Experimental Neurology 215 (2009) 101–109

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

High frequency stimulation and pharmacological inactivation of the subthalamic nucleus reduces 'compulsive' lever-pressing in rats

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ARTICLE INFO

Article history:
Received 10 June 2008
Revised 15 September 2008
Accepted 17 September 2008
Available online 7 October 2008

Keywords:
Deep brain stimulation
Animal model
Muscimol
Extinction

ABSTRACT

In recent years there have been several attempts to establish high frequency stimulation (HFS) as an additional treatment strategy for obsessive-compulsive disorder (OCD). Two studies reported that bilateral HFS of the subthalamic nucleus (STN) dramatically alleviated compulsions and improved obsessions in three patients with co-morbid Parkinson's disease and OCD. A recent study reported that HFS as well as pharmacological inactivation of the STN alleviate compulsive checking in the quinpirole rat model of OCD. As the quinpirole model is based on a dopaminergic manipulation, the aim of the present study was to test whether HFS and pharmacological inactivation of the STN exert an anti-compulsive effect also in the drug-naive brain, using the signal attenuation rat model of OCD. The main finding of the present study is that both HFS and pharmacological inactivation of the STN exerted an anti-compulsive effect, although the two manipulations differed in their effects on other behavioral measures. These findings support the possibility that HFS of the STN may provide an additional therapeutic strategy for OCD.

Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder with a lifetime prevalence of 1-3% (Rasmussen and Eisen, 1992; Sasson et al., 1997). To date, the most effective treatments for OCD are pharmacological treatment, using serotonin reuptake inhibitors (SRIs, e.g., Masand and Gupta, 1999; Piccinelli et al., 1995; Pigott and Seay, 1999; Stein et al., 1995; Zohar et al., 1992) and behavioral treatment, using the exposure and response prevention technique (e.g., Simpson et al., 2004). In patients refractory to pharmaco- and behavioral therapy, lesions to structures and pathways within basal ganglia-thalamo-cortical circuits can reverse clinical symptoms (for review see, Lopes et al., 2004). Following the replacement of ablative lesions by high frequency stimulation (HFS) in the treatment of several basal ganglia-related disorders (Breit et al., 2004; Deuschl et al., 2006; Krack et al., 2003; Temel and Visser-Vandewalle, 2004), there have been attempts to establish HFS also for the treatment of OCD. The results of recent studies suggest that HFS of the ventral striatum region may be particularly effective in alleviating symptoms in OCD (Aouizerate et al., 2004; Aouizerate et al., 2005; Sturm et al., 2003; Greenberg et al., 2006, in press; Rauch et al., 2006). Yet, the findings that not all patients respond to this treatment, and that most responders experienced only partial alleviation of symptoms (for a recent review see Greenberg et al., 2008), highlight the need for identifying additional brain regions whose stimulation may produce beneficial effects in OCD patients.

Recent studies reported that bilateral HFS of the subthalamic nucleus (STN) dramatically alleviated compulsions and improved obsessions in three patients with co-morbid Parkinson's disease and OCD (Fontaine et al., 2004; Mallet et al., 2002). We have recently found that HFS as well as pharmacological inactivation of the STN alleviate compulsive checking in the quinpirole rat model of OCD (Winter et al., 2008c). Because this rat model is based on a pharmacological manipulation, the aim of the present study was to test whether HFS and pharmacological inactivation of the STN also exert an anti-compulsive effect in the drug-naive brain. To this end we chose to use the signal attenuation rat model of OCD (for a recent review of the model see Joel, 2006a), which is to date the best validated behavioral rat model of OCD (for a recent critical review and comparison between currently used models of OCD see Joel, 2006b). In this model, attenuation of a signal indicating that a lever-press response was effective in producing food, leads, in a subsequent extinction test, to excessive lever-pressing that is not accompanied by an attempt to collect a reward. This behavior, which we have named 'compulsive' lever-pressing because it may be analogous to the excessive and unreasonable behavior seen in OCD, is abolished by the SSRIs fluoxetine, paroxetine and fluvoxamine, but not by the anxiolytic drug, diazepam, or the tricyclic antidepressant, desipramine (Joel and Avisar, 2001; Joel et al., 2004), in accordance with the differential efficacy of these drugs in alleviating obsessions and compulsions in OCD patients (e.g., Dolberg et al., 1996; Piccinelli et al., 1995; Zohar et al., 1992). Compulsive lever-pressing is also sensitive to manipulations of the orbitofrontal cortex (Joel et al., 2005a,b; Joel and Klavir, 2006) and of the dopaminergic system (Joel et al., 2001; Joel and

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doi:10.1016/j.expneurol.2008.09.017

Doljanski, 2003), in line with functional, biochemical and pharmacological evidence implicating these neural systems in the pathophysiology of OCD (for review see Friedlander and Desrocher, 2006; Stein, 2000).

Because the effects of signal attenuation are assessed under extinction conditions, the effects of HFS and of pharmacological inactivation of the STN were assessed in rats undergoing an extinction test of lever-press responding that was preceded by signal attenuation (i.e., the post-training signal attenuation [PTSA] procedure), and in rats undergoing a control procedure in which the extinction test was not preceded by signal attenuation (the 'regular extinction' procedure). This design enables the differentiation between the effects of signal attenuation and of extinction per se (for a detailed discussion see Joel, 2006a).

Methods

Subjects

Sprague Dawley (Tel Aviv University, Israel) male rats approximately 3-4 months old, were housed individually under a reversed 12-hr light–dark cycle (lights on 1900–0700) and maintained on a 22-hr food restriction schedule, with water freely available. All experimental protocols were carried out according to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University.

