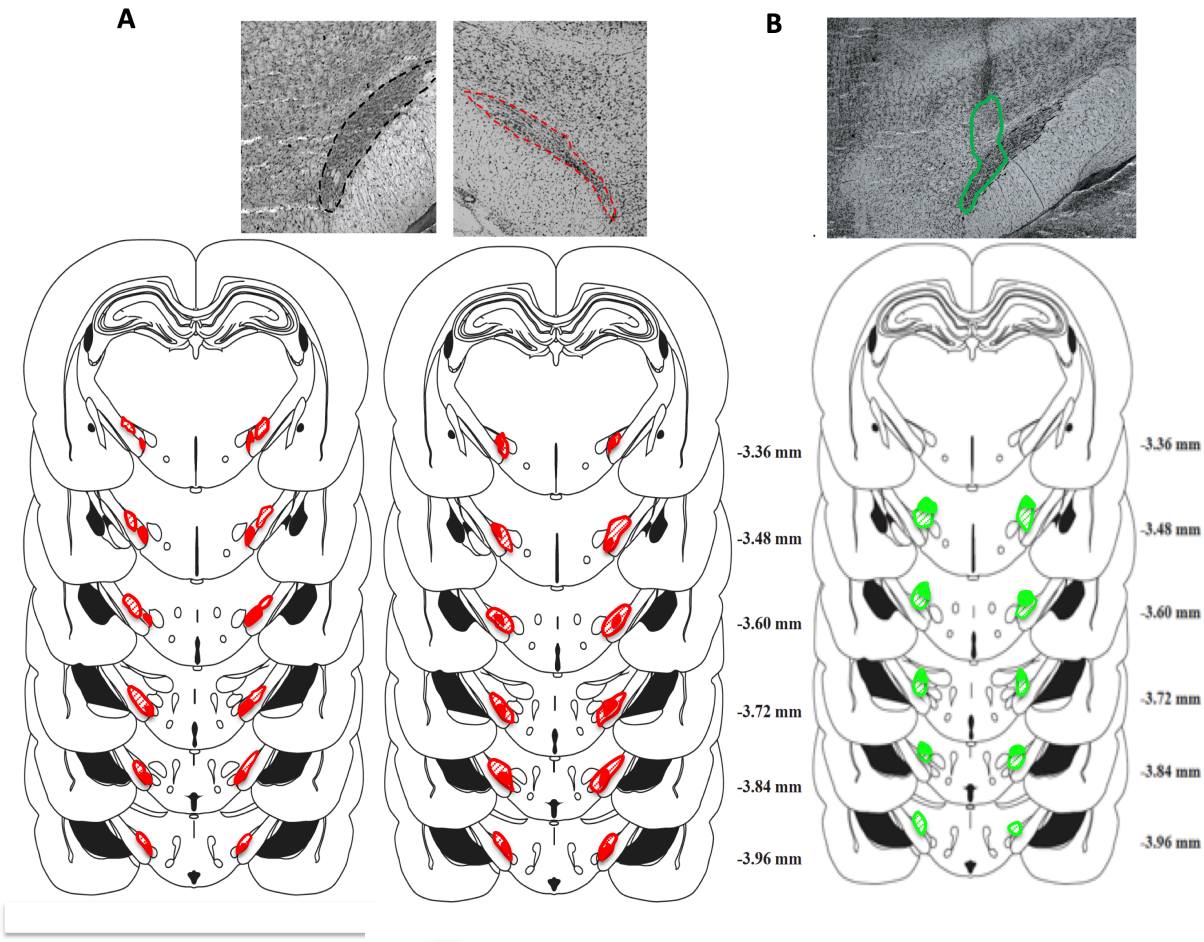

A
B
-3.36 mm
-3.48 mm
-3.60 mm
-3.72 mm
-3.84 mm
-3.96 mm
-3.36 mm
-3.48 mm
-3.60 mm
-3.72 mm
-3.84 mm
-3.96 mm

