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Alcohol Preference Influences the Subthalamic Nucleus Control on Motivation for Alcohol in Rats

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In addition to its role in motor and attentional processes, the subthalamic nucleus (STN) has also been recently demonstrated to be involved in motivational function. Indeed, bilateral STN lesions modulate differentially the motivation for natural rewards and drugs of abuse, increasing motivation for food and decreasing motivation for cocaine in rats. Here, we show that in outbred rats, the STN can modulate the motivation for alcohol according to alcohol preference, without affecting alcohol intake. When performed on 'High-Drinker' rats, STN lesions enhanced the breaking point (BP) under a progressive ratio schedule of reinforcement and increased the time spent in the environment previously paired with alcohol access in the place preference paradigm. In contrast, when performed on 'Low-Drinker' rats, STN lesions decreased the BP and increased the time spent in the environment paired with water. These results show that STN lesions enhance the motivation for alcohol in rats showing a high alcohol preference, whereas they decrease it in rats showing a low preference for alcohol. These results suggest that the STN plays a complex role in the reward circuit, that is not limited to a dissociation between motivation for natural rewards and drugs of abuse, but takes other factors, such as alcohol preference, into account. *Neuropsychopharmacology* (2008) **33,** 634–642; doi:10.1038/sj.npp.1301432; published online 25 April 2007

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INTRODUCTION

Alcohol is a ubiquitous substance widely used in moderate doses in our society. Alcohol is unique among drug preparations, as alcoholic beverages have both nutritional and drug effects. Indeed, alcohol is also the most widely used of all the substances of abuse and the one that cause the most harm to society (Koob and Le Moal, 2006). Therefore, one challenge in research on alcohol is to identify the factors involved in the transition from normal use to abuse.

In addition to their involvement in motor functions, the basal ganglia nuclei are involved in coding reward prediction and reward delivery (Arkadir *et al*, 2004; Darbaky *et al*, 2005; Hassani *et al*, 2001; Hollerman *et al*, 1998) and in the reinforcing properties of alcohol (Bassareo *et al*, 2003; Melendez *et al*, 2004). Within the cortico-basal ganglia-thalamocortical limbic loop, the subthalamic nucleus (STN) is a key structure that may modulate the basal ganglia outflow (Turner *et al*, 2001). The STN is, above all, currently known as a therapeutic target for Parkinson's disease treatment with high-frequency stimulation (HFS) (Limousin *et al*, 1995). Even if STN inactivation is used to alleviate motor symptoms (Benazzouz *et al*, 1993; Limousin *et al*, 1995), clinical and experimental studies have demonstrated that the STN is also involved in cognitive and motivational functions (Absher *et al*, 2000; Baunez *et al*, 1995; Baunez and Robbins, 1997; Temel *et al*, 2006; Trillet *et al*, 1995; Witjas *et al*, 2005). Only recently has the role of the STN on motivational processes been investigated. It has been shown that STN lesions do not affect primary processes of motivation assessed by consumption measures, but increase the reactivity to stimuli predicting food, suggesting a specific role for STN in 'secondary motivational processes' or associative motivational processes (Baunez *et al*, 2002). Interestingly, the STN modulates differentially the motivation for natural rewards and for drugs of abuse. Indeed, bilateral STN lesions enhance the motivation for food, whereas decreasing the motivation for cocaine (Baunez *et al*, 2002, 2005).

To investigate how motivation for alcohol, a substance with both nutritional and drug properties, is modulated by the STN, we studied the effects of bilateral excitotoxic lesions of this nucleus in rats. The effects of STN lesions on alcohol consumption were measured in forced and choice conditions. The effects of the lesions on motivation were assessed with two complementary tasks: the place conditioning paradigm, which measures the reinforcing properties of a substance (here voluntary intake of ethanol solution), and the progressive ratio schedule of reinforcement, which addresses the willingness of the rats to work for a few drops of alcohol. The use of outbred rats to eliminate any bias in the STN lesion effects revealed an interindividual variability in alcohol preference, justifying a split of the

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animals into two groups, 'High Drinkers (HD) and Low Drinkers (LD)'. The effects of STN lesions on motivation for alcohol were thus analyzed according to the rats' alcohol preferences.

MATERIALS AND METHODS

Animals

Male Long–Evans rats ($n = 168$; Janvier, Le Genest St Isle, France) weighing 350–400 g at surgery were maintained on a 12-h light–dark cycle at an ambient temperature of 21°C. Animals were housed in pairs in clear Perspex cages ($42 \times 26.5 \times 18.5$ cm) with free access to food and water, unless they were under a specific water-deprivation schedule. During the water-deprivation, they were housed individually. All procedures were conducted in accordance with the French Agriculture and Forestry Ministry decree 87–849.

Surgery

Rats were anaesthetized with a mixture of ketamine (Imalgène®; 100 mg/kg i.m.) and xylazine (Rompun®; 15 mg/kg i.m.). Bilateral 30-gauge stainless-steel injector needles were stereotaxically positioned into the STN. Rats received bilateral injections of ibotenic acid (9.4 μg/μl (53 mM); STN-lesioned group) or vehicle solution (phosphate buffer, 0.1 M; sham control group). Coordinates for the aimed site were (in mm, with tooth bar set at −3.3 mm): anteroposterior −3.8; lateral ±2.4 from bregma; dorsoventral −8.35 from skull (Paxinos and Watson, 2005). Rats were injected 0.5 μl per side over 3 min with a 10 μl Hamilton microsyringe fixed on a micropump and connected by Tygon tubing fitted to the injectors which were left in place for 6 min to allow diffusion.

Apparatus

Place conditioning apparatus consisted of two Plexiglas boxes divided into two main compartments ($40 \times 35 \times 33$ cm), which were separated by a small 'intermediate' compartment (10 cm in length). Each compartment had different color patterns on the wall and different textures on the floor: one was black with white adhesive pattern and a Plexiglas floor, the other was white with black adhesive pattern and a textured non-skid plastic floor.

