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High-frequency stimulation of the nucleus accumbens core and shell reduces quinpirole-induced compulsive checking in rats

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Abstract

Electrical deep brain stimulation (DBS) is currently studied in the treatment of therapy-refractory obsessive compulsive disorders (OCDs). The variety of targeted brain areas and the inconsistency in demonstrating anti-compulsive effects, however, highlight the need for better mapping of brain regions in which stimulation may produce beneficial effects in OCD. Such a goal may be advanced by the assessment of DBS in appropriate animal models of OCD. Currently available data on DBS of the nucleus accumbens (NAc) on OCD-like behavior in rat models of OCD are contradictory and partly in contrast to clinical data and theoretical hypotheses about how the NAc might be pathophysiologically involved in the manifestation of OCD. Consequently, the present study investigates the effects of DBS of the NAc core and shell in a quinpirole rat model of OCD. The study demonstrates that electrical modulation of NAc core and shell activity via DBS reduces quinpirole-induced compulsive checking behavior in rats. We therefore conclude that both, the NAc core and shell constitute potential target structures in the treatment of OCD.

Introduction

Obsessive compulsive disorder (OCD) represents a highly impairing psychiatric disorder with a lifetime prevalence of 1–3% (Rasmussen & Eisen, 1992; Sasson *et al.*, 1997). Although the etiology of OCD is largely unknown, several brain regions have been implicated in its pathophysiology, including the dopaminergic and serotonergic systems and the basal ganglia-thalamo-cortical circuits (Saxena *et al.*, 1998). In patients refractory to pharmacotherapy and behavioral therapy, ablative lesions of pathways within these circuitries, i.e. cingulotomy, limbic leucotomy, subcaudate tractotomy and anterior capsulotomy, have been shown to reverse clinical symptoms (Jenike, 1998; Lippitz *et al.*, 1999; Rauch *et al.*, 2001; Lopes *et al.*, 2004). In recent years, ablative lesions have been widely replaced by electrical deep brain stimulation at high frequencies [high-frequency stimulation (HFS)] in the treatment of several neurologic and psychiatric disorders (Krack *et al.*, 2003; Breit *et al.*, 2004; Temel & Visser-Vandewalle, 2004; Flaherty *et al.*, 2005; Deuschl *et al.*, 2006; Kupsch *et al.*, 2006; Blomstedt *et al.*, 2007). Meanwhile, there has also been an attempt to establish HFS of structures within or associated with the basal ganglia-thalamo-cortical circuits for the treatment of OCD. There are reports of anti-compulsive effects of HFS of the anterior limb of the internal capsule (Gabriels *et al.*, 2003; Abelson *et al.*, 2005), the ventral caudate nucleus (Aouizerate *et al.*, 2004, 2005), and the nucleus accumbens (NAc) and ventral capsule/ventral striatum (Sturm *et al.*, 2003; Greenberg *et al.*, 2006; Rauch *et al.*, 2006) in individual patients with OCD. There are also reports on anti-compulsive effects of HFS of the subthalamic nucleus in patients with co-morbid Parkinson's disease and OCD (Mallet *et al.*, 2002; Fontaine *et al.*, 2004). However, the variety of targeted brain areas highlights the need for better mapping of brain regions in which stimulation produces the most beneficial effects in the treatment of OCD. This goal may be advanced by the assessment of the effects of HFS in appropriate animal models of OCD (Klavir *et al.*, 2008; Kuyck *et al.*, 2008; Winter *et al.*, 2008b).

The aim of the present study was to test whether HFS of the NAc would induce an anti-compulsive effect in the quinpirole (QNP) rat model of OCD (Szechtman *et al.*, 1998; Man *et al.*, 2004; Eilam & Szechtman, 2005; Joel, 2006). Because the NAc is anatomically and

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functionally subdivided into a shell and a core subregion, and small changes in electrode placement have been shown to have a substantial effect on behavior (Okun *et al.*, 2003), the present project assessed the effects of HFS of the NAC shell and core separately. Recently, we showed that HFS and pharmacological inactivation (via intracerebral injection of the GABA agonist muscimol) of the subthalamic nucleus reversibly reduced compulsive checking in the QNP rat model of OCD (Winter *et al.*, 2008b). We found these data to be supported in the signal attenuation model of OCD (Klavir *et al.*, 2008). Together, our previous results and the present experiment may promote the establishment of a model serving as a screening tool for the detection of targets for HFS in OCD.

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 the care of laboratory animals and after approval of the local ethics committee (senate of Berlin). All efforts were made to reduce the number of animals used. Fifty-six naive male Wistar rats (Harlan-Winkelmann, Borchen, Germany, 220–450 g during the experiment) were housed in a temperature- and humidity-controlled vivarium with a 12 h light/dark cycle (lights on from 06:00 to 18:00 h). All experiments were performed during the day time. Food and water were available *ad libitum*.

Apparatus and behavioral procedure

Prior to the beginning of the experimental procedure, rats were handled for about 2 min daily for 5 days. At the start of the experiment, rats were injected subcutaneously twice weekly for a total of 15 injections with either saline (control group) or QNP (QNP group). At 15 min 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 cm and 20 cm high) with four plexiglas boxes varying in shape and size at fixed locations. The platform was subdivided into 25 rectangles (locales). A computer, interfaced with the video recorder, was used to score locomotor behavior during playback of video records (TSE VideoMot 2 system; Technical & Scientific Equipment, Bad Homburg, Germany).