Apparatus and behavioral procedure

Behavioral testing was conducted in operant chambers (Campden Instruments, Loughborough, UK), housed in sound-attenuated boxes and equipped with a 3 W house light, a Sonalert module (Model SC 628) that could produce a 80 dB 2.8 kHz tone, and two retractable levers on either side of a food magazine (fitted with a 3 W magazine light), into which 45 mg Noyes precision food pellets (Noyes, Sandown Chemical Limited, Hampton, England) could be delivered. Access to the food magazine was through a hinged panel, the opening of which activated a micro-switch. Equipment programming and data recording were controlled by a computer (intel x86 model 11 with 64 MB RAM and widows 98 2nd edition operating system) equipped with a specialized software (ABET I – animal behavior environment test system, Lafayette Instruments, Leics, U.K).

Prior to the beginning of the experiment, rats were handled for about 2 min daily for 5 days. On the last 3 days after handling, ~20 food pellets used as reinforcement for operant training were introduced into the home cages.

Post-training signal attenuation

The post-training signal attenuation procedure included 4 stages. The organization of a trial of each of these stages is presented in Fig. 1. Surgery for electrode/cannulae implantation was conducted within the second stage. *Stage 1: Magazine training*. On Days 1–3, rats were trained to collect food pellets from the food magazine in the operant chamber, with the levers retracted. On each day, each rat was trained until it completed 30 trials in which it inserted its head into the food magazine during stimulus presentation (collected trials), or until a total of 40 trials was reached. The number of collected trials and the total number of trials were recorded. *Stage 2: Lever-press training*. On Day 4, rats received a session of pre-training using a free-operant schedule. Throughout this session, the houselight was on and one lever was present in the operant box. Responding on this lever (reinforced lever, RL) resulted in the delivery of a single food pellet into the magazine, accompanied by the presentation of the compound stimulus (magazine light and tone). The stimulus was turned off after the rat's head entered the food magazine or after 15-s from the rat's first lever-press had elapsed. The lever designated as RL was counterbalanced over subjects and remained the same for each rat over the entire experimental procedure. Each rat was trained until it completed 30 trials, that is, pressed the lever and inserted its head into the food magazine during stimulus presentation. Rats that failed to attain 30 completed trials within 30 minutes, were returned to the test chamber at the end of the day for an additional session. On Days 5-6, rats were trained to lever-press in a discrete-trial procedure (Fig. 1). On each trial, both levers were inserted into the chamber. As on Day 4, responding on the RL resulted in the delivery of a single food pellet into the magazine, accompanied by the presentation of the compound stimulus. The levers were retracted and the compound stimulus was turned off, after the rat's head entered the food magazine or after 15-s (Day 5, 10-s Day 6) from the rat's first lever-press had elapsed. Further lever-presses on the RL as well as responding on the other lever (nonreinforced lever, NRL) had no programmed consequences. Each

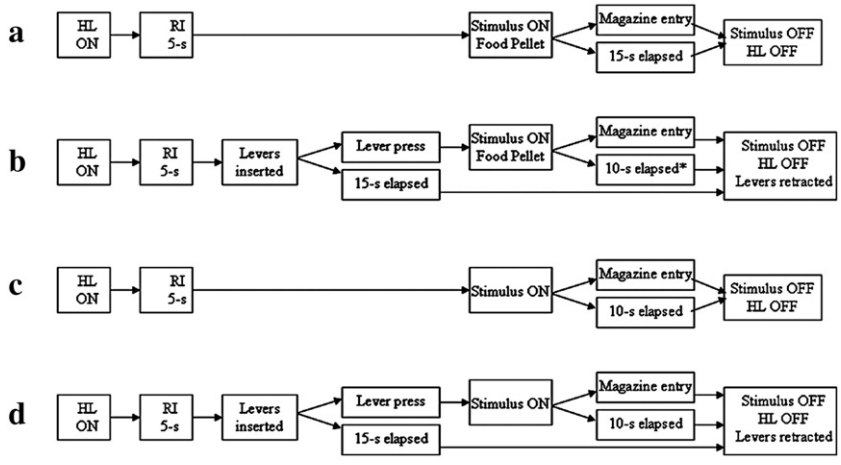

Fig. 1. A schematic diagram of the organization of a trial in each of the different training stages of the post-training signal attenuation procedure. (a) *Magazine training:* On each trial, a single food pellet was dropped into the food magazine, simultaneous with the onset of a compound stimulus consisting of the magazine light and the tone. The compound stimulus was turned off after the rat's head entered the food magazine or after 15-s had elapsed, and a 30-s intertrial interval began. (b) *Lever-press training:* On each trial, both levers were inserted into the chamber. Responding on the RL resulted in the delivery of a single food pellet into the magazine, accompanied by the presentation of the compound stimulus. The levers were retracted and the compound stimulus was turned off after the rat's head entered the food magazine or after 15-s (10-s post-surgery) from the rat's first lever-press had elapsed. Further lever-presses on the RL as well as responding on the other lever (nonreinforced lever, NRL) had no programmed consequences. Each trial was followed by a 30-s intertrial interval. (c) *Signal attenuation:* Training was identical to magazine training, except that no food was delivered and the compound stimulus was turned off after the rat's head entered the food magazine or after 10-s had elapsed. (d) *Test:* Training was identical to lever-press training except that no food was delivered. HL- House light; RI- Random interval.

