

## High frequency stimulation and temporary inactivation of the subthalamic nucleus reduce quinpirole-induced compulsive checking behavior in rats

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Received 24 August 2007; revised 29 October 2007; accepted 31 October 2007

Available online 17 November 2007

### Abstract

Obsessive-compulsive disorder (OCD) represents a highly prevalent and impairing psychiatric disorder. Functional and structural imaging studies implicate the involvement of basal ganglia-thalamo-cortical circuits in the pathophysiology of this disorder. In patients remaining resistant to pharmacological and behavioral therapy, modulation of these circuits may consequently reverse clinical symptoms. High frequency stimulation (HFS) of the subthalamic nucleus (STN), an important station of the basal ganglia-thalamo-cortical circuits, has been reported to reduce obsessive-compulsive symptoms in a few Parkinson's disease patients with comorbid OCD.

The present study tested the effects of bilateral HFS of the STN and of bilateral pharmacological inactivation of the STN (via intracranial administration of the GABA agonist muscimol) on checking behavior in the quinpirole rat model of OCD.

We demonstrate that both HFS and pharmacological inactivation of the STN reduce quinpirole-induced compulsive checking behavior.

We conclude that functional inhibition of the STN can alleviate compulsive checking, and suggest the STN as a potential target structure for HFS in the treatment of OCD.

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**Keywords:** High frequency stimulation; Deep brain stimulation; Obsessive compulsive disorder (OCD); Quinpirole; Rat; Subthalamic nucleus

### Introduction

Obsessive-compulsive disorder (OCD) represents a highly impairing psychiatric disorder with a lifetime prevalence of 1–3% (Rasmussen and Eisen, 1992; Sasson et al., 1997). Effective treatment options comprise pharmacological interventions, preferentially with selective serotonin reuptake inhibitors (Masand and Gupta, 1999; Piccinelli et al., 1995; Pigott and Seay, 1999; Stein et al., 1995; Zohar et al., 1992)

and behavioral therapy (Simpson et al., 2004). In patients refractory to pharmacological and behavioral therapy, ablative lesions of structures and pathways within the basal ganglia-thalamo-cortical circuits have been shown to reverse clinical symptoms (Lopes et al., 2004). In the treatment of basal ganglia-related neurological disorders, such as Parkinson's disease, ablative lesions have widely been replaced by deep brain stimulation (DBS) at high frequencies (high frequency stimulation, HFS), a reversible and customizable procedure leading to a similar clinical outcome (Breit et al., 2004; Deuschl et al., 2006; Krack et al., 2003; Temel and Visser-Vandewalle, 2004).

In recent years there has been an attempt to establish HFS of structures within the basal ganglia-thalamo-cortical circuits also for the treatment of OCD. Several case reports have assessed the

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effects of HFS of the anterior limb of the internal capsule (Abelson et al., 2005; Gabriels et al., 2003), the ventral caudate nucleus (Aouizerate et al., 2004; Aouizerate et al., 2005) and the nucleus accumbens and ventral capsule/ventral striatum (Greenberg et al., 2006; Rauch et al., 2006; Sturm et al., 2003) in OCD patients, and there are also reports on the effects of HFS of the subthalamic nucleus (STN) in patients with comorbid Parkinson's disease and OCD (Fontaine et al., 2004; Mallet et al., 2002). The results of these studies are encouraging in showing that HFS may be effective in the treatment of OCD, and that HFS of the ventral striatum region may be particularly effective in alleviating symptoms in OCD. Yet, the inconsistency in the demonstration of beneficial effects and the variability in the time needed to obtain a therapeutic effect, highlight the need for identifying additional brain regions whose stimulation may produce beneficial effects in OCD patients. This goal may be advanced by the assessment of the effects of HFS in appropriate animal models of OCD. To date, experimental data in animal models are limited to only one such report: van Kuyck et al. (2003) found in rats an increase, rather than a decrease, of compulsive-like behavior after electrical stimulation or ablative lesion of the nucleus accumbens. Congruently, the authors cautiously interpreted their results by concluding that either electrical stimulation of the nucleus accumbens may not represent a potential target in the treatment of OCD, or that the model itself did not adequately reflect compulsive-like behavior. Another plausible reason for van Kuyck et al.'s finding is that they have used low frequency stimulation, whereas HFS is typically used in the clinical situation, and the frequency of stimulation has been shown to be a critical factor in determining the behavioral effect of stimulation (for review: Perlmutter and Mink, 2006).

In the present study we have used quinpirole- (QNP) induced compulsive checking behavior in rats as a model of OCD ((Szechtman et al., 1998); for recent reviews of this model and a comparison to other models of OCD: (Eilam and Szechtman, 2005; Joel, 2006; Man et al., 2004)). Rats treated chronically with the dopamine D2/D3 receptor agonist QNP develop compulsive-like behaviors that resemble compulsive checking behavior of OCD patients (Szechtman et al., 1998, 2001). The present study was designed to test the effects of HFS and of pharmacological inactivation (by intracerebral muscimol microinjections) of the STN on compulsive checking in QNP-treated rats. This experimental set up enables the assessment of the STN as a potential neurosurgical target in the treatment of OCD and the elucidation of the mechanism(s) underlying the influence of STN-HFS on compulsive-like behavior.

## Materials and methods

### Animals

The present study was carried out in accordance with the European Communities Council Directive of November 24th, 1986 (86/609/EEC) for care of laboratory animals and after approval of the local ethic committee (senate of Berlin). All efforts were made to minimize animal suffering and to reduce the number of animals. Forty-seven naive male Wistar rats

(Harlan-Winkelmann, Borcheln, Germany, 220–450 g during the experiment) were housed in a temperature- and humidity-controlled vivarium with a 12-hour light-dark cycle (lights on, 6 a.m.–6 p.m.). All experiments were performed during day time. Food and water were available *ad libitum*.

### Apparatus and behavioral procedure

Prior to experiments, rats were handled for about 2 min daily for 5 days. With the start of the experiment, rats were injected subcutaneously twice weekly for a total of 13 or 15 injections with either saline (control group) or QNP (QNP group). Fifteen minutes after each injection, animals were placed in an open field and their behavior was videotaped continuously throughout a 30 min session. The open field consisted of a glass table (140×140 and 20 cm high) subdivided into 25 rectangles (locales) and equipped with 4 plexiglas boxes at fixed locations (Szechtman et al., 1998). A computer, interfaced with a video recorder, was used to score behavior during playbacks of video records (TSE VideoMot 2 system, Technical & Scientific Equipment, Bad Homburg, Germany).