Figure 2

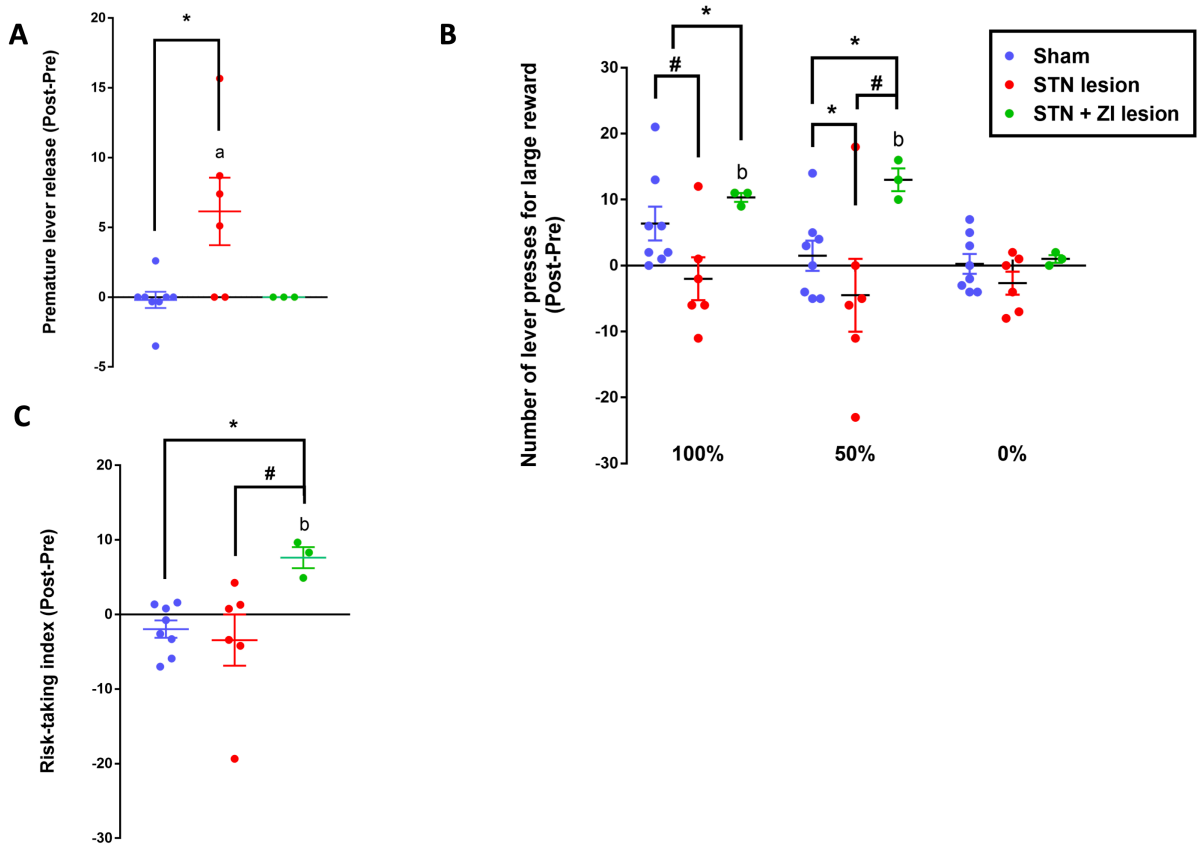

A
Premature lever release (Post-Pre)
20
15
10
5
0
-5
*
a
B
Number of lever presses for large reward (Post-Pre)
30
20
10
0
-10
-20
-30
*
#
b
*
#
*
b
100%
50%
0%
Sham
STN lesion
STN + ZI lesion
C
Risk-taking index (Post-Pre)
20
10
0
-10
-20
-30
*
#
b