rat was trained until it completed 40 trials, that is, pressed the lever and inserted its head into the food magazine during stimulus presentation, or for a total of 60 trials. Following these 2 sessions of lever-press training, rats underwent surgery for electrode/cannulae implantation (see below). Following at least 7 recovery days with ad lib food and water, rats were returned to the 22-hr food restriction schedule, and 3 days later were given 2 additional sessions of lever-press training (one session per day), identical to the session given pre-surgery (Day 6). In order to assess acquisition of the lever-press response, the number of trials on which the rat did not press the RL (unpressed trials) and the number of trials on which the rat pressed the RL without inserting its head into the food magazine (uncompleted trials) were recorded in addition to the number of completed trials. In order to assess rats' tendency for excessive lever-pressing, the number of lever-presses on the NRL, and the number of lever-presses on the RL after the first response (extra lever-presses, ELP) were recorded. The latter measure was further subdivided into ELP in uncompleted trials (that is, ELP not followed by insertion of the head into the food magazine; ELP-U), and ELP in completed trials (ELP-C). *Stage 3: Signal attenuation*. On the following 3 days, with the levers retracted, rats were exposed to the presentation of the compound stimulus as on Days 1–3, but no food was delivered to the food magazine (Fig. 1). Rats received 30 such trials on each day, and the number of collected trials was recorded. Rats that had more than 13 collected trials on the last day of signal attenuation were returned to the test chamber at the end of the day for an additional session. *Stage 4: Test*. On the following day, rats were trained as in the lever-press training stage, except that no food was delivered to the food magazine, that is, pressing the lever resulted in the presentation of the compound stimulus only (Fig. 1). The session lasted for 50 trials. The behavioral measures recorded were the same as in the lever-press training stage. Compulsive lever-pressing is operationally defined as the number of ELP-U in the test stage of the post-training signal attenuation procedure.

Regular extinction

Rats were run exactly as in the post-training signal attenuation procedure, with the exception that they did not undergo the signal attenuation stage. On these days, rats were brought to the laboratory and left in their home cages for a period equivalent to the average duration of the signal attenuation stage.

Surgery

Rats received 3-mg diazepam, and 20 minutes later were anaesthetized with i.p. injection of Avertin (10-ml/kg). *Experiment 1: HFS group:* two stainless steel concentric bipolar electrodes (SNE-100 with connector; RMI, Woodland Hills, CA, USI) were stereotaxically implanted bilaterally into the STN at the following coordinates (Paxinos and Watson, 2005): 3.6 mm posterior to bregma, 2.4 mm lateral to the midline, and 7.65 ventral to the dura. *NO HFS group*: Rats underwent the same surgical procedure as STN-HFS rats, but were implanted with stainless steel isolated wires (exposed at the tip), approximately the gage of the electrodes used in the *HFS* group, at the same coordinates. The electrodes/wires were fixed to the skull surface with stainless steel screws and dental acrylic cement (Popco dental, Israel). In all rats (*HFS* and *no HFS*) an additional connector was attached to the dental acrylic cement construct remotely from the site of the electrode connectors (in the *HFS* group) in order to allow the rats to get accustomed to attachment of wires to the head during the remaining lever press training sessions prior to the test stage, and to allow connection of *no HFS* rats to external wires during the test stage. *Experiment 2:* Bilateral 26 gauge, stainless steel, guide cannulae (Bilaney, Düsseldorf, Germany), were stereotaxically implanted at the same coordinates as in Exp. 1, but 7.4 ventral to dura. Cannulae were fixed to the skull surface with stainless steel screws and dental acrylic cement (Pupko dental LTD, Tel-Aviv, Israel). Removable stylets were placed in the guide cannulae and held in place with a screw-on dust cap. Rats were monitored on a daily basis, and were returned to behavioral training at least 1 week after recovery from operation.

High frequency stimulation

High frequency stimulation was conducted only during the test stage (Experiment 1). HFS was maintained for the whole duration of the test and was performed using an isolated stimulator (STG1004; Multichannel Systems, Germany) in a constant current and balanced biphasic pulse mode (frequency, 130 Hz; Pulse width, 100 μs; current intensity, 100 μA; charge density, 7.612μC/cm2/ph). These parameters were chosen because in our previous study which tested the effects of HFS-STN on 'compulsive' checking they were found to decrease compulsive behavior but not to affect locomotion (Winter et al., 2008c). The pattern of stimulation was supervised throughout the test via an analog oscilloscope, in order to ensure that a stable and continuous stimulation was applied. Rats were observed during the entire period of stimulation in order to ensure that no motor symptoms or impairments were visible, and that free access to the levers and magazine panel and recess was available.

Microinjection

Fifty minutes before the test, intracerebral microinjections were made bilaterally using a dual-syringe infusion pump (CMA/100 microinjection pump, Medecin AB, Solona Sweden). Rats were lightly dosed with Isoflurene (Sigma, Israel), the stylets were removed, and the injection needles (30-gauge) were inserted into the guide cannulae to protrude 0.3-mm) below their tips. 0.25-μl of muscimol (crystallized muscimol, Enco Diagnostics LTD, Petach-Tiqva, Israel, dissolved in phosphate buffered saline to a concentration of 0.005-μg/μl) were slowly delivered at a constant rate over 60-sec. One min following the injection, the needles were slowly removed and replaced by the stylet. Sham rats were lightly dosed with Isoflurene for an equivalent period

Table 1
Summary of experiments

Exp	Procedure	Manipulation	Num of rats in exp.	Num. of rats excluded	Group	Final n per group
1	SA & RE	HFS	71	1 - histology	PTSA-HFS	13
				3 - illness	PTSA-sham	14
				9 - computer failure	RE-HFS	11
				2 - statistical	RE-sham	18
2	SA & RE	Inactivation	45	9 - histology	PTSA-muscimol	8
					PTSA-vehicle	10
					RE-muscimol	9
					RE-vehicle	9

HFS – high frequency stimulation; RE – the regular extinction procedure; SA – the post-training signal attenuation procedure; Statistical: rats were excluded if their score on at least one variable was more than 4 standard deviations above their group mean (calculated without the deviant rat).