The following measures were assessed for each session and rat: (i) total distance traveled; (ii) frequency of stops at each open field locale; (iii) mean duration of return time to a given locale, i.e. the interval from departure from a given locale to the next arrival at the same locale; (iv) mean stop duration at a given locale; and (v) total duration of stops at a given locale, where stops/visits refer to periods of no locomotion (Szechtman *et al.*, 1998). For each rat the locale with the highest total duration of stops was defined as the home base (Eilam & Golani, 1989) and compulsive checking behavior was analysed with reference to the home base. According to Szechtman *et al.* (1998) compulsive checking is present if a rat meets the following three performance criteria: the rat returns to the home base excessively often, excessively rapidly and visits less places before returning to the home base compared with control rats. The following measures were therefore analysed: the total number of visits to the home base, the mean time to return to the home base and the mean number of stops/visits before returning to the home base. In addition, because repeated administration of QNP increases locomotion (Szechtman *et al.*, 1994a; Szumlinski *et al.*, 1997) and because checking behavior requires locomotion, a calculation was applied allowing the assessment of changes in checking behavior independent from changes in locomotion. Specifically, for each rat the expected rate of return to a locale was calculated by dividing the total number of visits made at a given session to the number of locales visited by the rat in this session. Next, the ratio of observed to expected home base visits was calculated by dividing the number of visits to the home base with the expected rate of return to a locale (Szechtman *et al.*, 1998; Winter *et al.*, 2008b). QNP-treated rats meet additional criteria for compulsive checking, i.e. ritual-like behavior and context dependency (Szechtman *et al.*, 1998), which have repeatedly been demonstrated to behave in a similar way to the parameters mentioned above (Szechtman *et al.*, 1998, 2001). Therefore, they were not evaluated in this study.

Design

The experiment consisted of two phases. In phase I, rats received 10 injections (two injections per week with a 3–4 day test-free period) of either 0.5 mg/kg QNP (QNP group, $n = 30$) or saline (control group, $n = 26$), followed by behavioral testing in the open field. We and others have shown that the behavioral effects of chronic treatment with QNP reach a plateau after 8–10 drug injections (Einat & Szechtman, 1993a; Szechtman *et al.*, 1994a, b; Szumlinski *et al.*, 1997; Winter *et al.*, 2008b). After the 10th behavioral testing, the QNP-treated rats were randomly assigned to four groups, i.e. stimulated core ($n = 10$), stimulated shell ($n = 10$), sham-stimulated core ($n = 5$) and sham-stimulated shell ($n = 5$). Equally, the NaCl-treated control rats were randomly assigned to four groups, i.e. stimulated core ($n = 8$), stimulated shell ($n = 8$), sham-stimulated core ($n = 5$) and sham-stimulated shell ($n = 5$). Directly after the 10th testing, QNP and control rats of all groups underwent bilateral implantation of electrodes into either the NAc core or shell. In phase II, control and QNP-treated rats underwent five additional injections (two injections per week) of saline or QNP, respectively, followed by behavioral testing (sessions 11–15), starting with the 11th test at 2–3 days post-operatively. HFS/sham HFS was applied during the 12–14th sessions. Stimulation started at the beginning of the behavioral session (15 min after QNP/NaCl injection) and continued for the 30 min of the behavioral session. Stimulation was applied in current intensities of 75, 100 and 150 μA in a random order on the 12–14th sessions. No stimulation was applied on the last (15th) test session, which served to assess the reversibility of the treatment manipulation. Sham-stimulated rats did not receive stimulation but were connected to the wires on sessions 12–14.

Surgery

Stereotaxic operations were performed after the 10th session and were carried out under sodium pentobarbital anesthesia (60 mg/kg i.p.). 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 either the NAc shell (1.2 mm anterior to bregma, 1.5 mm lateral to the midline and 8.2 mm ventral to dura) or the NAc core (1.6 mm anterior to bregma, 1.5 mm lateral to the midline and 7.0 mm ventral to dura) (Paxinos & Watson, 1997). Electrodes were fixed to the skull surface with stainless steel screws and dental acrylic cement (Technovit®, Heraeus-Kulzer, Hanau, Germany).

Systemic drug administration

Quinpirole hydrochloride 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.

Stimulation

The 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. The following parameters were used for stimulation: constant current mode, frequency 130 Hz, pulse width 60 μs, current intensity 75, 100 or 150 μA. A frequency of 130 Hz and a narrow pulse duration of 60 μs were chosen according to the parameters generally applied in rats for assessing the effects of HFS in other brain areas (Benazzouz *et al.*, 1995; Windels *et al.*, 2000; Salin *et al.*, 2002; Meissner *et al.*, 2003; Desbonnet *et al.*, 2004; Shi *et al.*, 2006; Baunez *et al.*, 2007; Winter *et al.*, 2008a, b) and are in close proximity to the clinical situation (Moro *et al.*, 2002; Sturm *et al.*, 2003; Okun *et al.*, 2007).

Histology

After the 15th session, rats were anesthetized 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 from the skulls and post-fixed overnight in the same fixative and then stored at 4 °C in 30% sucrose. Frozen coronal sections (40 μm) were cut using a cryostat. For histological examination, every second section was stained with cresyl violet. Verification of placements used the atlas of Paxinos & Watson (1997). Only animals with the electrodes placed correctly in the target areas were included in the statistical analysis of the results.

Statistical analysis

Statistical analysis was performed as described previously (Winter *et al.*, 2008b).

Phase I

t-tests were performed for comparisons between the performance of the two groups (QNP and control) on the last session (10th) of phase I.

Phase II

For comparisons between treatment conditions within a group, repeated-measures ANOVA was performed, followed by the Holm Sidak *post-hoc* tests comparing the stimulation and remission sessions with the baseline session, when appropriate (Winter *et al.*, 2008b). In order to study the effect of several factors on one of the outcome parameters simultaneously (QNP vs. NaCl treatment, electrode implantation/placement, HFS vs. sham HFS, measurement repetitions/current intensities), generalized estimating equations (GEEs) were performed using the GENMOD procedure (SAS 9.1.3) to analyse main effects (factors) and interaction terms (product of factors) (for detailed description of the GEEs please see Supporting information, Appendix S1). In order to study whether the therapeutic effects of HFS on measures of compulsive checking depended on locomotion, GEEs were performed using the GENMOD procedure (SAS 9.1.3) with locomotion as a covariate. The cut-off level for statistical significance was taken at $P = 0.05$.