Figure 3

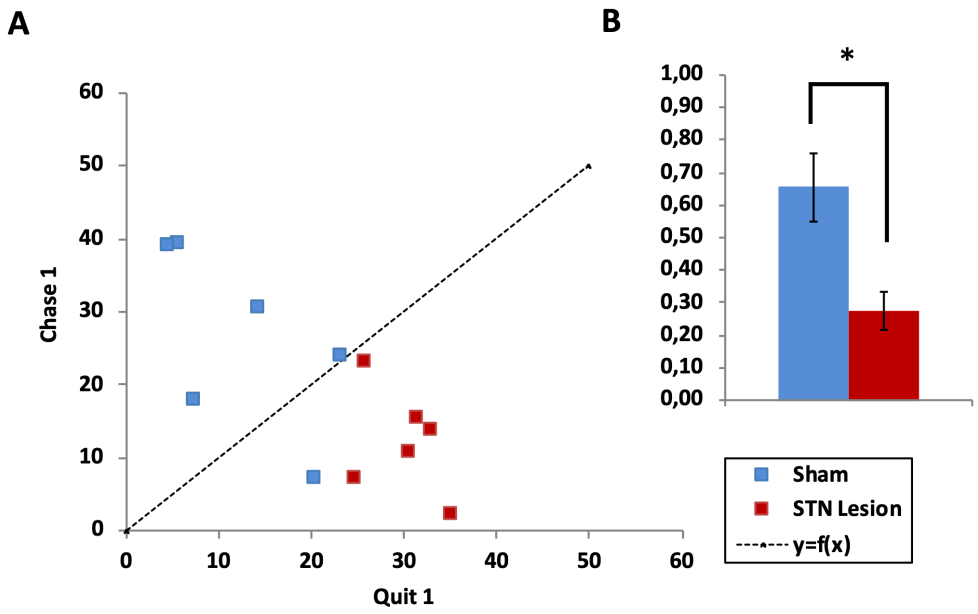

A
B
Chase 1
Quit 1
0
10
20
30
40
50
60
*
1,00
0,90
0,80
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
Sham
STN Lesion
y=f(x)

Figure 4

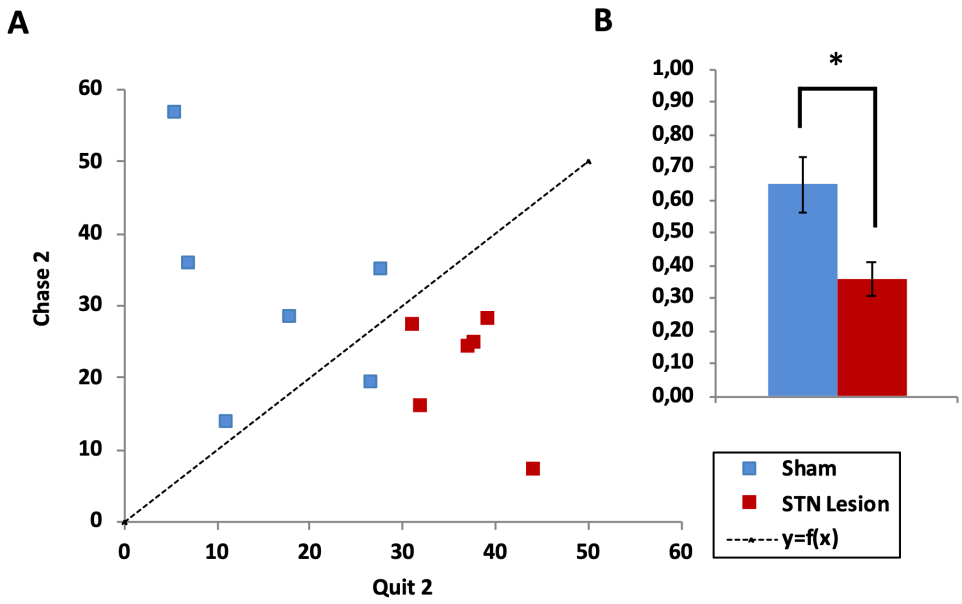

A
B
Chase 2
Quit 2
0
10
20
30
40
50
60
1,00
0,90
0,80
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
*
Sham
STN Lesion
y=f(x)