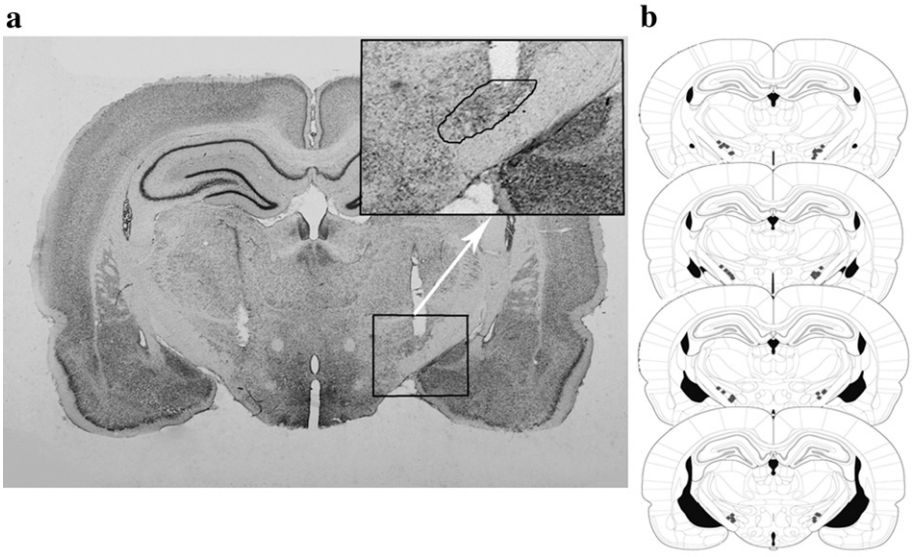

Fig. 2. (a) A photomicrograph of a coronal section taken through the STN in a representative STN HFS rat. (b) A reconstruction of electrode placement in STN HFS rats. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson (2005).

of time and infused with vehicle. The volume and concentration of muscimol injection were selected because in our previous study which tested the effects of STN inactivation on 'compulsive' checking they were found to decrease compulsive behavior without affecting locomotion (Winter et al., 2008c), and a pilot study in our laboratory found that infusion of 0.25-μl of muscimol at a dose of 0.01-μg/μl completely abolished rats lever-press responding during an extinction test.

Histology

After the completion of behavioral testing, all rats were overdosed with avertin (30 ml/kg, i.p.) and perfused intracardially with phosphate buffered saline followed by 10% buffered formalin. The brains were removed and placed in 10% buffered formalin for at least 24 hours, followed by 20% sucrose solution. The brains were sectioned in the coronal plane at 50-μm thickness and stained with Thionin Blue.

Results

Table 1 presents the number of rats allocated to each experiment, the number of rats that were excluded from each experiment, and the final number of rats in each group.

Experiment 1: The effects of bilateral HFS of the STN

Anatomical

Fig. 2a presents a photomicrograph of a coronal section taken from a representative STN-HFS rat. The only visible damage in these rats was the electrode tracks toward the target areas. Fig. 2b presents a schematic reconstruction of electrode placement in the STN. One rat was excluded from the analysis because the electrodes were not located within the STN. In all other rats, electrode tips were located within the STN.

Behavioral

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown). Figs. 3a and b present the mean number of ELP-C and ELP-U, respectively, in STN-HFS and no-HFS rats undergoing the test stage of the PTSA or regular extinction procedures. As can be seen, HFS of the STN decreased the number of ELP-C in the two procedures (Two-way ANOVA yielded significant main effects of Procedure, $F(1,52)=10.614$, $p<0.002$, and Stimulation, $F(1,52)=17.539$, $p<0.0001$, only). In contrast, HFS of the STN reduced the number of ELP-U in rats undergoing PTSA, but had no effect in rats undergoing regular extinction (Two-way ANOVA yielded a significant Procedure X Stimulation interaction, $F(1,52)=5.045$, $p<0.03$, only. Post hoc least significant difference (LSD) comparisons

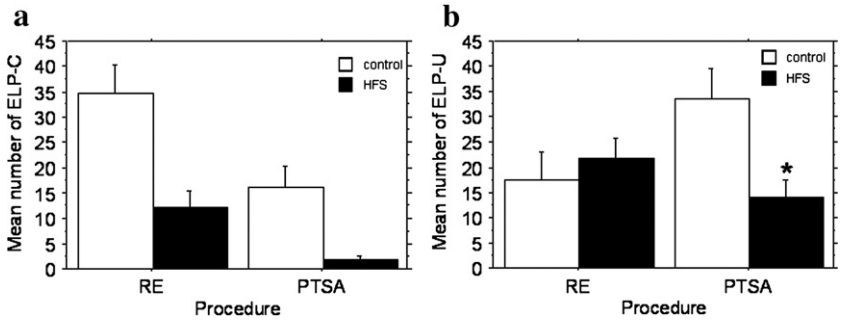

Fig. 3. The mean and standard error of the mean number of (a) ELP-C in the test of sham (empty bars) and STN-HFS (filled bars) rats undergoing the regular extinction (RE) or posttraining signal attenuation (PTSA) procedure. Significant effects of Procedure, $F(1,52)=10.614$, $p<0.002$, and Stimulation, $F(1,52)=17.539$, $p<0.0001$. (b)ELP-U in the test of sham (empty bars) and STN-stimulated (filled bars) rats undergoing the regular extinction (RE) or post-training signal attenuation (PTSA) procedure. A significant effect of Procedure × Stimulation interaction, $F(1,52)=5.045$, $p<0.03$, followed by LSD post hoc comparisons revealed a significant difference between STN stimulated and control rats within the PTSA procedure only, $p<0.02$, marked with *).