Results

Electrode placement

Figure 1A and B presents photomicrographs (at a magnification of 25×) of a coronal section taken from representative rats implanted with an electrode in either the NAc shell or core, respectively. The electrode tracks toward the targeted region are visible on the photomicrographs. Figure 1C and D presents a schematic reconstruction of electrode tips in the NAc shell and core, respectively, of all QNP-treated rats that underwent deep brain stimulation and were integrated into the study. Equivalent distribution patterns of electrode tip placements were found in NaCl-treated stimulated as well as QNP- or NaCl-treated sham-stimulated rats (data not shown). Due to dysfunction of the electrode (detectable during on-site oscilloscope recording) or inappropriate localization of the electrode (detectable via histological processing), four rats were excluded from the QNP-treated group (stimulated core, 2; stimulated shell, 1; sham-stimulated core, 1) and two rats were excluded from the NaCl-treated control group (stimulated shell, 1; sham-stimulated core, 1). Thus, the final analysis included the following number of animals: (i) in the QNP-treated group: stimulated core, 8; stimulated shell HFS, 9; sham-stimulated core, 4; sham-stimulated shell, 5 and (ii) in the NaCl-treated control group: stimulated core, 8; stimulated shell HFS, 7; sham-stimulated core, 5; sham-stimulated shell, 5.

Behavioral measures

Phase I

Quinpirole-induced compulsive checking behavior. Quinpirole treatment over a total of 10 injections induced compulsive checking behavior as demonstrated by three performance measures of compulsive checking previously introduced by Szechtman *et al.* (1998). (i) QNP-treated rats visited their home base significantly more often than did saline-treated animals (Fig. 2A, $P < 0.001$). This was also true when taking into account the higher total number of visits to all locales in QNP-treated rats compared with control rats. Thus, the ratio of observed to expected visits to the home base (Fig. 2B) was significantly higher in QNP-treated compared with control rats ($P < 0.001$). (ii) The mean return time to the home base (Fig. 2C) was about 10-fold shorter in QNP-treated than in control rats ($P < 0.001$). (iii) QNP-treated rats visited fewer places than control rats before returning to their home base (Fig. 2D, $P < 0.001$). In addition, chronic intermittent application of QNP led to locomotor sensitization, evident in the significantly longer total distance traveled by QNP-treated compared with control rats during the 10th session (Fig. 2E, $P < 0.001$).

Phase II

The effects of electrode implantation on locomotion and quinpirole-induced checking behavior. Electrode implantation into either the NAc shell or NAc core and sham HFS of both regions did not affect locomotion and parameters used for the quantification of compulsive checking behavior in QNP- and saline-treated control rats (data not shown).

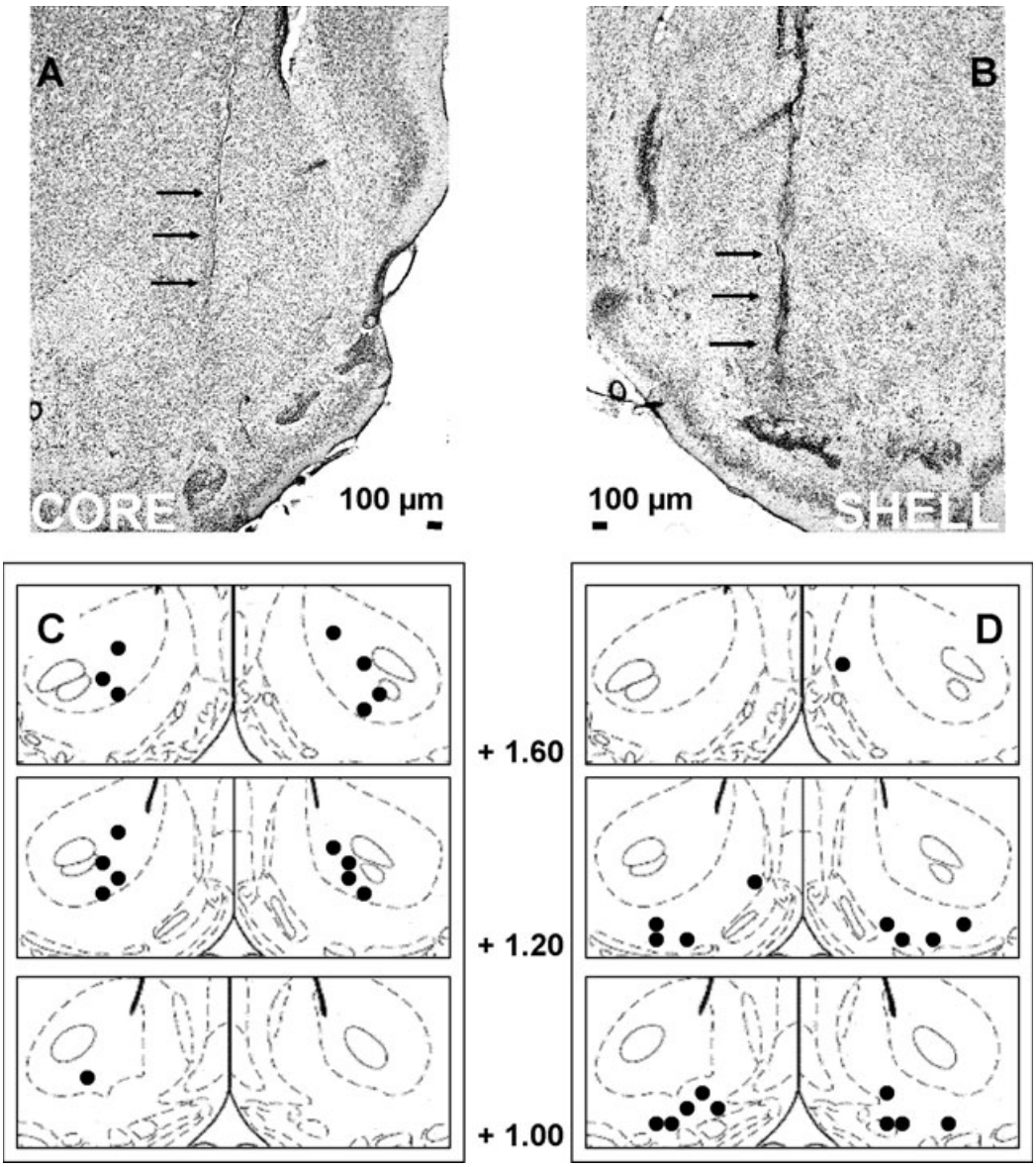

FIG. 1. Post-mortem histology. Photomicrographs of a coronal section stained with cresyl violet and taken from representative rats showing the tip of the electrode in the NAc core (A) or shell (B). Schematic reconstructions of electrode tip placement in the NAc core (C) or shell (D) of QNP-treated stimulated rats. Equivalent distribution patterns of electrode tip placements were found in NaCl-treated stimulated as well as QNP- or NaCl-treated sham-stimulated rats. Schematic reconstruction of these findings was left out in order to avoid confusion of the relevant data.