The following measures were assessed for each session and rat: 1. total distance traveled; 2. total time of activity/inactivity; 3. frequency of stops at each open field locale; 4. mean duration of return time to a given locale; 5. mean stop duration at a given locale; 6. total duration of stops at a given locale; 7. sequence of visits. The locale with the highest total duration of stops was individually defined as the home base (HB; Eilam and Golani, 1989) and compulsive checking behavior was analyzed with reference to the HB and in comparison to saline-treated controls. According to Szechtman et al. (1998) compulsive checking is present if the rat meets the following three performance criteria: the subject returns to the HB excessively often, excessively rapidly, and visits less places before returning to the HB, compared with control rats. The following measures were therefore analyzed: total number of visits to HB; mean time to return to HB; mean number of stops before returning to HB. In addition, because repeated administration of QNP increases locomotion (Szechtman et al., 1994a,b; Szumlinski et al., 1997) and since checking behavior requires locomotion, an arithmetic was applied allowing the assessment of checking behavior relatively independent from locomotion. Specifically, for each rat individually, the expected rate of return to a locale was calculated by dividing the total number of visits in a session by the number of locales visited. Next, the ratio of observed to expected HB visits was calculated by dividing the number of visits to the HB with the expected rate of return to a locale.

### Design

The experiment consisted of two phases. In *phase I*, rats received 10 injections (two injections per week with a 3–4 days test-free period) of either 0.5 mg/kg QNP (n=26) or saline (controls, n=21), followed by behavioral testing in the open field. Previous work has shown that the effects of chronic treatment with QNP reaches a plateau after 8 to 10 drug injections (Einat and Szechtman, 1993; Szechtman et al., 1994a,b; Szumlinski et al., 1997) as well as

reliable checking behavior (Szechtman et al., 1998). After the 10th behavioral testing, QNP-treated ( $n=26$ ) and control rats ( $n=9$ , 12 remaining rats were not further investigated as part of this project) were randomly assigned to HFS and pharmacological inactivation experiments. Rats in the HFS experiment underwent bilateral implantation of SNEX electrodes and rats in the pharmacological inactivation experiment underwent bilateral implantation of guide cannulae. In *phase II* the effects of STN-HFS and of muscimol microinjections into the STN were investigated using a within-subjects design. Specifically, control and QNP rats in the HFS experiment underwent three additional saline or QNP (respectively) injections (2 injections per week), each followed by behavioral testing (sessions 11–13). HFS was applied during the 12th session only. Control and QNP rats in the pharmacological inactivation experiment underwent five additional saline or QNP injections (2 injections per week), each followed by behavioral testing (sessions 11–15). Muscimol was applied in doses of 0.01, 0.005, and 0.001  $\mu\text{g}$  (dissolved in 0.5  $\mu\text{l}$  per side) in a random order on the 12th–14th sessions, saline (0.5  $\mu\text{l}$  per side) was applied on the 15th session. Thus, in both the HFS and the pharmacological inactivation experiments, the effects of the manipulation were assessed at least one week following electrodes/cannulae implantation, to allow recovery from the micro-trauma induced by implantation (Baunez et al., 2007; Bressand et al., 2002). Furthermore, because according to previous reports, an interval of 3–4 days between

sessions is sufficient to allow remission of the transient effects of HFS and of muscimol infusion (Baunez et al., 2005; Baunez and Robbins, 1999; Bergmann et al., 2004; Lee et al., 2004, 2006; Mehta et al., 2005; Meissner et al., 2002, 2003, 2001, 2004; Tai et al., 2003), the last test session in both the HFS and the pharmacological inactivation experiments served to assess reversibility of treatment manipulation.

### Surgery

Stereotaxic operations were performed after the 10th session and were carried out under sodium pentobarbital anesthesia (60 mg/kg i.p.). For each operation, the incisor bar was set at 3.3 mm below the interaural line. *Electrode implantation*: Two electrodes (Concentric bipolar SNEX 100 with connector, RMI Woodland Hills, CA, USA) were implanted bilaterally into the STN -3.8 mm posterior and 2.5 mm lateral from bregma as well as -7.6 mm ventral from dura (Paxinos and Watson, 1997). *Cannula implantation*: Two guide cannulae were implanted bilaterally at the same coordinates but above the STN (3 mm dorsal) so that the injector would protrude 3 mm below the cannula. Electrodes and cannulae were fixed to the skull surface with stainless steel screws and dental acrylic cement (Technovit<sup>®</sup>, Heraeus-Kulzer, Hanau, Germany). Wire stylets were inserted into the guide cannula to prevent occlusion.

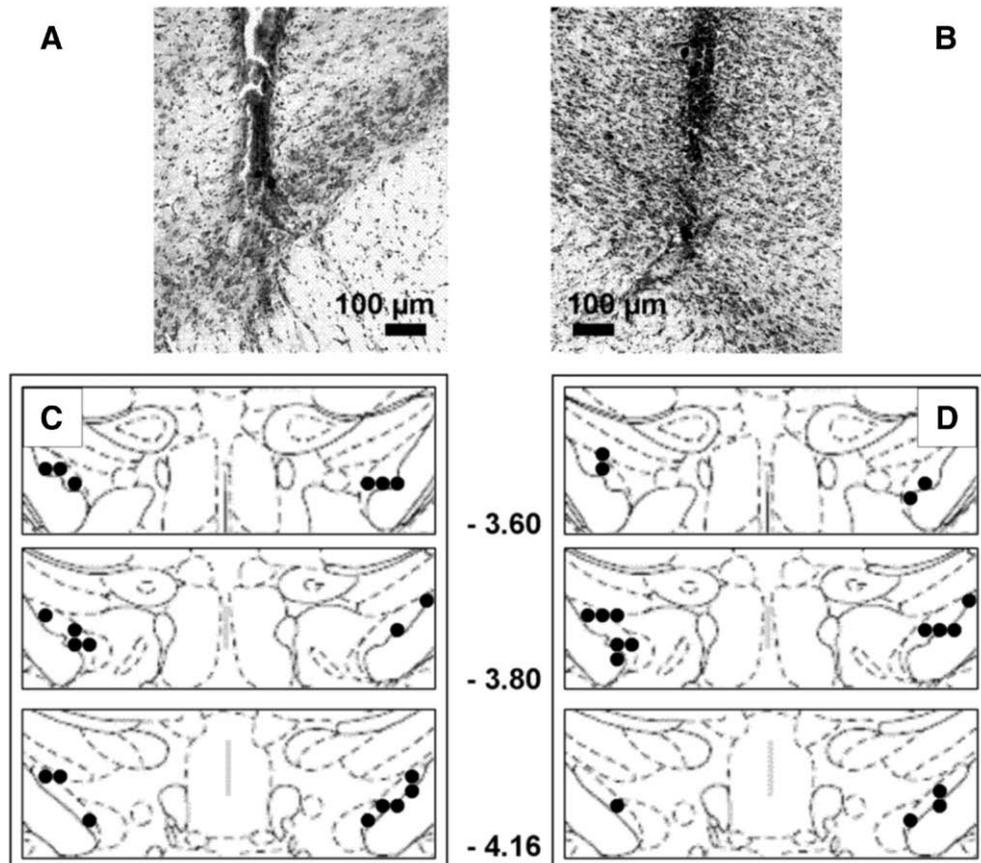


Fig. 1. Post Mortem Histology: A and B: photomicrographs of a coronal section stained with cresyl violet and taken from representative rats showing the tip of the electrode (A) or of the injection cannula (B) in the subthalamic nucleus. C and D: Schematic reconstructions of electrodes (C) or cannulae (D) placement in the subthalamic nucleus.