Table 2
Mean (SE) number of completed, uncompleted and unpressed trials, lever-presses on the reinforced lever (RL) and on the non-reinforced lever (NRL) and nose pokes during the Test (Experiment 1)

	Completed trials	Uncompleted trials	Unpressed trials	Lever-presses on RL	Lever-presses on NRL	Nose pokes
PTSA - sham	9.643(1.477)	7.929(1.066)	32.500(1.582)	67.357(9.005)	15.492(3.858)	72.357(11.222)
PTSA- HFS	2.385(1.190)	5.000(2.582)	42.538(1.141)	23.308(3.805)	4.308(1.100)	21.538(7.773)
RE - sham	25.500(1.349)	4.833(1.055)	19.667(1.603)	82.778(9.985)	5.222(0.629)	87.889(12.898)
RE- HFS	10.091(2.091)	7.091(1.522)	32.818(2.872)	51.091(8.762)	5.818(1.934)	74.364(22.184)
Procedure x Stimulation ANOVA						
Procedure	$F(1,52)=59.149$ $p<0.0001$	$F(1,52)=0.202$ $p=0.553$	$F(1,52)=38.140$ $p<0.0001$	$F(1,52)=5.882$ $p<0.0188$	$F(1,52)=3.887$ $p=0.054$	$F(1,52)=5.999$ $p<0.0178$
Stimulation	$F(1,52)=54.736$ $p<0.0001$	$F(1,52)=0.090$ $p=0.7654$	$F(1,52)=40.322$ $p<0.0001$	$F(1,52)=18.08$ $p<0.0001$	$F(1,52)=5.695$ $p<0.0208$	$F(1,52)=5.315$ $p<0.0253$
Procedure x Stimulations	$F(1,52)=7.077$ $p<0.0105$	$F(1,52)=5.377$ $p<0.025$	$F(1,52)=0.727$ $p=0.3979$	$F(1,52)=0.482$ $p=0.4908$	$F(1,52)=7.058$ $p<0.0106$	$F(1,52)=1.785$ $p=0.1873$

between STN stimulated and control rats within each procedure yielded a significant difference in the PTSA procedure only, $p<0.02$). Table 2 presents the mean (SE) number of completed, uncompleted and unpressed trials as well as the mean (SE) number of lever-presses on the reinforced and the non-reinforced lever (NRL) and of nose pokes during the test in the four groups. In the two procedures, HFS of the STN decreased the number of completed trials and of lever-presses on the reinforced lever, and increased the number of unpressed trials, compared to control rats. In addition, HFS of the STN decreased the number of uncompleted trials, nose-pokes and presses on the NRL only in rats undergoing the PTSA procedure (see Table for the full results of the statistical analyses).

Experiment 2: The effects of bilateral inactivation of the STN

Anatomical

Fig. 4a presents a photomicrograph of a coronal section taken from a representative STN-muscimol rat. The only visible damage in these rats was the cannulae tracks toward the target areas. Fig. 4b presents a schematic reconstruction of cannulae placement in the STN. In 5 rats (4 PTSA and 1 RE) the cannulae tips were located either rostral or caudal to the STN, and in 4 rats (RE) the brain was considerably damaged due to inflammation or hemorrhage. Thus, the final analysis included 8, 10, 9 and 9 rats in the PTSA-muscimol, PTSA-vehicle, regular extinction-muscimol and regular extinction-vehicle groups, respectively.

Behavioral

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown). Fig. 5a and b present the mean number of ELP-C and ELP-U, respectively, in STN-muscimol and STN-vehicle infused rats undergoing the test stage of the PTSA or regular extinction procedures. In both procedures, intra-STN infusion of muscimol had no effect on the number of ELP-C (Fig. 5a, two-way ANOVA: Procedure, $F(1,32)=4.889$, $p<0.035$, Inactivation, $F(1,32)=0.927$, $p=0.342$, Procedure x Inactivation interaction, $F(1,32)=0.47$, $p=0.830$). In contrast, microinjection of muscimol into the STN significantly decreased the number of ELP-U in rats undergoing PTSA but not in rats undergoing regular extinction (Fig. 5b, ANOVA: Procedure, $F(1,32)=1.383$, $p=0.248$, Inactivation, $F(1,32)=0.850$, $p=0.363$, Procedure x Inactivation interaction, $F(1,32)=6.162$, $p<0.02$, LSD post-hoc comparisons between the number of ELP-U in the vehicle and muscimol groups within each procedure revealed a significant difference within the PTSA procedure only, $p<0.023$). Table 3 presents the mean (SE) number of completed, uncompleted and unpressed trials as well as the mean (SE) number of lever-presses on the reinforced lever and on the NRL and of nose pokes during the test in the two groups. In the two procedures, inactivation of the STN did not affect the number of completed and unpressed trials, nor the number of lever-presses on the reinforced lever and of nose-pokes. Inactivation of the STN decreased the number of uncompleted trials (compared to control rats) in rats undergoing the PTSA procedure. Inactivation decreased the number of