Effects of high-frequency stimulation on locomotion and measures of compulsive checking behavior in control rats

High-frequency stimulation of the nucleus accumbens shell: HFS of the NAc shell significantly increased locomotion measured as the total distance traveled specifically at 100 μA ($F_{4,34} = 4.69$, $P = 0.008$, Table 1A). However, HFS of the NAc shell did not affect measures of compulsive checking behavior in control rats (Table 1A), as measured in the total number of returns to the home base ($F_{4,34} = 1.02$, $P = 0.422$), the ratio of expected to observed home base visits ($F_{4,34} = 0.3$, $P = 0.876$), the return time to the home base ($F_{4,34} = 1.11$, $P = 0.384$) and visits to other places before revisiting the home base ($F_{4,34} = 1.25$, $P = 0.32$).

High-frequency stimulation of the nucleus accumbens core: HFS of the NAc core significantly increased locomotion measured as the total distance traveled at 100 and 150 μA ($F_{4,39} = 3.98$, $P = 0.012$, Table 1B). However, HFS of the NAc core did not affect measures of compulsive checking behavior in control rats (Table 1B), as measured in the total number of returns to the home base ($F_{4,39} = 1.02$, $P = 0.422$), the ratio of expected to observed home base visits ($F_{4,39} = 0.22$, $P = 0.922$), the return time to the home base ($F_{4,39} = 0.43$, $P = 0.789$) and visits to other places before revisiting the home base ($F_{4,39} = 0.21$, $P = 0.93$).

Effects of high-frequency stimulation of the nucleus accumbens shell on locomotion and quinpirole-induced checking behavior. Figure 3A–E presents the total distance traveled by QNP-treated rats and the different measures of compulsive checking on the baseline session (session 10), under HFS with different current intensities (sessions 12–14) and without stimulation (session 15). As can be seen, HFS of the NAc shell did not affect locomotion in QNP-treated rats ($F_{4,44} = 1.84$, $P = 0.146$, Fig. 3A). However, on the four measures of compulsive checking, HFS of the NAc shell attenuated QNP-induced compulsive checking at a current intensity of 100 μA,