Operant measures of motivation for alcohol were recorded in eight standard operant boxes (Med Associates, St Albans, GA, USA), each box containing a retractable lever, a magazine equipped with a cup receptacle and a stimulus light located above the lever. Alcohol (0.1 ml) was delivered over 3 s in the cup located in the magazine. A 10-ml syringe fixed on a pump (MedAssociates) and connected to the cup by Tygon tubing permitted alcohol delivery. An interface (MedPC) and a computer controlled the session and collected data.

Locomotor activity was measured individually in 16 $370 \times 227 \times 235$ mm Perspex cages with a grid floor. Two infrared photocell beams crossed each cage at the front and the rear (100 mm from the entrance and 100 mm from the end). A computer using Imetronic (Bordeaux, France) extension recorded beam breaks in 1 min bins.

Behavioral Procedures

Consumption test. Forced consumption tests were conducted in standard laboratory Perspex cages. Rats (STN-lesion $n = 14$; SHAM $n = 14$) were water deprived for 24 h, before have access for 1 h to a bottle filled with one of the seven fluids (10% sucrose, water, 5% ethanol, 10% ethanol, 15% ethanol, choice between water and 10% ethanol, and 10% ethanol without deprivation).

Across all the experiments, ethanol (95%), pastis, pacific, and sugar were diluted in tap water to prepare 5, 10 and 15% ethanol, pastis containing 5% ethanol, pacific, and 10% sucrose (w/v), respectively.

Between tests, the rats had free access to water for 2 days. The amount of fluid drunk in the 1 h fluid access was measured and calculated in terms of g/kg, relative to the weight of the animal. The order in which the animals were exposed to the various fluids has been counterbalanced.

For choice-consumption tests, rats were housed individually in home cages and had access to two bottles that were weighted daily to measure the amount of fluid drunk. Rats tested three combinations: (1) 5% ethanol and water (STN-lesion $n = 19$; SHAM $n = 19$); (2) pastis solution containing 5% ethanol (pastis = local aniseed alcohol containing 45% ethanol and 10% sugar, Pastis 51®, Pernod–Ricard, France) and water (STN-lesion $n = 16$; SHAM $n = 16$); (3) then, same rats drank pastis and nonalcoholic pastis (ie, aniseed water with the same amount of sugar, Pacific®, Pernod–Ricard, France).

As the consumption of ethanol lead to a split between HD and LD, it was important to assess the effect of STN lesions on this split. Therefore, another group of rats (STN-lesion $n = 20$; SHAM $n = 14$) were tested in choice consumption test before and after the STN lesions. Rats had access to a 5% ethanol bottle and a water bottle for 9 days before surgery and 9 days after 1 week of recovering from surgery.

Place conditioning. In this task, rats (STN-lesion $n = 18$; SHAM $n = 18$) were water restricted. They had access to 70% of their basal water consumption in their home cages, to force them to drink a reasonable amount of fluid during the conditioning phase.

Preconditioning: The rats were placed for 15 min in the place preference apparatus. The time spent in each compartment was measured manually in seconds. The time spent in the 'intermediate' compartment was discarded.

Conditioning: On days 1,3,5, and 7, rats were placed in one compartment with access to a bottle of 5% ethanol for a 30-min period. Half of the rats were conditioned in the first compartment and the other half in the second compartment. On days 2,4,6, and 8, rats had access to a bottle of water for a 30-min period in the opposite compartment.

Testing: On day 9, rats were placed in the middle of the apparatus and were free to explore both compartments for 15 min. The time spent in each compartment was measured manually in seconds.

The amount of fluid drunk during each of the conditioning sessions was measured. Boxes were cleaned with H_2O_2 between rats for each session.

Operant responses for alcohol. Before being conditioned, rats had free access to a bottle of 5% ethanol and a bottle of water over an 8-day period.

Rats (STN-lesion $n=18$; SHAM $n=21$) were trained to press a lever for 5% ethanol in a continuous reinforcement schedule (fixed ratio 1: FR1). Each lever press resulted in the onset of the stimulus light and the delivery of 0.1 ml of ethanol. Each daily session ended when rats had obtained 100 rewards or 30 min had elapsed. To facilitate learning, rats had access to only 80% of basal water consumption in their home cages. This reduced deprivation of water access (in comparison with the place conditioning experiment) was due to the length of the procedure that may have been too stressful for the animals. After stabilization of their performance (ie homogenous performance for three consecutive sessions), rats were subjected to the progressive ratio schedule. In this task, steps of five lever presses arithmetically increased the number of lever presses required to obtain a single reward after rats had had three repetitions at the same step (ie 1,1,1,5,5,5,10,10,10…). The lever press that completed each ratio resulted in the onset of the stimulus light and the delivery of 0.1 ml of fluid. The light switched off when the rat's nose was detected in the magazine. Additional lever presses (perseverative lever presses) had no consequences. The session ended if the rat failed to lever press for 5 or 90 min had elapsed. For each session, the value of the last ratio reached, the number of rewards obtained, the number of visits in the magazine and the duration of the session were recorded. Rats' performance was measured for various fluids: ethanol 5%, ethanol 10%, and pastis (STN-lesion $n=12$; SHAM $n=12$).

Locomotor activity. To assess whether or not HD and LD subgroups differed in their response to ethanol, due to a difference on ethanol sensitivity, locomotor activity following alcohol injection was measured. After the end of the progressive ratio experiment, locomotor activity was recorded after an intraperional (i.p.) injection of ethanol, given at various doses following a Latin-square schedule (0, 0.25, 0.5, and 1 g/kg) on 4 days, each separated by 3 days. Each testing day, rats were placed for a 60-min habituation period in the locomotor activity cages before receiving the i.p. injection, they were then placed back in the cages and their activity was measured for 120 min. The results were analyzed with regard to the HD, LD split.