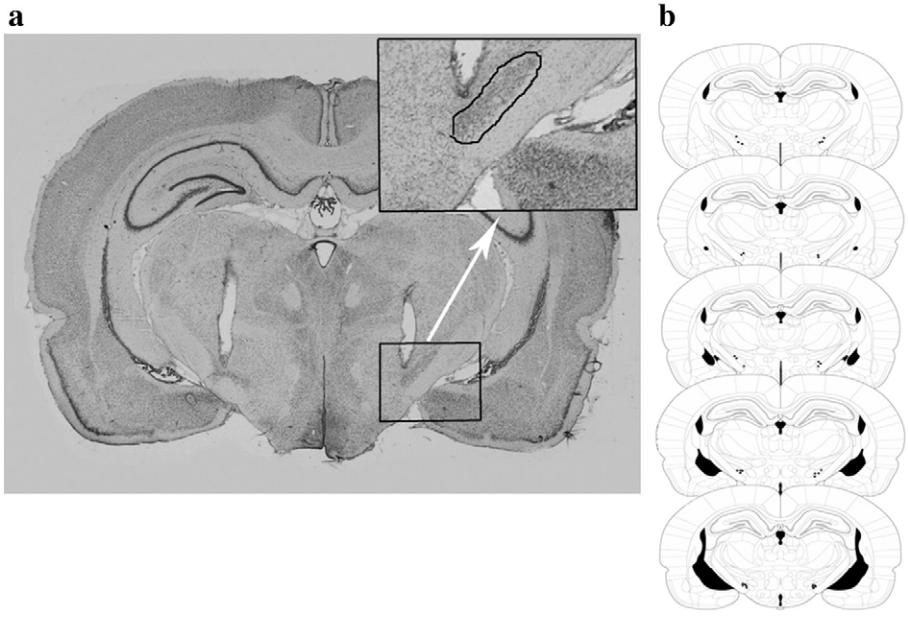

Fig. 4. (a) A photomicrograph of a coronal section taken through the STN in a representative STN inactivated rat. (b) A reconstruction of cannulae placement in STN inactivated rats. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson (2005).

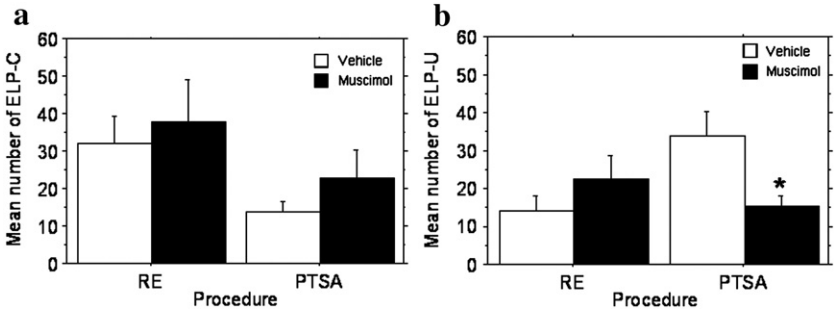

Fig. 5. The mean and standard error of the mean number of (a) ELP-C in the test of vehicle (empty bars) and STN-muscimol infused (filled bars) rats undergoing the regular extinction (RE) or post-training signal attenuation (PTSA) procedure. Significant effects of Procedure, $F(1,32)=4.889$, $p<0.035$. (b) ELP-U in the test of vehicle (empty bars) and STN-muscimol infused (filled bars) rats undergoing the regular extinction (RE) or post-training signal attenuation (PTSA) procedure. A significant effect of Procedure × Inactivation interaction, $F(1,32)=6.162$, $p<0.02$, followed by LSD post hoc comparisons revealed a significant difference between the vehicle and muscimol groups within the PTSA procedure only, $p<0.023$, marked with *.

NRL in the PTSA procedure but increased it in the regular extinction procedure (see Table for the full results of the statistical analyses).

Discussion

The present study tested the effects of pharmacological inactivation and HFS of the STN on compulsive lever-pressing, assessed in the signal attenuation rat model of OCD. The effects of each of these manipulations were assessed in rats undergoing an extinction test of lever-press responding that was preceded by signal attenuation (the PTSA procedure), and in rats undergoing a control procedure in which the extinction test was not preceded by signal attenuation (the 'regular extinction' procedure). This design enables the differentiation between the effects of signal attenuation and of extinction per se. Briefly, a manipulation-induced effect on compulsive responding is evidenced in a change in the number of excessive lever-presses that are not followed by magazine entry (ELP-U) in the PTSA procedure but not in the regular extinction procedure, whereas a manipulation-induced effect on extinction is manifested in a change in the number of excessive lever-presses that are followed by magazine entry (ELP-C) in both the PTSA and regular extinction procedures (for a detailed discussion see Joel, 2006a).

The main finding of the present study is that both HFS and pharmacological inactivation of the STN exerted an anti-compulsive effect, although the two manipulations differed in their effects on other behavioral measures. More specifically, HFS, but not pharmacological inactivation, decreased the number of ELP-C as well as the total number of lever-presses on the reinforced lever in the two procedures, and in addition, decreased the number of nose-pokes in the PTSA procedure; the two manipulations decreased the number of lever-presses on the non-reinforced lever (NRL) in the PTSA procedure, HFS did not affect this behavioral measure in regular extinction whereas pharmacological inactivation increased it. In contrast, both HFS and pharmacological inactivation of the STN selectively decreased the number of compulsive lever-presses, that is, ELP-U in the PTSA but not in the regular extinction procedure.

The decrease in compulsive lever-pressing cannot be attributed to a non-selective effect of HFS and pharmacological inactivation of the STN on lever-press responding, because the two manipulations did not affect the number of ELP-U in regular extinction. Interestingly, HFS and pharmacological inactivation did decrease the number of lever-presses on the NRL in rats undergoing PTSA. While clearly lever-presses on the NRL are a form of inappropriate behavior, they do not seem to reflect compulsive responding. This is mainly because SSRIs do not affect this type of behavior in a consistent way. Thus, at a dose that decreases compulsive lever-pressing, paroxetine decreased lever-presses on the NRL in both the PTSA and regular extinction procedures, whereas fluvoxamine increased this behavior in regular extinction but tended to decrease it in PTSA (unpublished data; for further discussion of similarities and differences between compulsive lever-presses and lever-presses on the NRL see Joel and Klavir, 2006). The anti-compulsive effect of HFS and of pharmacological inactivation of the STN also cannot be explained by their effects on the tendency to nose-poke, because HFS decreased and inactivation did not affect the number of nose-pokes in rats undergoing PTSA. It is noteworthy that in the five-choice serial reaction time task, HFS and pharmacological inactivation of the STN resulted in perseverative nose-poking (Baunez and Robbins, 1999b; Baunez et al., 2007), in contrast to the present findings. The reason for this inconsistency is not clear, but may be attributed to differences between the task used in the above studies and those used in the present study, including assessment of behavior under rewarded or extinction conditions (serial reaction time task vs PTSA and regular extinction, respectively); the location/role of nose-poking in the behavioral sequence (being the instrumental response in the serial reaction time task but not in PTSA and regular extinction, where lever-pressing is the instrumental response); the need to