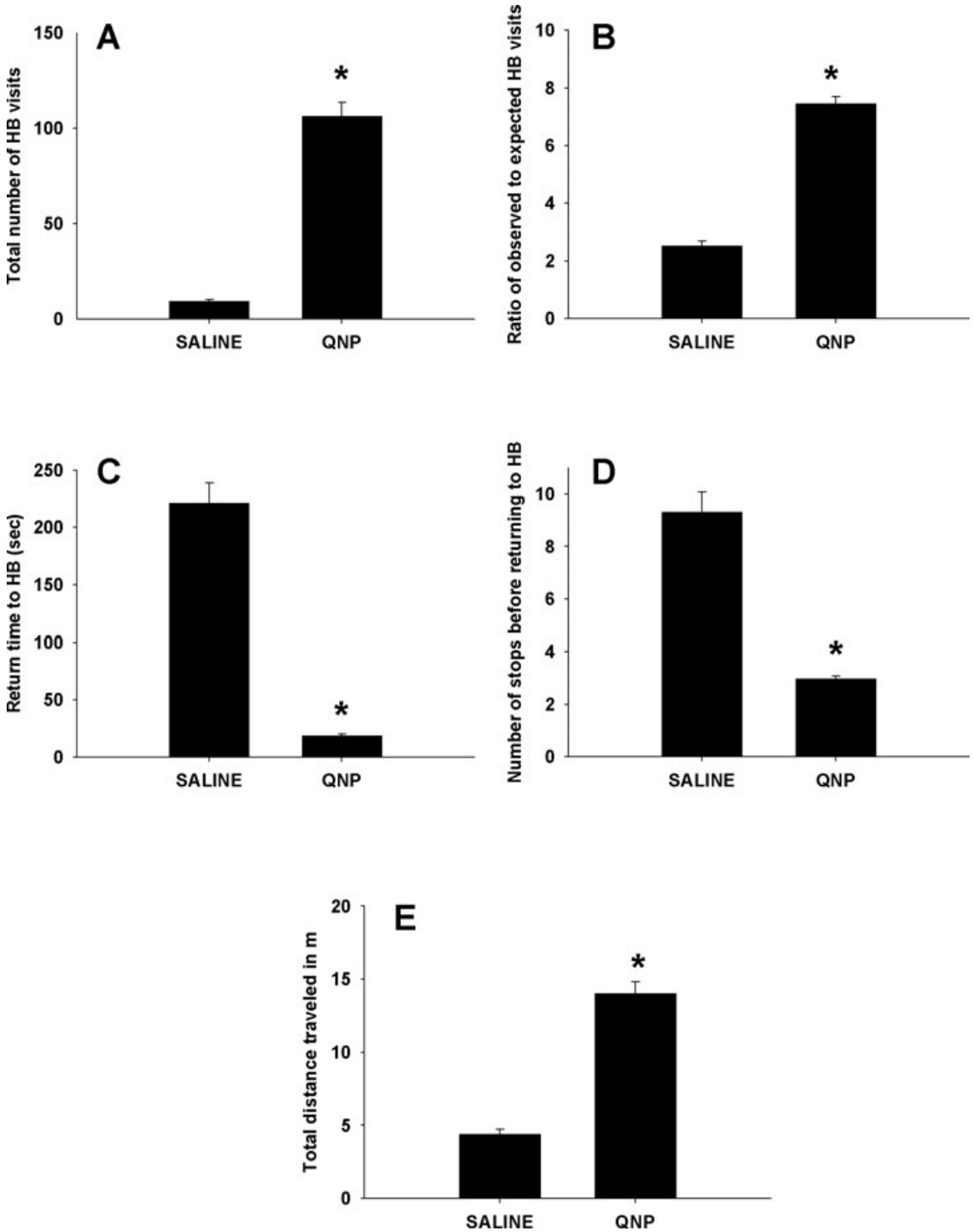

FIG. 2. Induction of compulsive checking behavior. Compulsive checking behavior is analysed with reference to the home base established by each rat during the 10th session and recognized as the locale with the longest total duration of stops. QNP-treated animals met compulsive checking criteria: (A) more frequent returns to the home base, (B) a higher than 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 compared with saline-treated controls. Additionally, QNP-treated rats displayed an increased locomotion as measured in the mean and SE of the mean total distance traveled over the 30 min observation period (E). *$P < 0.05$, *t*-test. Values are expressed as mean ± SEM.

whereas at current intensities of 75 and 150 μA it had no effect on compulsive checking measures. Specifically, QNP-treated rats under HFS with 100 μA visited their home base significantly less often than they did without HFS (sessions 10 and 15) or under HFS with current intensities of 75 and 150 μA ($F_{4,44} = 3.357$, $P = 0.022$, Fig. 3B). Also, after adjusting for the total number of visits, returns to the home base were significantly reduced in QNP-treated rats under HFS with 100 μA. Thus, the ratio of observed to expected visits to the home

TABLE 1. Performance of NaCl-treated control rats stimulated in the NAc shell or core

	Distance traveled (m)	Total number of HB visits	Observed/expected HB visits	Return time to HB (s)	Number of stops before revisiting HB
(A) NAc shell					
Baseline	3.1 ± 0.3	7.6 ± 1.2	3.1 ± 0.2	208.2 ± 18.3	6.2 ± 0.8
75 μA	5.8 ± 0.8	12.9 ± 2.1	3.3 ± 0.4	171.0 ± 34.1	7.4 ± 1.7
100 μA	9.1 ± 0.2*	12.3 ± 4.4	2.9 ± 0.4	162.5 ± 41.2	8.8 ± 1.0
150 μA	5.3 ± 0.5	12.5 ± 1.5	3.0 ± 0.6	150.9 ± 19.3	9.0 ± 2.8
0 μA	5.5 ± 0.3	11.9 ± 1.8	3.3 ± 0.5	174.1 ± 26.4	7.4 ± 1.3
Repeated-measures ANOVA					
$F_{4,34}$-value	4.69	1.02	0.3	1.11	1.25
P-value	0.008	0.422	0.876	0.384	0.32
(B) NAc core					
Baseline	5.1 ± 0.7	13.1 ± 2.0	2.6 ± 0.3	172.2 ± 35.8	8.9 ± 0.8
75 μA	4.7 ± 0.9	11.5 ± 2.1	2.7 ± 0.3	211.2 ± 46.7	8.5 ± 1.3
100 μA	8.1 ± 1.6*	14.8 ± 1.9	2.7 ± 0.2	171.7 ± 31.6	9.4 ± 1.2
150 μA	8.8 ± 1.6*,†	14.8 ± 1.4	2.8 ± 0.4	158.6 ± 27.0	9.3 ± 1.7
0 μA	6.0 ± 0.8	13.2 ± 3.6	2.5 ± 0.4	182.7 ± 36.7	9.9 ± 1.9
Repeated-measures ANOVA					
$F_{4,39}$-value	3.98	0.48	0.22	0.43	0.21
P-value	0.012	0.75	0.922	0.789	0.93

Values are expressed as mean ± SEM. High-frequency stimulation (HFS) of the NAc core and shell significantly increased locomotion as expressed in the total distance traveled at current intensities of 100 μA (NAc shell) or 100 and 150 μA (NAc core). HFS of the NAc core and shell had no effect on the behavioral parameters specific for compulsive checking in saline-treated control rats. *$P < 0.05$ vs. 10th session and $^{\dagger}P < 0.05$, vs. 15th session (remission), repeated-measures ANOVA, followed by Holm Sidak *post-hoc* test for B and C. HB, home base.

base was significantly lower under HFS with 100 μA than without HFS (sessions 10 and 15) or under HFS with current intensities of 75 and 150 μA ($F_{4,44} = 3.822$, $P = 0.013$, Fig. 3C). The mean return time to the home base was almost twofold longer in the QNP-treated rats under HFS with 100 μA than in the same QNP-treated rats without HFS (sessions 10 and 15) or under HFS with current intensities of 75 and 150 μA ($F_{4,44} = 5.22$, $P = 0.003$, Fig. 3D). QNP-treated rats under HFS visited significantly more locales before returning to their home base than they did under all other conditions ($F_{4,44} = 6.871$, $P < 0.001$, Fig. 3E).

Effects of high-frequency stimulation of the nucleus accumbens core on locomotion and quinpirole-induced checking behavior. Figure 4A–E presents the total distance traveled by QNP-treated rats and the different measures of compulsive checking on the baseline session (session 10), under HFS with different current intensities (sessions 12–14) and without stimulation (session 15). As can be seen, HFS of the NAc core significantly reduced locomotion in QNP-treated rats at 150 μA but had no effect on locomotion at 100 and 75 μA ($F_{4,39} = 3.972$, $P = 0.014$, Fig. 4A). Furthermore, on the four measures of compulsive checking, HFS of the NAc core attenuated QNP-induced compulsive checking at current intensities of 100 and 150 μA, whereas it had no effect at 75 μA. Specifically, the high current intensity (150 μA) significantly decreased the number of visits to the home base compared with the no-stimulation sessions (sessions 10 and 15), the intermediate current intensity (100 μA) decreased this measure only in comparison to the 10th but not the 15th session, and the lowest intensity (75 μA) had no effect ($F_{4,39} = 3.32$, $P = 0.025$, Fig. 4B). After adjusting for the total number of visits, returns to the home base were significantly reduced by the two higher current intensities (100 and 150 μA) but not by the lowest current intensity (75 μA, $F_{4,39} = 9.55$, $P < 0.001$, Fig. 4C). Similarly, the mean return time to the home base was significantly increased by the higher current intensities (100 and 150 μA) but not by the lowest current intensity (75 μA) when compared with the 10th session (but not when compared with the 15th session) ($F_{4,39} = 3.46$, $P = 0.023$, Fig. 4D). The number of stops before returning to the home base was significantly increased by the higher current intensities (100 and 150 μA) but not by the lowest current intensity (75 μA) when compared with both sessions without stimulation (sessions 10 and 15) ($F_{4,39} = 6.54$, $P < 0.001$, Fig. 4E).