Histology. At the end of experiment, rats were decapitated. Brains were removed and frozen, and to be then cut with a cryostat. Frontal 40-μm thick sections of the STN were stained with Cresyl violet for assessment of the extent of the lesion.

Data Analysis

Results were expressed as means of each variable (last ratio reached, percentage of ethanol preference, preference score, and so on).

For further analysis, as a lack of ethanol consumption could prevent place conditioning to be developed, we assessed the amount of liquid taken during conditioning and then divided the animals into subgroups: HD and LD using the median of alcohol preference (total alcohol intake/total (alcohol + water intake). To parallel this split in the progressive ratio experiment, we have applied the same split to the animals, based on their alcohol preference during the choice consumption experiment. Using Statview program (SAS institute, Cary, NC), data were analyzed with mixed design ANOVAs with group (sham *vs* STN lesioned) and drinker (HD *vs* LD) as the between subject factors and sessions, days, fluid, pre/post surgery, or compartment as the within subject factor when appropriate. When significant effect was found, *post hoc* comparisons were performed using simple main effect analysis. Correlation between alcohol preference pre- and post-surgery was tested with the Spearman's correlation test.

RESULTS

Histology

Seventeen rats were discarded from the analysis, as the lesions were either unilateral or incomplete. A complete lesion of the STN, sparing only a few cells in the lateral part of the nucleus, was required to include rats in the analysis (Figure 1). It is important to note that there was no obvious difference between the subgroups 'HD' and 'LD' in terms of lesion extent.

Alcohol Consumption Test

Bilateral STN-lesioned rats (STN $n=11$) drank the same amount of alcohol as control rats ($n=14$) in the 1-h forced condition (Figure 2a). For each of the various fluids tested, STN lesions did not affect the rat's intake (ANOVA group effect for sucrose: $F_{(1,21)}=0.176$; water: $F_{(1,21)}=1.197$; 5% ethanol: $F_{(1,21)}=0.176$; 10% ethanol: $F_{(1,21)}=0.685$; 15% ethanol: $F_{(1,21)}=0.039$; 10% ethanol not deprived: $F_{(1,21)}=0.058$; $p>0.05$). Likewise, when given the choice between one alcoholic fluid (ethanol or pastis) and one non-alcoholic fluid (water or non-alcoholic pastis), STN-lesioned rats ($n=19$ and 10, respectively, for ethanol and pastis experiments) consumed as much alcohol as control rats ($n=19$ and 16, respectively, for ethanol and pastis experiments) (ANOVA group effect: ethanol *vs* water $F_{(1,34)}=0.01$; pastis *vs* water $F_{(1,22)}=0.913$; pastis *vs* non-alcoholic pastis $F_{(1,22)}=0.472$; $p>.05$).

Furthermore, alcohol preference (ie, alcohol/total intake) was not different between the two groups in either forced (group effect, $F_{(1,21)}=1.064$) or choice condition (Figure 2b) (group effect: ethanol *vs* water $F_{(1,34)}=0.686$; pastis *vs* water: $F_{(1,22)}=1.758$; pastis *vs* non-alcoholic pastis: $F_{(1,22)}=0.036$).

Whatever the group, HD or LD, there was no significant effect of STN lesions on either alcohol intake or alcohol preference in forced (group × drinker interaction, sucrose: $F_{(1,21)}=0.462$; eau: $F_{(1,21)}=1.416$; 5% ethanol: $F_{(1,21)}=1.917$; 10% ethanol: $F_{(1,21)}=0.135$; 15% ethanol: $F_{(1,21)}=0.208$; 10% ethanol not deprived: $F_{(1,21)}=0.109$; $p>0.05$), and choice conditions (group × drinker interaction, alcohol intake: ethanol *vs* water $F_{(1,34)}=0.392$; pastis *vs* water: $F_{(1,22)}=0.187$; pastis *vs* non-alcoholic pastis: $F_{(1,.22)}=0.101$; alcohol preference: ethanol *vs* water $F_{(1,34)}=0.849$; pastis *vs* water: $F_{(1,22)}=0.157$; pastis *vs* non-alcoholic pastis: $F_{(1,22)}=0.288$).

In the choice condition, the total fluid intake was also measured and did not differ between groups (group

effect, ethanol *vs* water: $F_{(1,34)} = 0.107$; pastis *vs* water: $F_{(1,22)} = 3.239$; pastis *vs* non-alcoholic pastis: $F_{(1,22)} = 0.282$; group × drinker effect: ethanol *vs* water: $F_{(1,34)} = 0.14$; pastis *vs* water: $F_{(1,22)} = 0.146$; pastis *vs* non-alcoholic pastis: $F_{(1,22)} = 0.04$, $p > 0.05$).

In the comparison between pre- and post-surgery (Figure 3), the level of alcohol preference did not differ between groups (STN $n = 17$ and Sham $n = 14$), (group effect: $F_{(1,27)} = 0.270$; group × pre/post interaction: $F_{(1,27)} = 0.082$; group × drinker interaction: $F_{(1,27)} = 0.005$; $p > 0.05$). The difference between the HD and LD before the surgery (drinker effect: $F_{(1,27)} = 62.029$; $p < 0.01$) was maintained also after the surgery (drinker effect: $F_{(1,27)} = 12.070$; $p < 0.01$). Within the HD and LD groups, alcohol preference was not different between the STN-lesioned and the sham-operated groups neither before nor after surgery (group effect: pre-surgery, HD: $F_{(1,12)} = 8.42 \times 10^{-5}$; LD: $F_{(1,15)} = 0.264$; post-surgery, HD: $F_{(1,12)} = 0.54$; LD: $F_{(1,15)} = 0.302$; $p > 0.05$). Furthermore, in each group, the difference between HD and LD was maintained after the surgery (drinker effect: pre-surgery, Sham: $F_{(1,12)} = 28.333$; STN: $F_{(1,15)} = 34.458$; $p < 0.01$, post-surgery, Sham: $F_{(1,12)} = 5.929$; LD: $F_{(1,15)} = 6.024$; $p < 0.05$).