## Systemic and intracerebral drug administration

QNP hydrochloride (Sigma® Aldrich) was dissolved in 0.9% NaCl to a concentration of 0.5 mg/ml and injected subcutaneously under the nape of the neck at a dose of 0.5 mg/kg body weight. Control subjects received the same volume of saline.

Muscimol (Sigma® Aldrich) was dissolved in 0.9% NaCl to a dose of 0.01, 0.005, 0.001 µg per 0.5 µl. These doses have previously been shown to affect rats' performance following administration to the STN (Baunez et al., 2005; Baunez and Robbins, 1999). In addition, in a pilot study in our lab we have found that at a dose of 0.1 and 0.025 µg per 0.5 µl per side muscimol suppressed locomotion to an extent that compulsive checking behavior could not be analyzed (data not shown). Saline and muscimol were applied right before systemic QNP or saline injection. Rats were lightly anaesthetized by a q-tip soaked with flurothane and positioned in front of the rats' noses. 25 gauge stainless steel injection needles were inserted into the guide cannulae to protrude 3 mm below their tips. Needles were attached via fine polyethylene tubing to a 20 µl Harvard microsyringe and muscimol or saline was delivered at a constant rate over one min. Thereafter, injection needles were left in place for another one min before being slowly removed and replaced by stylets.

## Stimulation

STN-HFS was performed with an isolated stimulator (Coulbourn Instruments, Allentown, PA, USA). Implanted electrodes were connected to the stimulator via an isolated cable system hanging from the ceiling of the behavioral room. A swivel and a minimal resistance hairspring connected the cable system to the implanted electrodes and allowed the rat to freely turn and move on the entire platform without being constricted or tangled up by the cable system during stimulation or sham-stimulation. For stimulation the following parameters were used: constant current mode, frequency 130 Hz, pulse width 60 µsec, current intensity 100 µA. Frequencies of 130 Hz and a narrow pulse duration of 60 µsec were chosen according to the parameters generally applied in rats for inducing effects of the STN (Baunez et al., 2007; Benazzouz et al., 1995; Desbonnet et al., 2004; Meissner et al., 2003; Salin et al., 2002; Shi et al., 2006; Windels et al., 2000) and were comparable to the clinical situation (Moro et al., 2002). A current intensity of 100 µA was chosen on the basis of minimal tissue damage (Harnack et al., 2004) at a value that has previously been shown to induce behavioural and biochemical changes (own unpublished data: 50–300 µA; Baunez et al., 2007: 50 µA; Boulet et al., 2006: 60/200 µA; Darbaky et al., 2003: 50/300 µA; Desbonnet et al., 2004: 30, 150). In addition, in a pilot study we have found that at higher current

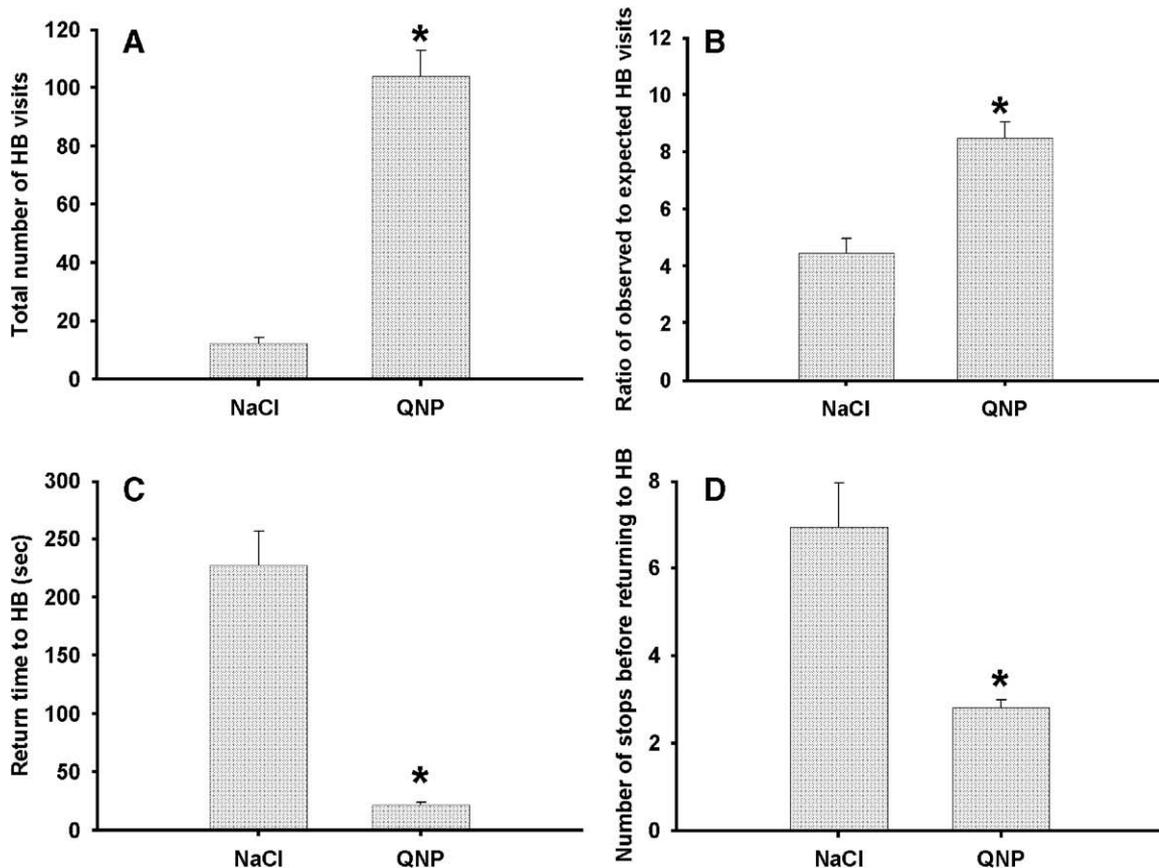


Fig. 2. Induction of compulsive checking behavior. Compulsive checking behavior is analyzed with reference to home base (HB) established by the rat during 10th test shown here, and recognized as the locale with the longest total duration of stops. QNP-treated animals met compulsive checking criteria as defined previously and displayed when comparing to saline-treated controls (A) more frequent returns to the home base, (B) a higher than an expected rate of returning to the home base, (C) reduced return time to home base, and (D) fewer visits to other places before revisiting home base. \* $P < 0.05$ ,  $t$ -test. Values are expressed as mean  $\pm$  SEM.

intensities HFS of the STN decreases locomotion, an effect that could interfere with the detection of a beneficial effect on compulsive checking behavior. Stimulation was started at the beginning of the behavioral assessment (15 minutes after QNP injection) and continued for the 30 minutes of it.