The GEE analysis basically corroborated the results detailed above (please see supporting Appendix S1). GEE analysis with locomotion as a covariate revealed that, in QNP-treated rats stimulated in the NAc shell, HFS significantly affected the total number of home base visits (depending on the current intensity, $P = 0.001$), the return time to the home base ($P = 0.029$) and the number of stops before coming back to the home base ($P = 0.008$). These parameters were not affected by locomotion (each $P > 0.05$). Notably, the behavioral parameter 'ratio of observed to expected home base visits' was significantly affected by both HFS (depending on current intensity, $P < 0.0001$) and locomotion ($P < 0.0001$). GEE analysis with locomotion as a covariate further revealed that, in QNP-treated rats stimulated in the NAc core, HFS but not locomotion significantly affected the ratio of observed to expected home base visits (depending on the current intensity, $P < 0.0001$) and the number of stops before coming back to the home base ($P = 0.024$; depending on current intensity, $P = 0.010$). Notably, the behavioral parameters 'total number of home base visits' and 'return time to the home base' were significantly affected by both HFS (total number of home base visits: depending on current intensity, $P < 0.0001$; return time to the home base: depending on current intensity, $P = 0.002$) and locomotion (total number of home base visits: $P = 0.002$; return time to the home base: $P = 0.003$). The effects of HFS and locomotion on behavioral measures of compulsive checking are independent in the sense of a subtle unstated assumption of multivariate models of regression: 'the effects of each variable are independent, so that the effect of

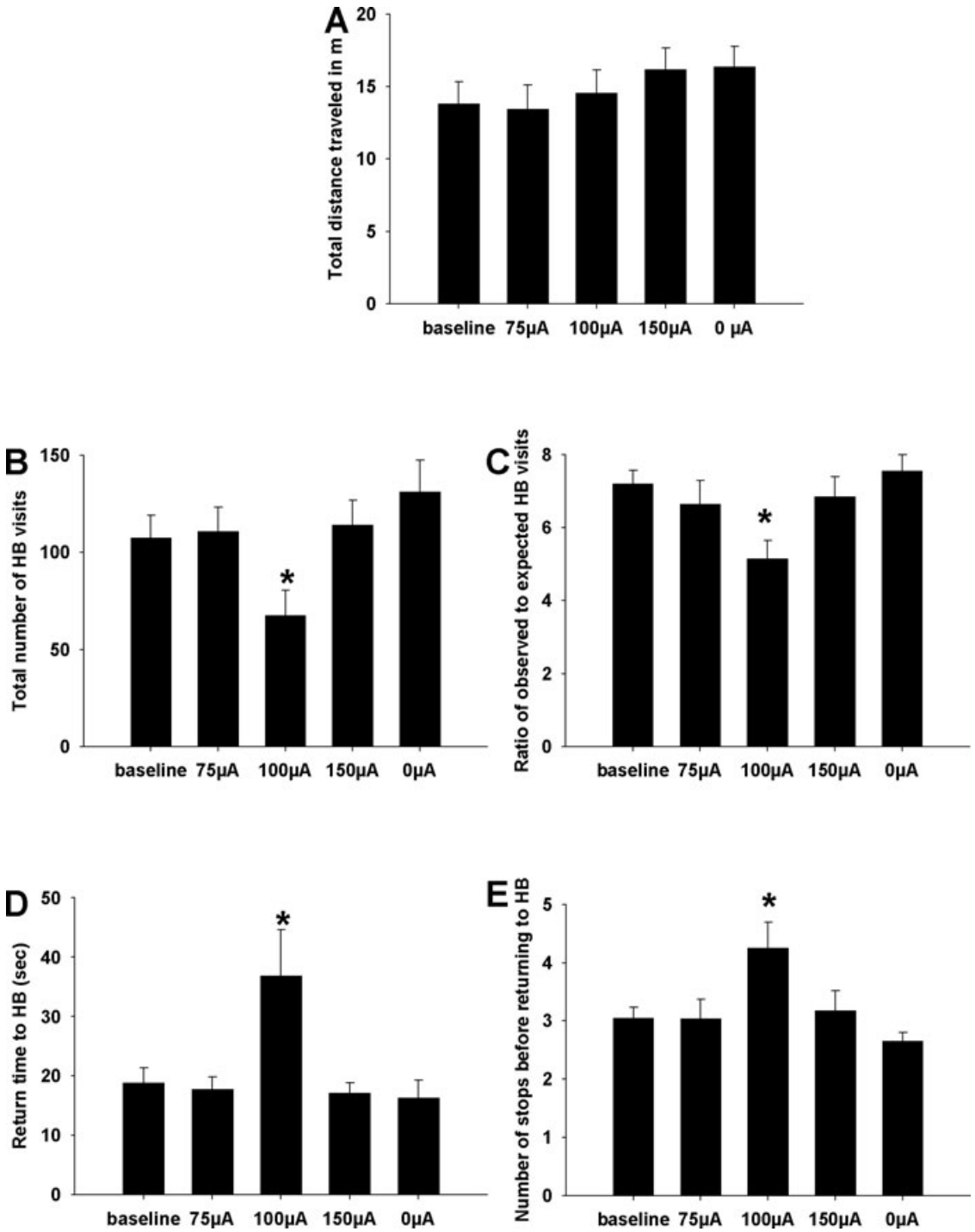

FIG. 3. The effects of HFS of the NAc shell on locomotion and compulsive checking behavior. HFS of the NAc shell did not affect locomotion as measured in the mean and SEM total distance traveled over the 30 min observation period (A). HFS of the NAc shell (current intensities 75, 100 and 150 μA) differentially and transiently reduced QNP-induced compulsive checking behavior when compared with the 10th (baseline) and 15th (remission, 0 μA) sessions as measured in the mean and SEM of (A) the mean total distance traveled over the 30 min observation period, (B) number of returns to the home base (HB), (C) ratio of expected to observed HB visits, (D) return time to the HB and (E) visits to other places before revisiting the HB. *Significant difference from the baseline session, §significant difference from the 15th session (remission), $P < 0.05$; repeated-measures ANOVA, followed by Holm Sidak *post-hoc* test.

one variable is the same regardless of the values of the other variables in the model' (Altman, 1991, p. 350). For more explicit description of the analysis and for further information on the effects of HFS and locomotion on the different measures of compulsive checking in NaCl-treated control rats, please see supporting Appendix S1.