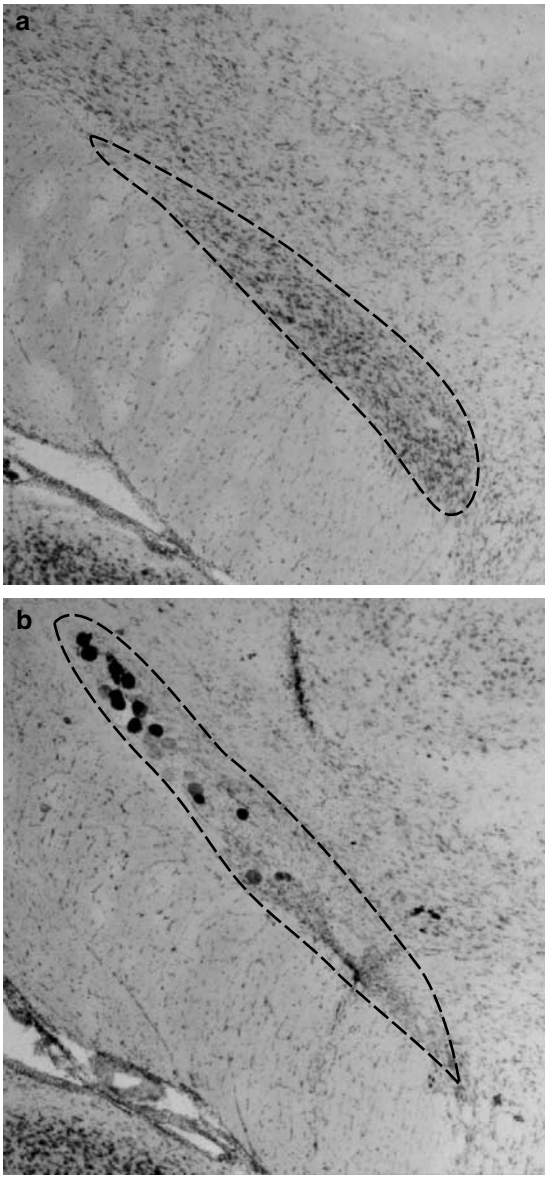

Figure 1 Frontal sections stained with cresyl violet, at the level of the STN. Dashed lines outline the STN in sham-operated rat (a) and STN-lesioned rat (b).

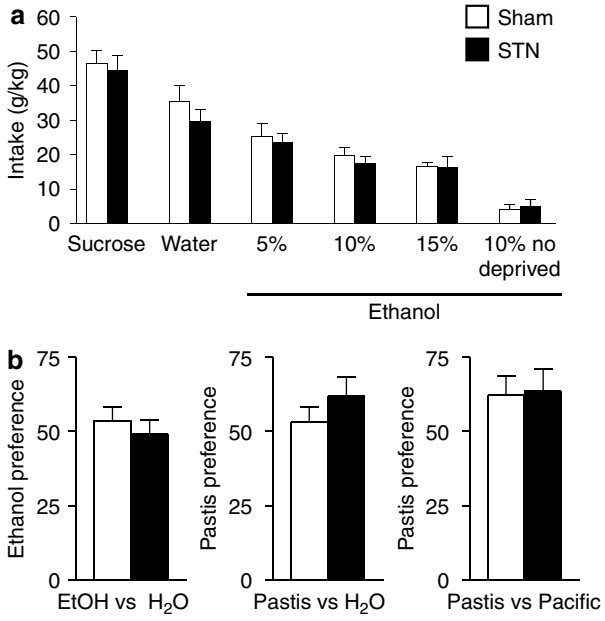

Figure 2 Effects of bilateral STN lesions on alcohol consumption. (a) Mean fluid intake (g/kg) (±SEM) in 1 h fluid access after 24 h of water deprivation in STN-lesioned ($n = 11$, black bars) and sham-lesioned rats ($n = 14$, white bars). (b) Mean alcohol preference (% alcohol intake/total intake) (±SEM) in choice condition: ethanol *vs* water (left) (STN $n = 19$ and sham $n = 19$, black and white bars, respectively), pastis *vs* water (middle) and pastis *vs* pacific (right) (STN $n = 10$ and sham $n = 16$).

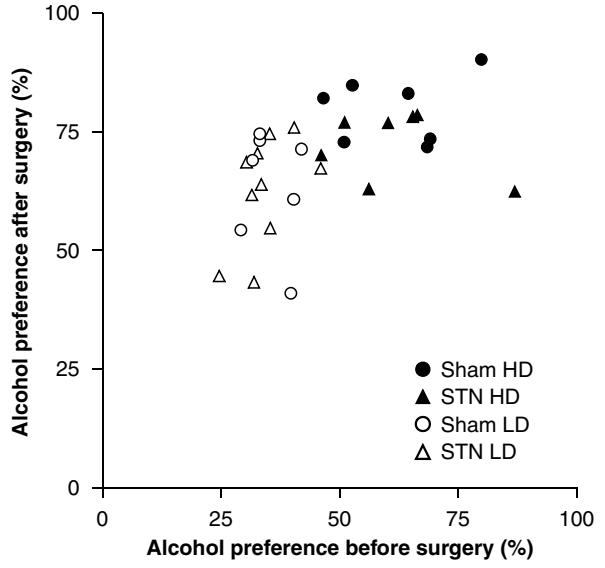

Figure 3 Effect of bilateral STN and Sham lesions on alcohol preference before and after surgery. The correlation between alcohol preference before (x axis) and after surgery (y axis) is illustrated for each rats: HD rats (STN $n = 7$, plain triangle and Sham $n = 7$, plain circle) and LD rats (STN $n = 10$, open triangle and Sham $n = 7$, open circle).