## Histology

After the 13th (HFS experiment) or the 15th (pharmacological inactivation experiment) session, rats were anaesthetized with chloral hydrate (50 mg/kg, Merck, Darmstadt, Germany) and perfused transcardially with 0.1 M phosphate buffered saline, followed by ice-cold 4% paraformaldehyde. Brains were removed and postfixed overnight in the same fixative and then stored at 4 °C in 30% sucrose. 40 µm frozen coronal sections were cut using a cryostat. For histological examination, every second section was stained with cresyl violet. Verification of placements used the atlas of Paxinos and Watson (1997). Only animals with electrodes or guide cannulae placed correctly within the anatomical boundaries of the STN were included in the statistical analysis (Paxinos and Watson, 1997; Fig. 1 C+D).

## Statistical Analysis

Phase I: For comparisons between the performance of the two groups (QNP and control) on the last session (10th – baseline) of phase I, *t*-tests were performed. Phase II: For comparisons between treatment conditions within a group (10th, 12th to 15th test), one way repeated measures analysis of variance (ANOVA) was performed, followed by the Holm Sidak post hoc test for pair wise multiple comparisons, when appropriate. A probability level (*p*) of less than 0.05 was considered statistically significant.

## Results

### Anatomical

Figs. 1A and B present a photomicrograph of a coronal section taken from representative rats implanted with an electrode and with a cannula, respectively. The only visible damage in these rats was the electrode/cannulae tracks toward the STN. Figs. 1C and D present a schematic reconstruction of electrodes and cannulae tips, respectively, in the STN. Four QNP-treated rats from the STN-HFS group and 2 QNP-treated rats from the muscimol group were excluded due to inappropriate localization or dysfunction/occlusion of the electrode/cannula. Thus, the final analysis included 10 rats in the QNP STN-HFS group, 10 rats in the QNP muscimol group, 4 rats in the saline STN-HFS group, and 5 rats in the saline muscimol group.

## Behavioral

### Phase I

#### QNP-induced Compulsive Checking Behavior

QNP treatment over a total of 10 injections induced compulsive checking behavior as demonstrated with the three performance

criteria of compulsive checking introduced by Szechtman et al. (1998). In particular: 1. QNP-treated rats revisited their HB significantly more often than did saline-treated animals (Fig. 2A,  $P < 0.05$ ). This was also true when taking into account the higher total number of visits to locales in QNP-treated rats compared to control rats. Thus, the ratio of observed to expected visits to the HB (Fig. 2B) was higher in QNP compared to control rats ( $P < 0.05$ ). 2. The mean return time to the HB (Fig. 2C) was more than 10-fold shorter in the QNP-treated than in control rats ( $P < 0.05$ ). 3. QNP-

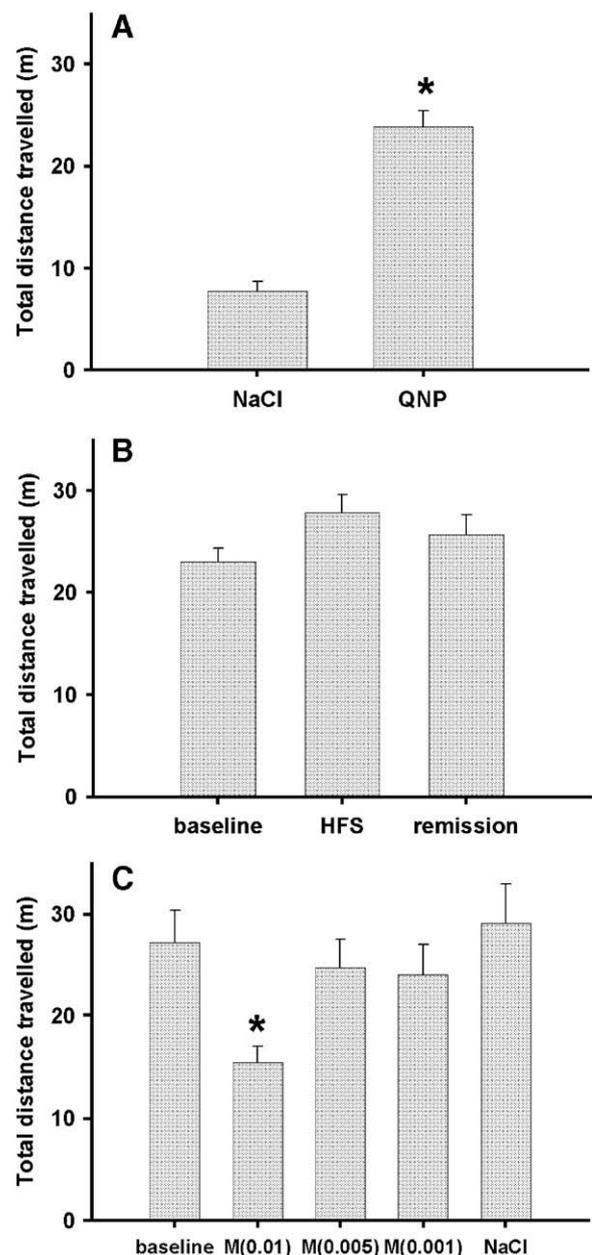


Fig. 3. Locomotion. Effect of chronic intermittent QNP treatment in comparison to saline application (A), of HFS in QNP-treated rats in comparison treatment conditions without HFS (baseline, remission, (B)) and muscimol in QNP treated rats in comparison to baseline and saline application (C) on locomotion as measured in the total distance traveled over the observation period of 30 min. Values are expressed as mean  $\pm$  SEM. \*denotes significant difference from all other groups,  $P < 0.05$  (*t*-test for A, and repeated measures ANOVA, followed by Holm Sidak post hoc test for B and C).

treated rats visited only a few places before returning to their HB, in contrast to control rats, which visited almost 3-times as many locales before returning to the HB (Fig. 2D,  $P < 0.05$ ).

Fig. 3A presents the total distance that control and QNP rats traveled during the 10th session. As can be seen, QNP treatment significantly increased locomotion as demonstrated in the total distance traveled ( $P < 0.05$ ).