Discussion

The present study assessed the effects of HFS of the NAc shell and core in the QNP rat model of OCD. As has previously been reported (Szechtman *et al.*, 1998, 2001; Winter *et al.*, 2008b), 10 injections of QNP (given twice a week) led to the emergence of compulsive

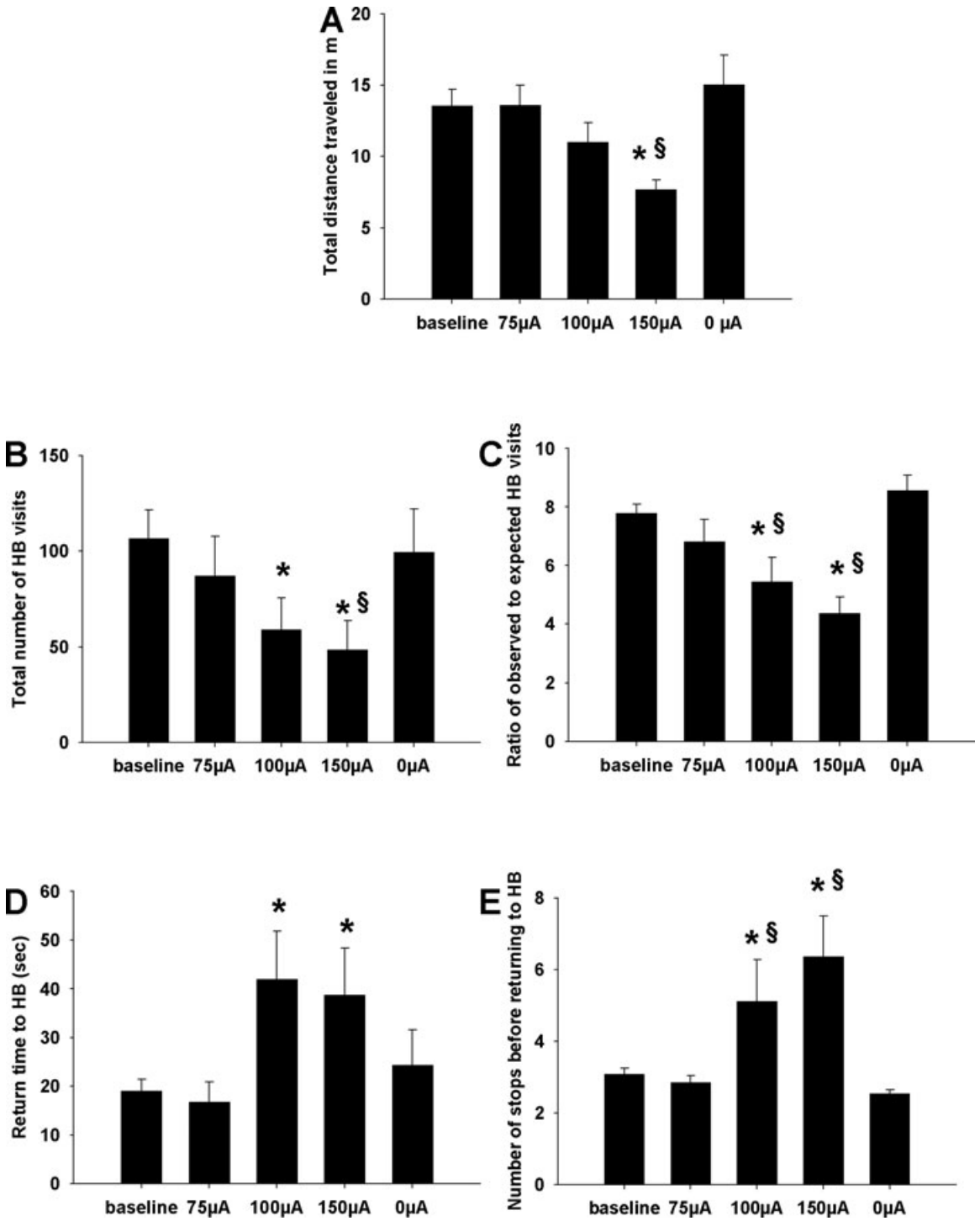

FIG. 4. The effects of HFS of the NAc core on locomotion and compulsive checking behavior. HFS of the NAc shell did not affect locomotion as measured in the mean and SEM total distance traveled over the 30 min observation period (A). HFS of the NAc core (current intensities 75, 100 and 150 μA) differentially and transiently decreased locomotion when compared with the 10th (baseline) and 15th (remission, 0 μA) sessions as measured in the mean and SEM total distance traveled over the 30 min observation period (A). Furthermore, HFS of the NAc core (current intensities 75, 100 and 150 μA) differentially and transiently reduced QNP-induced compulsive checking behavior when compared with the 10th (baseline) and 15th (remission, 0 μA) sessions as measured in the (B) number of returns to the home base (HB), (C) ratio of expected to observed HB visits, (D) return time to the HB and (E) visits to other places before revisiting the HB. *Significant difference from the baseline session, §significant difference from the 15th session (remission), $P < 0.05$; repeated-measures ANOVA, followed by Holm Sidak *post-hoc* test.

checking in QNP-treated rats. Specifically, QNP-treated rats revisited their home base excessively often and rapidly compared with other locales and with saline-treated controls, and stopped at only a few other locales before returning to the home base. In addition to compulsive checking, QNP-treated rats also developed locomotor sensitization, as reported previously (Einat & Szechtman, 1993b; Mattingly *et al.*, 1993; Szechtman *et al.*, 1994a, b; Kostrzewa, 1995; Einat *et al.*, 1996; Szumlinski *et al.*, 1997; Culver *et al.*, 2000; Winter *et al.*, 2008b).