Whatever the group, alcohol preference was enhanced after surgery (pre/post effect: $F_{(1,27)} = 75.035$; Sham: $F_{(1,12)} = 29.785$; STN: $F_{(1,15)} = 47.405$; HD: $F_{(1,12)} = 12.063$; LD: $F_{(1,15)} = 95.088$; $p < 0.01$), but without difference between groups (group × pre/post interaction: HD: $F_{(1,12)} = 0.153$; LD: $F_{(1,15)} = 0.005$; $p > 0.05$).

Besides, alcohol preference after surgery was positively correlated with alcohol preference before surgery (Spearman's correlation test: $\rho = 0.573$; $p < 0.01$).

Place Conditioning

Eight rats (STN $n = 5$ and Sham $n = 3$) did not drink during the conditioning and were therefore discarded from the analysis.

The amount of ethanol intake during the conditioning and the ethanol preference were not different between the STN-lesioned ($n = 10$) and sham-operated ($n = 15$) groups (sum of ethanol 5% intake: STN: 53.7 ± 3.0 g/kg; sham: 52.6 ± 9.0 g/kg; group effect: $F_{(1,21)} = 0.002$, $p > 0.05$; percentage of ethanol preference: STN: 47.7 ± 2.7; sham: 43.8 ± 2.0; group effect: $F_{(1,21)} = 2.272$, $p > 0.05$). The subdivision into HD and LD did not affect this lack of difference between sham and STN rats (sum of 5% ethanol intake: group-drinker effect, $F_{(1,21)} = 0.628$; percentage of ethanol preference: group × drinker effect, $F_{(1,21)} = 0.01$).

In the HD subgroup (Figure 4a), the STN-lesioned rats spent significantly more time in the ethanol-paired compartment than in the water-paired compartment ($p < 0.01$, Fisher's PLSD after a significant ANOVA compartment × group × drinker interaction: $F_{(1,21)} = 11.268$; $p < 0.01$). They also spent more time in the ethanol-paired compartment than the sham-controls (ANOVA; group effect: $F_{(1,10)} = 14.002$; $p < 0.01$ after a group × drinker interaction: $F_{(1,21)} = 12.283$; $p < 0.01$). In contrast, the sham HD rats exhibited an opposite preference for the water-paired compartment ($p < 0.05$, Fisher's PLSD). In the LD subgroup (Figure 4b), whereas sham LD rats did not show any preference between the two compartments, STN-lesioned rats spent less time in the ethanol-paired environment than in the water-paired compartment ($p < 0.01$, Fisher's PLSD). Furthermore, the time spent in each compartment were significantly different between HD and LD STN-lesioned rats (ethanol-paired compartment: drinker effect: $F_{(1,8)} = 15.821$, 13.395; $p < 0.01$; for ethanol and water-paired compartment, respectively).

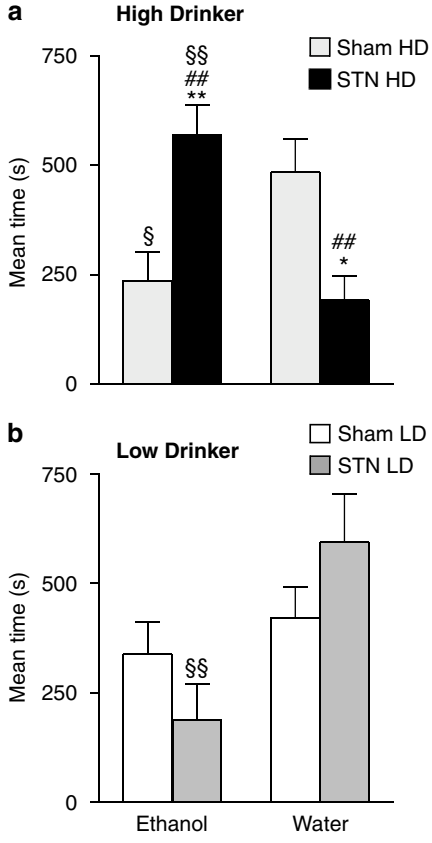

Figure 4 Effects of bilateral STN lesions on place conditioning for ethanol 5%. Mean time (±SEM) spent in the ethanol-paired environment (ie, ethanol; left) and in the water-paired environment (ie, water; right) on the test day in (a) the HD rats (STN $n = 5$, black bar and sham $n = 7$, pale gray bar) and (b) the LD rats (STN $n = 5$, dark gray bar and sham $n = 8$, white bar). $^{*}p < 0.01$; $^{**}p < 0.05$ compared with the sham control group, $^{\#\#}p < 0.01$ compared with the LD group, $^{\S}p < 0.01$; $^{\S\S}p < 0.05$ compared with the water-paired compartment.

Progressive Ratio Test

Whatever reward given, the last ratio (ie, 'breaking point' (BP)) reached by the two groups (ethanol STN $n = 16$ and sham $n = 21$; pastis: STN $n = 12$ and sham $n = 12$) was not different (ANOVA; 5% ethanol: $F_{(1,33)} = 0.605$; 10% ethanol: $F_{(1,33)} = 2.076$; pastis: $F_{(1,20)} = 0.136$; $p > 0.05$).

Nevertheless, the BP was dependent on the rat's propensity to drink alcohol, and STN lesions had an opposite effect on the BP with regards to the level of alcohol intake (Figure 5). Indeed, in the HD subgroup (STN $n = 8$ and sham $n = 10$), the STN-lesioned rats reached a higher BP for 5% ethanol than the sham control rats (group effect; $F_{(1,16)} = 8.155$; $p < 0.05$ after a group × drinker significant interaction $F_{(1,33)} = 13.842$; $p < 0.01$). When the reward was 10% ethanol and pastis (STN $n = 6$ and sham $n = 6$), there was no significant difference between sham and STN rats, although there was a trend towards higher BP for STN rats.