Figure 5

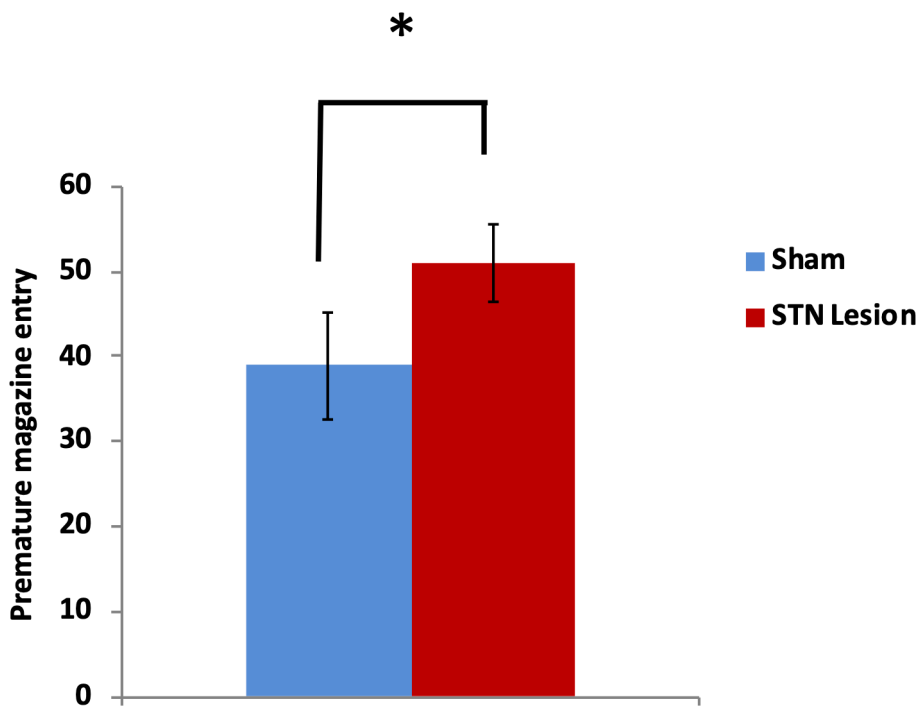
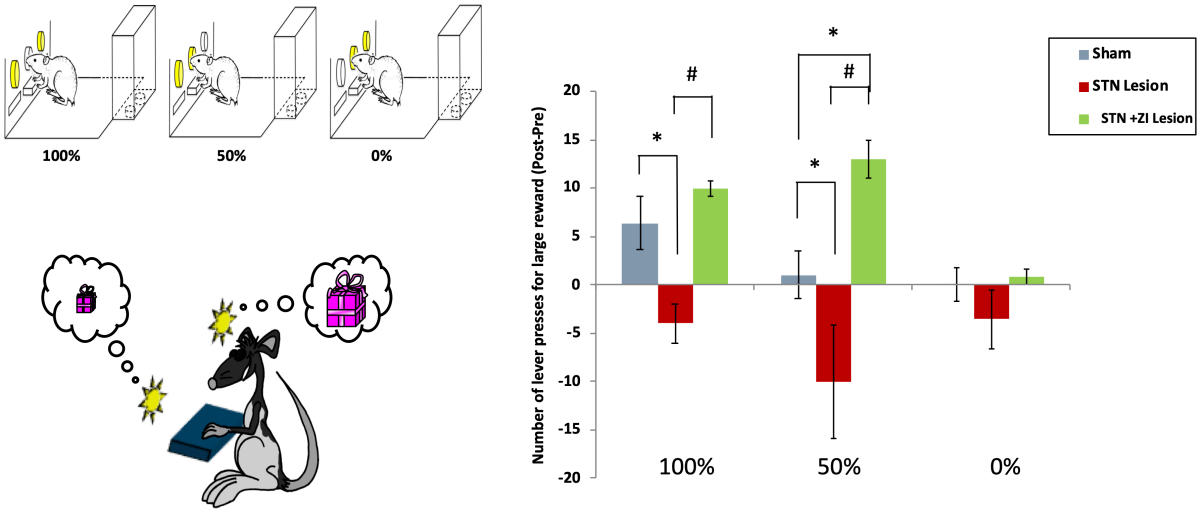


Figure 6



Graphical abstract:
Lesion of the subthalamic nucleus (STN) was tested in two decision-making tasks involving uncertainty for either delivery of a large reward (Probability Discounting Task) or avoidance of a large punishment/loss (delay) (Loss chasing task). In both contexts positive (reward) or negative (punishment/loss), STN lesions reduce risk-taking. These results support the choice of STN as a target for the treatment of impulse control disorders in Parkinson's Disease and in obsessive compulsive disorders.