## Phase II

### *The effects of HFS on QNP-induced checking behavior*

#### *Control rats*

HFS of the STN had no effect on the behavior of control rats (Table 1). Specifically, HFS did not affect compulsive checking behavior as measured in the frequency of returns and the return time to the HB as well as in the number of locales visited before coming back to the HB. In addition, HFS did not affect the general amount of locomotion exhibited by control rats.

#### **QNP rats**

Fig. 3B presents the total distance traveled by QNP-treated rats on sessions 10, 12 and 13. As can be seen, STN-HFS did not affect locomotion in QNP treated rats ( $F(2,29) = 2.61$ ,  $P = 0.10$ , Fig. 3B).

Fig. 4 presents the different measures of compulsive checking of QNP-treated rats on sessions 10 (no stimulation), 12 (during STN-HFS) and 13 (no stimulation). As can be seen, STN-HFS transiently attenuated QNP-induced compulsive checking in the four measures: 1. QNP-treated rats under HFS (session 12) revisited their HB significantly less often than did the same animals without HFS (sessions 10 and 13,  $F(2,29) = 9.98$ ,  $P < 0.05$ , Fig. 4A). Also, after adjusting for the total number of visits, returns to the HB were significantly reduced in QNP rats

under HFS. Thus, the ratio of observed to expected visits to the HB was significantly lower under HFS (session 12) than without HFS (session 10 and 13,  $F(2,29) = 8.18$ ,  $P < 0.05$ , Fig. 4B). 2. The mean return time to the HB was about 2-fold longer in the QNP-treated rats under HFS than in the same QNP-treated rats without HFS ( $F(2,29) = 9.79$ ,  $P < 0.05$ , Fig. 4C). 3. QNP-treated rats under HFS visited more than two times as many locales before returning to their home base than the same QNP-treated animals without HFS ( $F(2,29) = 15.071$ ,  $P < 0.05$ , Fig. 4D).

### **The effect of muscimol on QNP-induced checking behavior**

#### *Control rats*

Microinjections of muscimol into the STN of control rats resulted in a dose-dependent effect on locomotion (Table 1). Specifically, the lowest dose tested (0.001  $\mu\text{g}$  per side) had no effect, whereas the higher doses tested (0.01 and 0.005  $\mu\text{g}$  per side) differentially decreased the total distance traveled, the number of visits to the HB and the return time to the HB. Notably, muscimol at the three doses tested did not affect behavioral measures that are not dependent on the level of locomotion, namely, the ratio of observed to expected HB visits and the number of locales visited before coming back to the HB.

#### **QNP rats**

Fig. 3C presents the total distance traveled by QNP-treated rats following intra-STN injection of muscimol. As can be seen, the highest dose of muscimol (0.01  $\mu\text{g}$  per side) significantly decreased locomotion whereas the two lowest doses (0.005 and 0.001  $\mu\text{g}$  per side) had no effect on locomotion ( $F(4,49) = 5.64$ ,  $P < 0.05$ ).

Fig. 5 presents the effects of muscimol (0.01, 0.005 and 0.001  $\mu\text{g}$  per side) on compulsive checking in QNP-treated rats.

Table 1

HFS and pharmacological silencing of the STN on locomotion and behavioral parameters specific for compulsive checking in saline treated control rats

	Distance traveled in m	Total number of HB visits	Observed/ expected HB visits	Return time to HB in sec	Number of stops before revisiting HB
<b>HFS</b>					
Session 10	7.0 +/- 0.7	11.7 +/- 4.2	4.3 +/- 0.8	219.2 +/- 66.2	5.1 +/- 0.7
Session 12	8.8 +/- 0.8	13.0 +/- 9.5	5.2 +/- 2.4	244.6 +/- 94.5	5.0 +/- 1.4
Session 13	5.8 +/- 1.1	11.3 +/- 4.5	4.0 +/- 1.3	309.9 +/- 127.9	6.3 +/- 1.5
Repeated-measures ANOVA	$F(2,11) = 0.24$ $P = 0.16$	$F(2,11) = 0.53$ $P = 0.61$	$F(2,11) = 0.43$ $P = 0.67$	$F(2,11) = 2.11$ $P = 0.2$	$F(2,11) = 1.88$ $P = 0.23$
<b>MUSCIMOL</b>					
Session 10	5.1 +/- 1.7	14.0 +/- 2.4	4.8 +/- 1.1	152.4 +/- 38.0	5.2 +/- 1.7
0.01 mg/kg muscimol	3.2 +/- 3.5*§	3.8 +/- 1.4*§	2.2 +/- 0.7	790.0 +/- 276.8*§	6.2 +/- 3.5
0.005 mg/kg muscimol	3.0 +/- 0.8*§	10.2 +/- 2.7§	3.6 +/- 0.7	198.2 +/- 34.3	3.1 +/- 0.8
0.001 mg/kg muscimol	4.9 +/- 0.6	15.8 +/- 0.8	4.3 +/- 1.3	115.1 +/- 5.8	3.6 +/- 0.5
Session 15	4.8 +/- 0.4	16.8 +/- 1.1	5.4 +/- 0.3	108.9 +/- 6.9	4.0 +/- 0.4
Repeated-measures ANOVA	$F(4,24) = 3.61$ $P = 0.03$	$F(4,24) = 10.88$ $P < 0.05$	$F(4,24) = 1.9$ $P = 0.16$	$F(4,24) = 5.11$ $P < 0.05$	$F(4,24) = 0.5$ $P = 0.74$

HFS of the STN had no effect on the behavior of control rats.

Pharmacological silencing of the STN of control rats via muscimol in the following dosages: 0.01  $\mu\text{g}$ , 0.005  $\mu\text{g}$ , 0.001  $\mu\text{g}$  per 0.5  $\mu\text{l}$  per side resulted in a dose-dependent effect on locomotion, as expressed in the total distance traveled, the number of visits and the return time to the home base. Notably, muscimol at all doses tested did not affect behavioral measures that are not dependent on the level of locomotion, namely, the ratio of observed to expected home base visits and the number of locales visited before coming back to the home base. Values are expressed as mean +/- SEM.