In the LD group, whatever the reward, STN-lesioned rats reached a lower BP than the sham control rats (5% ethanol (STN $n = 8$ and sham $n = 11$): group effect; $F_{(1,17)} = 5.545$; $p < 0.05$ after significant group × drinker interaction $F_{(1,33)} = 13.842$; $p < 0.01$; 10% ethanol: group effect; $F_{(1,17)} = 8.549$; $p < 0.05$ after significant group × drinker interaction $F_{(1,33)} = 6.539$; $p < 0.05$; and pastis (STN $n = 6$ and sham $n = 6$): group effect; $F_{(1,10)} = 5.432$; $p < 0.05$ after significant group × drinker interaction $F_{(1,20)} = 8.829$; $p < 0.01$).

Whereas no significant differences were measured in the sham control groups in terms of BP for the HD *vs* LD, the STN rats belonging to the HD group reached a higher BP than the LD rats (drinker effect, 5% ethanol: $F_{(1,14)} = 15.244$; $p < 0.01$; 10% ethanol: $F_{(1,14)} = 6.296$; $p < 0.05$; pastis: $F_{(1,10)} = 11.307$; $p < 0.01$).

The duration of the session was the same for both STN and sham groups (ANOVA; group effect, 5% ethanol: $F_{(1,33)} = 2.2$; 10% ethanol: $F_{(1,33)} = 0.688$; pastis: $F_{(1,20)} = 0.465$; $p > 0.05$). Only when pastis was the reward, the STN

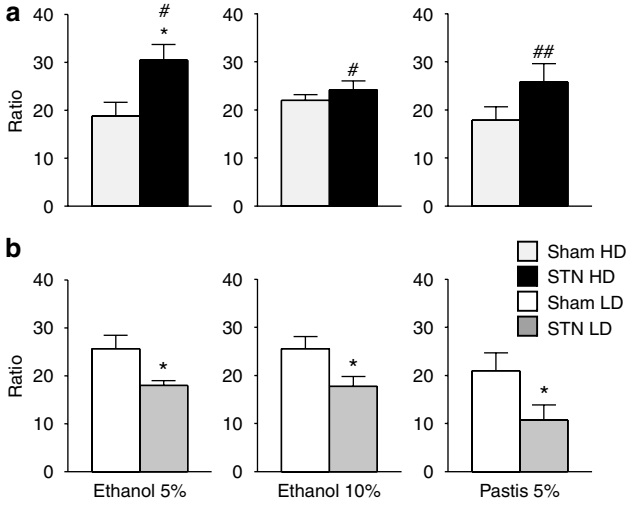

Figure 5 Effects of bilateral STN lesions on the performance in the progressive ratio task for alcohol. Final ratio (±SEM) reached during each session (averaged over five sessions) for ethanol 5 % (left), ethanol 10 % (middle) and pastis (right) in the HD rats (a) (STN $n=8$, black bars and sham $n=10$, pale gray bars for ethanol, and respectively, 6 and 6 for pastis) and the LD rats (b) (STN $n=8$, dark gray bars and sham $n=11$, white bars for ethanol, and respectively, 6 and 6 for pastis). $^{*}p<0.05$ compared with the sham control group, $^{\#}p<0.05$; $^{\#\#}p<0.01$ compared with the LD group.

rats worked longer than the sham control rats in the HD group (ANOVA; group effect: $F_{(1,10)}=6.66$; $p<0.05$ after significant group × drinker interaction $F_{(1,20)}=5.569$).

The number of visits to the magazine was the same for all groups and rewards (group effect $p>0.05$, 5% ethanol: $F_{(1,33)}=2.55$; 10% ethanol: $F_{(1,33)}=1.637$; pastis: $F_{(1,20)}=0.415$; and group × drinker interaction, 5% ethanol: $F_{(1,33)}=4.067$; 10% ethanol: $F_{(1,33)}=0.324$; pastis: $F_{(1,20)}=0.177$; $p>0.05$).

Locomotor Activity

Locomotor activity was equivalent in both groups (STN $n=11$ (one rat died in the middle of the experiment) and sham $n=12$) (group effect: $F_{(1,19)}=0.118$; $p>0.05$) during the habituation phase (Figure 6a, inset). The amount of locomotor activity was also equivalent in both HD (STN $n=6$; sham $n=6$) and LD groups (STN $n=5$; sham $n=6$) (no group × drinker interaction: $F_{(1,19)}=0.197$; $p>0.05$).

As the rat's inactivity during the last 90 min hid the differences between groups and ethanol doses, statistical analyses on locomotor activity following injection were performed on the first 30 min after injection. As illustrated in Figure 6a, alcohol dose-dependently decreased locomotor activity in sham control rats (dose effect: $F_{(3,57)}=32.815$; $p<0.01$). This decreasing effect was attenuated in STN rats, leading to an increased locomotor activity in STN rats when compared with sham controls at the dose of 0.5 and 1 g/kg (0.5 g/kg: $F_{(1,19)}=4.342$; $p=0.05$; 1 g/kg: $F_{(1,19)}=4.667$).

Locomotor activity following injection was also equivalent in HD and LD groups (group × drinker interaction, vehicle: $F_{(1,19)}=0.527$; 0.25 g/kg: $F_{(1,19)}=0.31$; 0.5 g/kg: $F_{(1,19)}=4.071$; 1 g/kg: $F_{(1,19)}=0.0001$; $p>0.05$) (Figure 6b).