Table 3
Mean (SE) number of completed, uncompleted and unpressed trials, lever-presses on the reinforced lever (RL) and on the non-reinforced lever (NRL) and nose pokes during the Test (Experiment 2)

	Completed trials	Uncompleted trials	Unpressed trials	Lever-presses on RL	Lever-presses on NRL	Nose pokes
PTSA - vehicle	7.300(1.342)	7.700(1.430)	35.000(1.915)	62.600(9.929)	16.800(2.435)	93.100(20.359)
PTSA- muscimol	12.500(3.591)	3.500(0.627)	34.000(3.412)	54.125(11.238)	7.750(6.331)	62.625(11.796)
RE - vehicle	22.444(2.897)	4.000(0.764)	23.556(2.667)	72.667(10.997)	6.111(0.629)	117.333(26.396)
RE- muscimol	19.778(2.493)	4.222(1.064)	26.000(3.014)	84.333(18.154)	19.556(1.934)	109.111(37.917)
Procedure x Inactivation ANOVA						
Procedure	F(1,32)=18.583 p<0.0001	F(1,32)=1.925 p=0.1749	F(1,32)=12.593 p<0.0013	F(1,32)=2.399 p=0.1313	F(1,32)=0.021 p=0.8854	F(1,32)=1.800 p=0.1891
Inactivation	F(1,32)=0.237 p=0.6295	F(1,32)=3.434 p=0.0731	F(1,32)=0.069 p=0.7938	F(1,32)=0.015 p=0.9031	F(1,32)=0.327 p=0.5715	F(1,32)=0.539 p=0.4682
Procedure x Inactivation	F(1,32)=2.287 p=0.1402	F(1,32)=4.245 p<0.0477	F(1,32)=0.395 p=0.5341	F(1,32)=0.600 p=0.4443	F(1,32)=8.563 p<0.0064	F(1,32)=0.178 p=0.6757

respond fast (within 5 seconds in the serial reaction time task versus 10 seconds in PTSA and regular extinction).

The finding that HFS and pharmacological inactivation of the STN decreased compulsive responding is in line with previous reports of decreased responding following STN manipulations. Thus, animals sustaining STN lesions worked less for cocaine reward (Baunez et al., 2005) and showed less impulsive choice compared to control animals (Winstanley et al., 2005; Uslaner and Robinson, 2006). Moreover, we have previously found that HFS and pharmacological inactivation of the STN, using the exact same parameters used in the present study, decreased compulsive checking in the quinpirole rat model of OCD (Winter et al., 2008c). The present findings are also in line with two recent reports that bilateral STN-HFS dramatically alleviated compulsions and improved obsessions in three PD patients with severe comorbid OCD (Fontaine et al., 2004;Mallet et al., 2002). These results, however, seem to contradict the common notion that the STN plays a major role in the suppression of unwanted actions. This notion is based on observations in humans and animals. Specifically, in humans, lesions to the STN typically result in hemichorea and hemiballism (Dewey and Jankovic, 1989; Martin, 1927; Vidakovic et al., 1994), and there is also a report of a patient who became disinhibited, extroverted and logorrheic following unilateral STN lesion (Trillet et al., 1995). Recent studies reported that HFS of the STN in humans leads to increased libido (Krause et al., 2001), impulsivity (Trepanier et al., 2000; Saint-Cyr et al., 2000; Sensi et al., 2004) and aggressive behavior (Sensi et al., 2004). In animals, (permanent and reversible) STN lesions increase behavioral disinihibition, as reflected in increased perseverative and premature (impulsive) responding (Baunez and Robbins, 1997, 1999a,b; Uslaner and Robinson, 2006; Wiener et al., 2008), and impair stopping, as measured in the stop-signal reaction time task (Eagle et al., 2008). Moreover, we have recently found that lesions to the STN made prior to training in the PTSA procedure led to a selective increase in compulsive lever-pressing (Winter et al., 2008a).

There have been a few attempts to explain the seemingly contradictory effects of STN manipulations in different tasks. For example, Winstanley et al. (2005) suggested that STN lesions may increase 'impulsive action', but decrease 'impulsive choice'. Uslaner and Robinson (2006) suggested that the opposite effects of STN lesions on these two forms of impulsivity, as well as in additional tasks, may reflect the role of this nucleus in regulating incentive motivation. More specifically, Uslaner and Robinson (2006) suggested that lesions of the STN magnify the incentive value of rewards, and that therefore the effects of STN manipulations depend on the specific design of the task (see Eagle et al., 2008 for the application of this hypothesis to explain the effects of STN manipulations on additional tasks). The "incentive value" hypothesis may also be relevant to the present study because the incentive value of the light & tone stimulus is lower for rats undergoing the PTSA procedure compared with rats undergoing the regular extinction procedure, as a result of the extinction of the stimulus-food contingency in the signal attenuation stage.

It is difficult, however, to account for the effects of STN manipulations in the present study using the "incentive value" hypothesis, for several reasons. First, an increase in incentive value may be expected to retard extinction of lever-press responding during the test stage, because one of the properties of Pavlovian stimuli is their ability to maintain operant responding in extinction (a property typically referred to as conditioned reinforcement, Mackintosh, 1974). Indeed, Baunez et al. (2002) found that, compared with control rats, STN-lesioned rats were slower to extinguish conditioned locomotor activity, and responded more to a lever associated with the presentation of a Pavlovian stimulus (another procedure used to assess the conditioned reinforcement properties of a stimulus, Mackintosh, 1974). In the present study, however, pharmacological inactivation of the STN had no effect on extinction, as reflected in the number of completed trials, unpressed trials, ELP-C and the total number of lever-presses during the test (Table 3 and Fig. 5), whereas HFS of the STN facilitated extinction (Table 2 and Fig. 3).