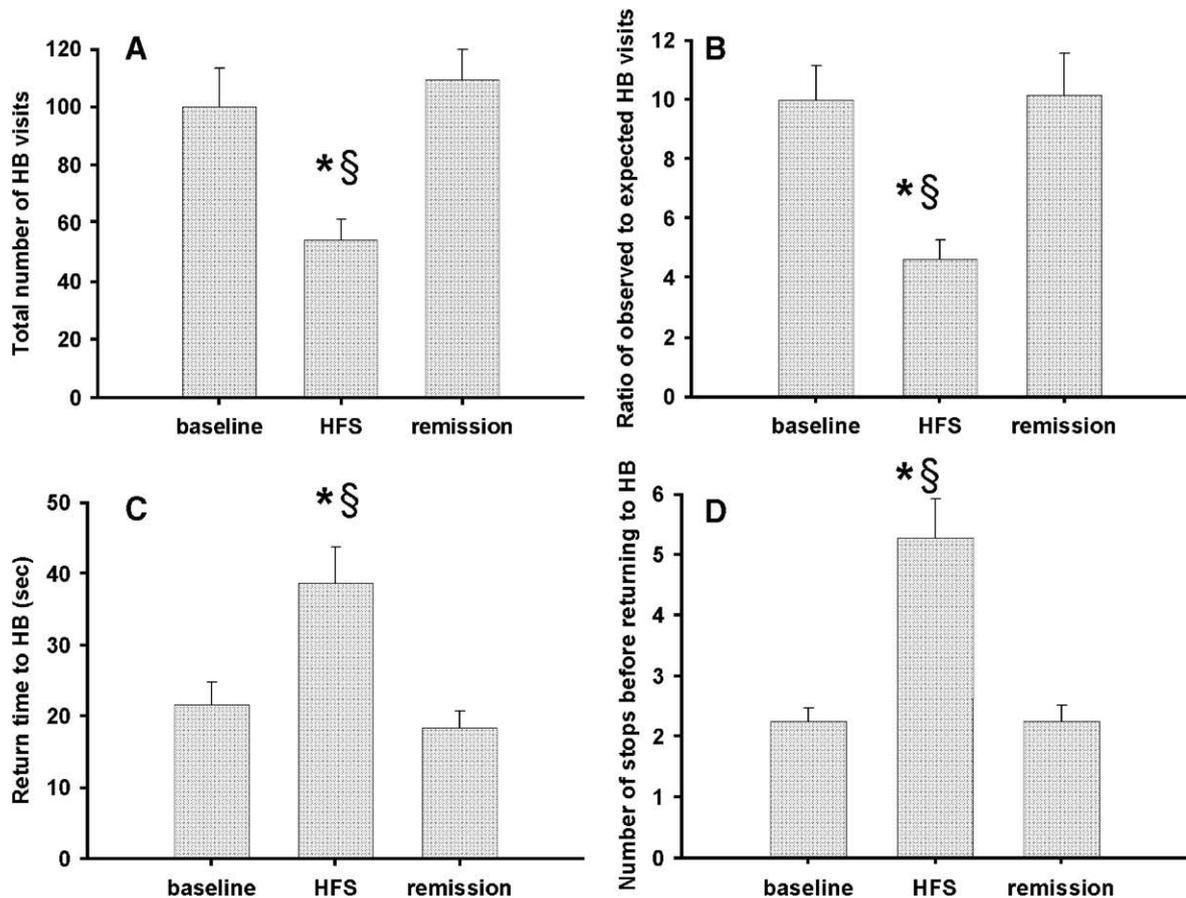


Fig. 4. STN HFS on compulsive checking behavior. STN-HFS (12th test) significantly and transiently reduces QNP-induced compulsive checking behavior when compared to 10th (baseline) and 13th (remission) test in all investigated parameters specific for OCD like behavior: (A) total number of return to the home base (HB), (B) ratio of expected to observed home base visits, (C) return time to home base, and (D) visits to other places before revisiting home base. \*  $P < 0.05$  vs. 10th test (baseline), §  $P < 0.05$  vs. 13th test (remission), repeated measures ANOVA, followed by Holm Sidac post hoc test. Values are expressed as mean  $\pm$  SEM.

In general, the effects of muscimol on compulsive checking were dose-dependent, yet the specific relation between muscimol dose and the behavioral effect was different in the different measures. Specifically, the number of visits to the HB (Fig. 5A) was reduced by the high doses of muscimol (0.01 and 0.005  $\mu\text{g}$  per side) but not by the lowest dose (0.001  $\mu\text{g}$  per side,  $F(4,49) = 14.75$ ,  $P < 0.05$ ). After adjusting for the total number of visits, returns to the HB were significantly reduced by the three doses of muscimol ( $F(4,49) = 15.45$ ,  $P < 0.05$ , Fig. 5B). The mean return time to the HB (Fig. 5C) was significantly increased by the highest dose of muscimol (0.01  $\mu\text{g}$  per side) but not by the lower doses (0.005 and 0.001  $\mu\text{g}$  per side;  $F(4,49) = 3.42$ ,  $P < 0.05$ ), and the number of stops before returning to the HB (Fig. 5D) was increased by the high muscimol doses (0.01 and 0.005  $\mu\text{g}$  per side) but not by the lowest dose (0.001  $\mu\text{g}$  per side;  $F(4,49) = 15.28$ ,  $P < 0.05$ ). It is important to note that whereas the general locomotion-suppressing effects of 0.01  $\mu\text{g}$  muscimol could account for the compulsivity-reducing effects of muscimol at this dose, the attenuation of compulsive checking following administration of muscimol at 0.005  $\mu\text{g}$  per side, cannot be attributed to non-specific effects on locomotion, and may therefore represent a “true” anti-compulsive effect.

## Discussion

The present study assessed the effects of HFS and of pharmacological inactivation of the STN in the QNP rat model of OCD. As has previously been reported (Szechtman et al., 1998, 2001), 10 injections of QNP (given twice a week), led to the emergence of compulsive checking in QNP-treated rats. Specifically, QNP-treated rats revisited their HB excessively often and rapidly compared to other locales and to saline-treated controls, and stopped at only a few other locales before returning to the HB. In addition to compulsive checking, QNP-treated rats also developed locomotor sensitization, as has been reported by others (Culver et al., 2000; Einat et al., 1996; Einat and Szechtman, 1993; Szechtman et al., 1994b; Szechtman et al., 1994a; Szumlinski et al., 1997).