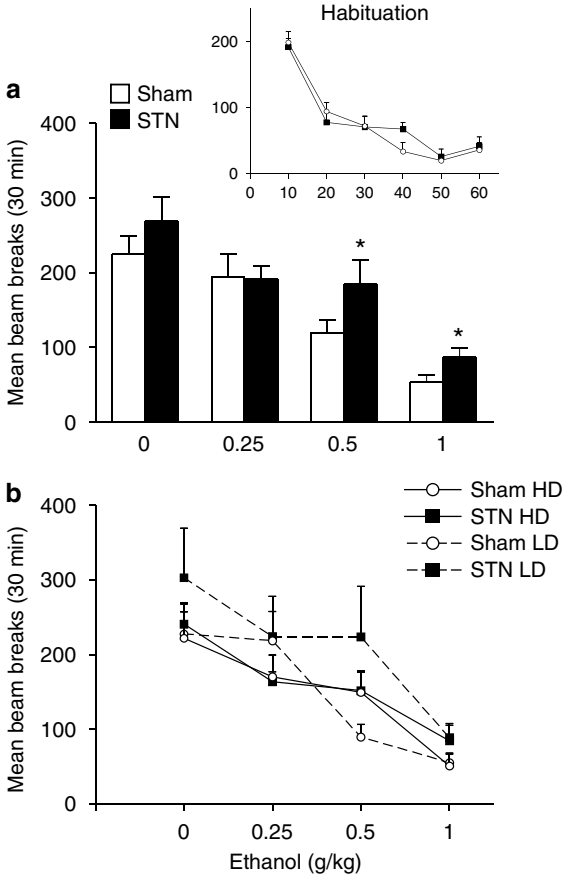

Figure 6 Effects of bilateral STN lesions on locomotor activity after ethanol injections. Locomotor activity (±SEM) is illustrated as the average number of beam breaks recorded by 10-min bins during the 60-min habituation (inset) and as the average of the total number of beam breaks during the first 30 min following injection (a) for the STN-lesioned rats ($n=12$, black bars and squares) and sham-lesioned rats ($n=12$, white bars and circles) and (b) for the HD (plain line) (STN $n=6$, plain squares and sham $n=6$, plain circles) and LD (dashed line) (STN $n=6$,open squares and sham $n=6$, open circles) rats. $^{*}p<0.05$ compared with the sham control group.

DISCUSSION

In the present study, converging results show that STN lesions have opposite effects on motivation for alcohol according to the rat's alcohol preference. Indeed, bilateral STN lesions increased the motivation for alcohol in rats preferring alcohol (ie, HD), whereas decreasing it in those exhibiting a lower preference for alcohol (ie, LD). STN lesions did not affect the level of preference for alcohol nor did they affect the level of consumption.

In most of the studies using a standard place-conditioning design, ethanol was given i.p. or orally by gavage, and outbred rats showed an aversion for the environment associated with ethanol (Asin *et al*, 1985; Bormann and Cunningham, 1998; Busse *et al*, 2005; Fidler *et al*, 2004; Stewart and Grupp, 1981; Stewart *et al*, 1996; Van der Kooy *et al*, 1983). Only in three studies, place conditioning was assessed with voluntary ethanol consumption. Of these three studies, one showed a place preference for ethanol (Gauvin and Holloway, 1992), whereas two showed a place aversion (Stewart and Grupp, 1986, 1989). In the present

experiment, only the HD sham rats exhibited a preference for water, whereas the LD sham animals did not show any preference. We can however rule out the possibility that a low intake during conditioning may have prevented these latter animals from associating the environment with the ethanol presentation. Indeed, the STN-lesioned animals belonging to the LD group were able to associate ethanol-induced effects with the environment they experienced, as they exhibited a preference for water. The place conditioning paradigm allows the measurement of the reinforcing properties, either positive or negative, of a drug treatment (Bardo and Bevins, 2000; Tzschentke, 1998). Therefore, from the present results, ethanol does not seem to have a positive reinforcing effect in the sham group. In contrast, in the STN rats, the reinforcing properties of ethanol depend on the ethanol preference as the lesions increase preference for the ethanol-paired environment in the HD group and decrease it in the LD group. These opposite effects have been further confirmed in the progressive ratio experiment.

The progressive ratio task is classically used to measure the willingness of the animals to work for a reinforcer, as measured by the BP (Hodos, 1961). As STN lesions enhances the BP when sucrose is the reinforcer, we could not experiment with the commonly used sucrose-fading procedure (Samson, 1986). That is the reason why animals were water-restricted to perform the task. In this condition, STN lesions induced dramatic opposite effects in the HD and LD groups. They heightened the BP reached on the progressive ratio schedule in the HD group, whereas reducing the BP reached in the LD group. The converging results obtained in this task and in the place conditioning suggest that ethanol had positive reinforcing properties in the HD group and negative ones in the LD rats, and that STN lesions affect associative motivational processes rather than primary consummatory processes (Samson and Czachowski, 2003). It is unlikely that the effect of STN lesions on motivation is due to a change in consummatory behavior. Indeed, whatever the group HD or LD, or the condition (forced or choice), the amount of alcohol intake and alcohol preference was not different between sham and STN-lesioned rats. Furthermore, the surgery did not affect the basal alcohol preference and the belonging to the HD or LD groups, even though alcohol preference was enhanced in all rats (Sham and STN) after surgery. This latter effect could be explained by the alcohol-deprivation effect during the recovering week after surgery as described previously by Spanagel and Hölter (2000). This confirms previous studies showing that STN lesions do not modify food and cocaine intake and is not involved in consummatory processes (Baunez *et al*, 2002, 2005).

Instead of an effect on motivation for alcohol, STN lesions may have influenced the aversion mechanisms, as it has been shown that alcohol aversion is lower in alcohol preferring rats (tolerance to aversion) (Bice and Kiefer, 1990). As there was no difference between sham and STN rats on alcohol consumption, it is unlikely that STN lesions have induced a shift in alcohol-induced aversion tolerance. Furthermore, the difference between LD and HD did not seem to be the result of a different sensitivity to ethanol, nor to an endogenous difference that could affect general activity, as assessed by locomotor activity, as the amount of locomotor activity was the same for the LD and HD rats. However, STN-lesioned rats seemed to be less sensitive to the depressant effect of alcohol, as shown by increased locomotor activity after the two highest doses of ethanol tested.