Second, with regard to the effects of pharmacological inactivation and HFS of the STN on the number of ELP-U in the two procedures, it is clear that manipulating the STN counteracted the effects of signal attenuation on the number of ELP-U. It is not at all clear, however, whether this is related to the effects of STN manipulations on incentive value, because there are currently no data on the effects of changes in incentive value on the number of ELP-U in the PTSA and regular extinction procedures. There is, however, indirect evidence to suggest that the critical factor in inducing compulsive lever-pressing is not the reduction in the motivational value of the stimulus in the signal attenuation stage. Specifically, we have found that lesions to the basolateral nucleus of the amygdala, which has been suggested to be primarily involved in the acquisition of the motivational significance of stimuli (e.g., Pickens et al., 2003; Rolls, 2000), do not affect compulsive lever-pressing (Joel et al., 2005b).

Another difficulty in applying current accounts for the different effects of STN manipulations in different procedures to the PTSA procedure is that whereas post-training STN manipulations decreased compulsive lever-pressing (present study), pre-training STN lesions increased it (Winter et al., 2008a). Thus, our results highlight an additional factor that determines the effects of STN manipulations, namely, the time of the lesion relative to the acquisition of the task. This factor has also been found to play a major role in determining the effects of orbitofrontal manipulations in the PTSA (Joel et al., 2005a, 2005b; Joel and Klavir, 2006) as well as other procedures (e.g., cue-induced reinstatement, Fuchs et al., 2004; see Joel and Klavir, 2006 for more detail). In situations where the effects of pre-training and post-training manipulations of the same structure are different, the effects of post-training manipulations may better reflect the role of the intact structure, because in the pre-training lesioned brain the acquisition of the task may rely on different neural systems than in the intact brain. It may therefore be suggested that in the intact brain, the STN may be involved in the production of compulsive behaviors. This conclusion is non-intuitive if we view compulsive behaviors as resulting from an inability to inhibit a response in a learned behavioral sequence so that the next response in the sequence can be performed (Chudasama et al., 2003; Robbins, 2002). However, the common notion that compulsive behaviors result from 'capture' of the system in a specific behavior due to inability to switch to another behavior (e.g., Saxena et al., 1998), together with the notion that a major function of the STN is the inhibition of pre-potent responses (e.g., Baunez and Robbins, 1997, 1999b; Eagle et al., 2008) may be retained if we assume that compulsive behaviors result from improper inhibition of the next response in the sequence, resulting in excessive emission of the preceding response.

Although the above discussion is highly speculative, and there is currently no theory which can account for all the data on the effects of STN manipulations in different tasks, it is important to note that pharmacological inactivation and HFS of the STN have been found to exert an anti-compulsive effect in two very different animal models of OCD (the present study and Winter et al., 2008c). The converging evidence from the two models strongly suggests that the anti-compulsive effect of pharmacological inactivation and HFS of the STN is a real phenomenon and not an artifact of the experimental method used.

The finding that both HFS and pharmacological inactivation of the STN exerted an anti-compulsive effect suggests that these two manipulations have a similar effect at the system level, although it is likely that they achieve this effect via different mechanisms (Liu et al., 2008; McIntyre et al., 2004a, 2004b; Montgomery and Gale, 2008). More specifically, muscimol administration has been reported to block the activity of STN neurons thereby decreasing or eliminating STN output (Baufreton et al., 2001; Smith and Grace, 1992), whereas stimulation of the STN at high frequencies suppresses the activity of subthalamic neurons, but increases activity in STN efferents and may

also lead to the antidromic activation of neurons in other nuclei whose axons pass through the STN (e.g., Hashimoto et al., 2003; Maurice et al., 2003). It is possible that these latter effects are responsible for the decreased number of ELP-C and of nose pokes following HFS of the STN, which were not evident following pharmacological inactivation of this structure. It is noteworthy that both HFS and pharmacological inactivation of the STN were reported to *increase* dopamine content in the striatum (Bruet et al., 2001; Meissner et al., 2001; Lee et al., 2006; Winter et al., 2008b), as we have recently suggested that a *decrease* in striatal dopamine and serotonin may provide a final common pathway by which different brain pathologies lead to a pro-compulsive state (Winter et al., 2008a).

The possibility that increased dopamine activity may mediate the anti-compulsive effect of STN manipulations on compulsive responding is of particular interest given that the same mechanism has been previously suggested to underlie STN lesion-induced increase in the incentive value of rewards (Uslaner and Robinson, 2006). As detailed above, this latter effect has been suggested to account for the seemingly opposite effects of STN manipulations in different tasks. In this respect it is of particular significance that whereas previous reports that HFS of the STN exerts an anti-compulsive effect have been obtained in dopamine modified systems (i.e., in Parkinson's disease patients and in quinpirole-treated rats), the present study has used dopamine-intact rats.

In summary, although the extrapolation from rat models to the clinical condition should be made with great caution, the finding that HFS and pharmacological inactivation of the STN decreased compulsive behaviors in two very different rat models of OCD (for review and comparison of the two models see Joel, 2006b) supports the possibility that STN-HFS may be effective in alleviating symptoms in OCD patients. Moreover, the fact that STN-HFS has been shown to exert an anti-compulsive effect in a rat model in which intact rats are used (signal attenuation model, present study), suggests that the anti-compulsive effect of STN-HFS is not restricted to the parkinsonian brain, as has already been found in humans.

Acknowledgments

We want to thank Moshe Zer for his invaluable assistance with setting up the stimulation device. This study was supported by GIF grant (851/2004).

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