In saline-treated control rats, HFS of the STN had no effect, whereas inactivation of the STN by muscimol resulted in a dose-dependent decrease in locomotion. There are only a few studies which assessed the effects of HFS and of pharmacological inactivation of the STN in otherwise intact rats, and most of these studies have used a choice reaction time task, which does not allow a direct assessment of rats' locomotor activity. Yet, the results obtained in these studies seem to agree with our

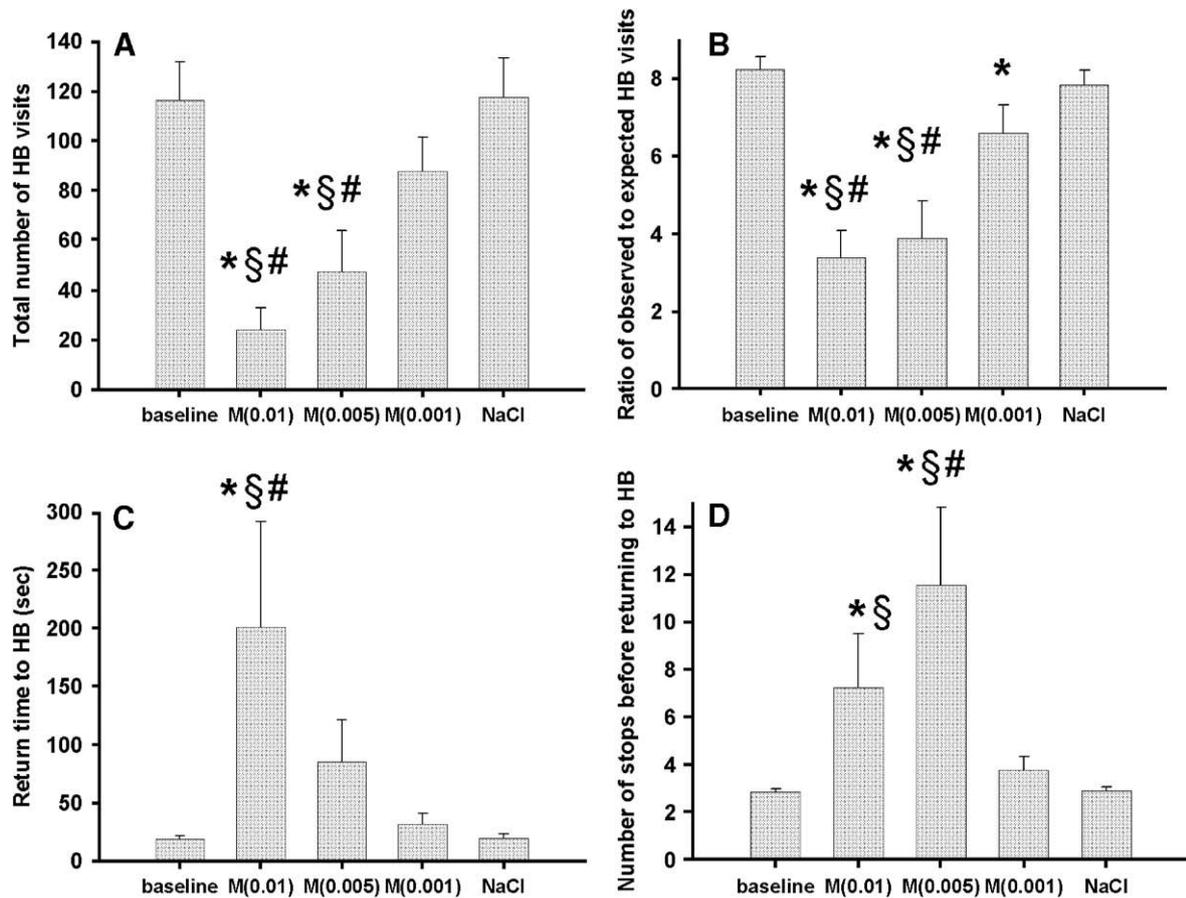


Fig. 5. Pharmacological silencing of the STN on compulsive checking behavior. Pharmacological silencing of the STN via intracerebral microinjection of muscimol in the following dosages: 0.01  $\mu\text{g}$ , 0.005  $\mu\text{g}$ , 0.001  $\mu\text{g}$  per 0.5  $\mu\text{l}$  per side differentially and transiently reduces QNP-induced compulsive checking behavior when compared to 10th (baseline) and intracerebral saline application (15th test) in the investigated parameters specific for OCD like behavior: (A) total number of return to the home base (HB), (B) ratio of expected to observed home base visits, (C) return time to home base, and (D) visits to other places before revisiting home base. \*  $P < 0.05$  vs. 10th test (baseline), §  $P < 0.05$  vs. saline microinjection, #  $P < 0.05$  vs. muscimol microinjection in doses of 0.001  $\mu\text{g}$  per side (M0.001), repeated measures ANOVA, followed by Holm Sidac post hoc test. Values are expressed as mean  $\pm$  SEM.

findings, as HFS of the STN was found to have no effect in these tasks (Darbaky et al., 2003; Desbonnet et al., 2004), and pharmacological inactivation of the STN resulted in slower correct responses, fewer premature responses and more omissions (Baunez and Robbins, 1999), all suggestive of a general decrease in behavioral output. Two earlier studies which have reported increased locomotor activity following pharmacological inactivation of the STN (Scheel-Kruger et al., 1981; Williams and Herberg, 1987) have used much higher doses of muscimol (15 to 250 ng) compared to a previous (1–3 ng, (Baunez and Robbins, 1999) and the present study (1–10 ng). It is therefore possible that in these earlier studies the increase in locomotion was a result of muscimol diffusion beyond the boundaries of the STN into adjacent (motor) areas as a result of the higher dosages used.

The novel finding of the present study is that HFS of the STN attenuated compulsive checking in QNP rats. Importantly, STN-HFS had no effect on locomotion in QNP-treated rats, suggesting that the decrease in compulsive checking following STN-HFS was a result of an anti-compulsive effect of stimulation rather than of a non-selective effect on locomotion. In addition, the anti-compulsive effect of STN-HFS was transient,

as evidenced by the fact that compulsive checking returned to its baseline level in the session (13th) that followed the stimulation session (12th). We would like to note that it is unlikely that the differences in rats' behavior between the stimulation and remission sessions were simply reflecting the differences in the time post-surgery (7 and 10–11 days, respectively) because 1. at this time interval, implantation-induced tissue damage and inflammation processes have largely recovered as evidenced by the fact that one week following electrodes implantation, STN-HFS has very different behavioural (Baunez et al., 2007) and electrophysiological (Bressand et al., 2002) effects compared to STN lesion; 2. there were no differences between rats' compulsive behavior on session 10 (pre-surgery) and session 11 (3–4 days post-surgery; data not shown), suggesting that already at this early stage post-surgery, the effects of surgery were no longer affecting rats' behavior. 3. In the pharmacological inactivation experiment, 3 sessions of inactivation were conducted (Sessions 12–14), yet, there was no interaction between the effects of muscimol dose and order of dose administration, suggesting that the time post-lesion was not interacting with muscimol's effects. This indirectly supports our claim that in the HFS experiment there were no major tissue changes between

session 12 (HFS) and session 13 (remission). It is noteworthy that the effects of HFS (and of pharmacological inactivation, see below) were observed immediately after the onset of stimulation, whereas in OCD patients the anti-compulsive effects of HFS are delayed (Fontaine et al., 2004; Mallet et al., 2002; Sturm et al., 2003). This discrepancy may reflect the specificity of the target of stimulation or pre-existing pathological conditions (PD).