These results are in line with some studies in rat lines bred for high and low alcohol preference. For example, Marchigian Sardinian alcohol-preferring rats have an obvious preference for the environment associated with alcohol and the alcohol-preferring (P) rats show less aversion than the alcohol non-preferring (NP) rats (Ciccocioppo *et al*, 1999; Stewart *et al*, 1996). In addition, P rats and high alcohol drinking (HAD) rats self-administered more alcohol than NP and low alcohol drinking (LAD) rats, respectively, both in fixed and progressive ratio schedule (Ritz *et al*, 1994; Samson *et al*, 1998). Interestingly, STN lesions in outbred rats reproduced the motivational behavior observed in inbred alcohol-preferring rats.

It is now well established that the STN is involved in cognitive and motivational behavior both in rats and monkeys (Baunez *et al*, 2002, 2005; Baunez and Robbins, 1997, 1999; Darbaky *et al*, 2005; Winstanley *et al*, 2005) and in humans (Temel *et al*, 2006; Witjas *et al*, 2005). STN lesions can differentially modulate the motivation for natural reward and drugs of abuse. Indeed, bilateral STN lesions enhance the motivation for food, whereas decreasing the motivation for cocaine (Baunez *et al*, 2002, 2005). Although Baunez *et al* (2002, 2005) demonstrate that STN lesion enhance the motivation for cocaine, Uslaner *et al* (2005) show an opposite result (Baunez *et al*, 2005). But the basal cocaine intake of both control and lesioned rats in the Uslaner *et al* (2005) study is so low, that no possible decrease could have been observed and it might well be possible that the potentiation observed after STN lesions on the progressive ratio performance has more to do with acquisition than with motivation for the drug itself.

Alcohol is a drug of abuse, but it is also a nutritional product that elicits either hedonic or aversive taste reactions (Kiefer and Dopp, 1989). Interestingly, ethanol elicits a biphasic increase of dopamine in the NAC (nucleus accumbens) shell. The first increase, related to taste reaction, undergoes habituation after the first exposure (as also observed with food), whereas the second increase, related to the increase on dialysate ethanol, remains unchanged at the second exposure (as also observed with psychostimulant drugs) (Bassareo *et al*, 2003; Di Chiara, 2002). Ethanol thus seems to act on the dopaminergic system in the NAC shell both like a natural reward and like a drug of abuse. Furthermore, sucrose, saccharin, and fat taste and diet preferences are positively correlated with alcohol preference in animal and human studies (Gosnell and Krahn, 1992; Kampov-Polevoy *et al*, 1997; Krahn and Gosnell, 1991). Ethanol thus has two distinct components, one closely related to natural reward and one related to drugs of abuse. STN lesions led to the dissociation in their motivation for alcohol between HD and LD, in addition to the dissociation between motivation for natural reward and drugs of abuse shown previously (Baunez *et al*, 2005). These results suggest that the STN affects differentially the motivation according to the value of the reinforcer, in line with preliminary electrophysiological data showing differential activity of STN neurons in response to sucrose and cocaine rewards (Baunez *et al*, 2006). Furthermore, ethanol

seems to act as a natural reinforcer such as food for HD rats, whereas it seems to act as a 'drug of abuse-like' reinforcer such as cocaine in the LD rats. This rather surprising effect may be due to the fact that for HD animal's alcohol may become more 'natural' than for the rats belonging to the LD groups.

STN is in a central position in the motor, associative and limbic circuit within the cortico-basal ganglia-thalamocortical loops (Albin *et al*, 1989; Alexander *et al*, 1986). In the limbic circuit, the NAC, the VP (ventral pallidum), and the prefrontal cortex are known to be involved in ethanol reinforcement (Bassareo *et al*, 2003; Doyon *et al*, 2003; Samson and Czachowski, 2003). The limbic areas of the prefrontal cortex activate the STN, either by a direct excitatory input (the so-called 'hyperdirect pathway') or by an indirect disinhibitory pathway linking the NAC core and the STN via the VP (Maurice *et al*, 1998a, b). In return, the VP receives glutamatergic projections from the STN (Groenewegen and Berendse, 1990), thus allowing the STN to regulate the limbic output of the basal ganglia (Turner *et al*, 2001). Electrophysiological data have demonstrated that various neuronal populations in the NAC and the ventral striatum are activated by natural reward and drugs of abuse in behaving rats and monkeys (Bowman *et al*, 1996; Carelli, 2002; Carelli *et al*, 2000). Within the limbic loop, several parallel pathways seem to mediate the motivation for various types of reward. Recently, a similar pharmacological dissociation has been demonstrated between motivation for natural reward and drugs of abuse. In this study, the blockade of NMDA receptors with MK801 (dizocilpine) enhanced the motivation for food but decreased the motivation for morphine (Yonghui *et al*, 2006). The authors have suggested that these results could be due to the blockade of NMDA receptors into the STN as the injection of NMDA antagonist into the STN produces almost all the deficits observed after bilateral STN lesion in the five-choice attentional task (Baunez and Robbins, 1999). However, only the injection of $GABA_A$ agonist into the STN led to an increase in perseverations toward the food magazine, suggesting a possible predominant role of the GABAergic projection arising from the VP in motivated behavior (Baunez and Robbins, 1999). Therefore, via its afferences from the VP and from the cortex and the thalamus, the STN may modulate differentially the motivation for a reinforcer according to its value.

In conclusion, our study has demonstrated that bilateral STN lesions do not affect consummatory processes, but can differentially modulate the motivation for alcohol according to the level of alcohol preference, suggesting that ethanol is considered as 'natural' for the HD rats and as 'drug of abuse' in the LD rats. This finding suggests that, more than dissociating between the motivation for natural reward and drugs of abuse (Baunez *et al*, 2005), the STN seems to play a more complex role in the circuit of motivation. Furthermore, as HFS of the STN applied in human patients can lead to motivational effects in line with those observed after STN lesions in rats (Temel *et al*, 2006; Witjas *et al*, 2005), it would be very interesting to assess the effects of STN HFS on motivation for alcohol in patients. It may be also very critical to take into account the alcohol intake history of these Parkinsonian patients before implanting HFS electrodes.

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DISCLOSURE/CONFLICT OF INTEREST:

The authors declare that, except for income received from my primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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