Inactivation of the STN by muscimol exerted a dose-dependent effect on compulsive checking and on locomotion, with the highest dose tested (0.01  $\mu\text{g}$  per side) decreasing both locomotion and compulsive checking, the intermediate dose (0.005  $\mu\text{g}$  per side) decreasing compulsive checking while having no effect on locomotion, and the lowest dose tested (0.001  $\mu\text{g}$  per side) having no effect on locomotion and only a slight effect on compulsive checking. The finding that muscimol at a dose of 0.005  $\mu\text{g}$  per side had an anti-compulsive effect that cannot be attributed to a non-selective effect on locomotion is further supported by the findings that muscimol at this dose significantly decreased the ratio of observed to expected visits to the HB, which is a measure of compulsive checking that is not affected by general changes in locomotion, and increased the number of stops before returning to the HB, which, if anything, should be inversely correlated with the general level of locomotion. It is of interest to note that also the highest muscimol dose decreased the ratio of observed to expected visits to the HB and increased the number of stops before returning to the HB, suggesting that at this dose, muscimol exerted an anti-compulsive effect in addition to its hypo-locomotion effect.

The finding that pharmacological inactivation of the STN decreased locomotion in both saline- and QNP-treated rats, whereas HFS of the STN had no effect on locomotion in either, may simply be a result of the specific current intensity used in the present study, as in a pilot study we found that at higher current intensities (150  $\mu\text{A}$ ) STN-HFS decreases locomotion in rats. However, the difference in the effects on locomotion exerted by HFS and by pharmacological inactivation may also reflect (1) the possibility that inactivation-induced hypo-locomotion was due to diffusion of muscimol into the neighboring zona incerta, because a recent study in rats found that whereas pharmacological activation of the STN did not affect locomotion, pharmacological activation of the zona incerta increased locomotion (Perier et al., 2002); (2) the possibility that HFS of the STN excited subthalamic axons (Desbonnet et al., 2004) that provide input to brainstem locomotor regions (for review see (Hamani et al., 2004)); activation of these axons by HFS may have masked the hypo-locomotion effect exerted by HFS-induced inhibition of STN neurons (Benazzouz et al., 2004; Meissner et al., 2005; Salin et al., 2002; Tai et al., 2003).

The present finding that HFS and pharmacological inactivation of the STN exerted a similar effect on compulsive checking adds to previous reports on the similar behavioral effects of HFS and of lesions or pharmacological inactivation of the STN in PD patients, animal models of parkinsonism and intact animals (Baunez et al., 2007; Darbaky et al., 2003; Levy et al., 2001; Limousin et al., 1995; Wichmann et al., 1994). The similar

behavioral effects of HFS and of pharmacological inactivation of the STN suggest that these two manipulations have a similar effect at the system level, although it is likely that they achieve this effect via different mechanisms (McIntyre et al., 2004a,b). 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).

The mechanism by which reduction in the activity of STN neurons following HFS- or pharmacological inactivation of the STN leads to attenuation of compulsive checking, is not clear. Although the neural substrates of QNP-induced compulsive checking are not known, repeated administration of QNP using similar dose and administration regimen to those used in the present study has been shown to alter the functioning of basal ganglia-thalamocortical circuits involved in motor control and compulsive behavior (Carpenter et al., 2003; Richards et al., 2005, 2007). It has been further speculated that repeated administration of QNP alters the balance between activity in the direct and the indirect pathways of these circuits (Perreault et al., 2006). The present finding that compulsive checking may be counteracted by pharmacological inactivation and by HFS of the STN, a key structure in the indirect pathway (Alexander et al., 1986; Alexander and Crutcher, 1990; Joel and Weiner, 1997) is in line with this speculation.

It should be noted, however that in intact rats STN-HFS has been reported to decrease activity in the output nuclei of the basal ganglia (Benazzouz et al., 1995), an effect which according to current functional-anatomical models of basal ganglia circuitry should result in increased, rather than decreased, behavioral output (Albin et al., 1989; Baxter et al., 1996; Joel and Weiner, 1997; Parent and Hazrati, 1995; Saxena and Rauch, 2000). It thus seems that current models of basal ganglia circuitry cannot accommodate the findings that STN-HFS decreases compulsive behaviors in PD patients and in QNP-treated rats. Although the present behavioral study does not provide the relevant biochemical evidence, the “normalization” of compulsive checking suggests that HFS and pharmacological inactivation of the STN may antagonize some of the neural changes induced by repeated QNP administration. This suggestion is in line with a growing body of evidence suggesting that a general characteristic of the basal ganglia-thalamocortical circuits is that the behavioral and neural effects induced by manipulation to a given station of these circuits can be counteracted by a manipulation to a different station of these circuits. This is best exemplified by the well documented ability of lesion/inactivation/stimulation of the internal globus pallidus and STN to alleviate the behavioral effects of striatal dopamine denervation (Chang et al., 2003; Darbaky et al., 2003; Deuschl et al., 2006; Shi et al., 2006, 2004; Temel and Visser-Vandewalle, 2004), and has recently also been demonstrated in the ability of lesion/inactivation of the external globus pallidus to alleviate some of

the behavioral and neural consequences of striatal lesion (Ayalon et al., 2004; Joel et al., 1998, 2003; Tarrasch et al., 2005).

The finding that HFS of the STN attenuates compulsive behavior in a rat model of OCD is in line with two recent reports that bilateral STN-HFS dramatically alleviated compulsions and improved obsessions in three PD patients with severe co-morbid OCD (Fontaine et al., 2004; Mallet et al., 2002). The fact that the anti-compulsive effect of STN-HFS was obtained in a rat model which is characterized by dopaminergic hyper-activity rather than hypo-activity suggests that the anti-compulsive effect of STN-HFS is not restricted to the parkinsonian brain. This is not trivial because, as detailed above, the effects of STN-HFS may be different in normal vs parkinsonian subjects (Salin et al., 2002; Windels et al., 2000).

## Conclusion

The present study demonstrated that acute HFS of the STN has a specific and selective anti-compulsive effect in a rat model of OCD. Although the extrapolation from an animal model to the clinical condition is problematic, this finding adds to previous reports of alleviation of obsessive-compulsive symptoms in PD patients, and supports the possibility that STN-HFS may be effective in alleviating symptoms in OCD patients. To assess the full implication of these data, further studies will be needed to assess these effects of STN-HFS in comparison to the effects of HFS of further brain areas pathophysiologically relevant in OCD.

## Disclosure/Conflict of interest

There is no conflict of interest, financial or otherwise, related directly or indirectly to the submitted work for all authors.

## Acknowledgment

We wish to thank C. Koelske and R. Winter for their excellent technical assistance. This study was supported by GIF grant (851/2004). C.W. is a Rahel-Hirsch Fellow of the Humboldt University, Berlin, Germany.

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