In saline-treated control rats, HFS of the NAc core and shell resulted in a current intensity-dependent increase in locomotion. This is in line with previous studies that have shown that electrical stimulation and electrolytic lesion of the NAc increase locomotion and explorative behavior in naive rats (Kelly & Roberts, 1983; Kubos *et al.*, 1987; Starkstein *et al.*, 1988; van Kuyck *et al.*, 2003) as well as rats pre-treated with a selective serotonin 1A receptor agonist (van Kuyck *et al.*, 2003). The similar effects of HFS of either the NAc shell or core on locomotion in drug-naive rats reflects the ongoing controversy on whether the NAc shell or core is more involved in locomotion (Maldonado-Irizarry & Kelley, 1994; Johnson *et al.*, 1996; Weiner *et al.*, 1996, 1998; Gal *et al.*, 1997).

Interestingly, HFS induced a converse effect on locomotion in QNP-sensitized, i.e. hyperlocomotive, rats, i.e. HFS of the NAc core reduced locomotion in QNP-treated rats when stimulation was performed at the highest current intensity. ANOVA revealed that HFS of the NAc shell did not affect locomotion. The differential findings on locomotion may reflect functional differences between the NAc shell and core region, which become apparent only after dopamine challenge, i.e. chronic intermittent QNP treatment, but not under control conditions (see above). These findings may further suggest that a locomotor sensitization induced by HFS of both the NAc core and shell may not become apparent in already sensitized, i.e. hyperlocomotive, rats. It may also be hypothesized that the reduction of checking behavior is paralleled by reduced locomotion that is outweighed by the hyperlocomotive effects of HFS in all treatment conditions except the above mentioned, where the potential decrease in locomotion paralleling the anti-compulsive effect of HFS is stronger than the hyperlocomotive effect of QNP.

The main finding of the present study is that HFS of the NAc shell and core attenuated compulsive checking in QNP-treated rats. This effect was reversible as demonstrated by the fact that compulsive checking returned to its baseline level on the last session (15th), when no stimulation was applied. Specifically, under HFS, QNP-treated rats behaved more similarly to saline-treated rats with respect to the number of visits to the home base, the number of stops in other locales before returning to the home base and the time spent away from the home base. This anti-compulsive effect cannot be accounted for by a non-selective effect on locomotion because (i) HFS of the shell and core decreased the ratio of observed to expected visits to the home base, which is a measure of compulsive checking that is not dependent on general changes in locomotion, and increased the number of stops before returning to the home base, which, if anything, should be inversely correlated with the general level of locomotion; (ii) HFS of the NAc core at 150 μA reduced both compulsive checking and locomotion but, at 100 μA, HFS of the NAc core decreased only compulsive checking; and (iii) GEE analysis with locomotion as a covariate revealed no correlation between the effect of HFS on behavioral measures of locomotion and of compulsivity in QNP-treated rats (see supporting Appendix S1). Taken together, the present experiments reveal a specific effect of HFS on compulsive measures not biased by effects on locomotion. Furthermore, these data reinforce the notion that compulsive checking, as defined in the QNP model, is not merely a by-product of QNP-induced locomotor sensitization.

The finding that HFS of the shell was effective only at 100 μA, whereas HFS of the core was more effective at 150 μA than at 100 μA, may have implications as to the best target for HFS within the NAc. The differential effect may be due to either an unspecific mechanism such as current spread to neighboring nerve fibers and brain areas or, alternatively, may reflect HFS-dependent modulations of different subregion-specific efferents.

The distance up to which current spreads depends on (i) current intensity and (ii) electrode and tissue properties (Ranck, 1975; Perlmutter & Mink, 2006). It is therefore likely that, at a given electrode and tissue condition, the distance up to which neurons are affected by HFS positively correlates with the current intensity. Furthermore, at a given electrode and current intensity, the distance up to which neurons are affected by HFS crucially may depend on tissue properties such as cell bodies (small- vs. large-diameter axons and dendrites are differentially sensitive towards electrical stimulation) (Holsheimer *et al.*, 2000; Yousif & Liu, 2007). Considering the interplay of current intensity and tissue properties, current intensities of 150 μA may induce a certain profile of activated/inhibited cell bodies and different types of axons within a certain region adjacent to the stimulation site that may be distinctly different from the profile induced in another adjacent region and under a current intensity of 100 μA or even lower current intensities. The finding that a stronger anti-compulsive effect of HFS of the NAc core was obtained under current intensities of 150 μA rather than 100 μA therefore suggests that stimulation of structures neighboring the NAc core contributed to the anti-compulsive effect. In the rat, the NAc core is surrounded by the NAc shell as well as the caudate putamen and is nerved by the anterior commissure. In fact, HFS of the caudate nucleus (Aouizerate *et al.*, 2004), the NAc shell (Sturm *et al.*, 2003) and the anterior commissure (Nuttin *et al.*, 1999, 2003) have previously been reported to be effective in the treatment of OCD in humans. In contrast, possible explanations for the finding that stimulation of the NAc shell was anti-compulsive only at 100 μA but not at the higher current intensity (150 μA) include the possibility that stimulation of neighboring areas (e.g. the anterior ventral pallidum, the nucleus of the vertical limb of the diagonal band, the Island of Calleja and the 'a' component of the medial forebrain bundle) (Paxinos & Watson, 1997) exerted a pro-compulsive effect.

Alternatively, the differential effects may reflect HFS-dependent modulations of different subregion-specific efferents (Heimer *et al.*, 1997; Groenewegen *et al.*, 1999; Zahm, 1999, 2000). There is still debate about how HFS may work. Most of what is known stems from studies assessing the effects of HFS of the subthalamic nucleus or the globus pallidus in the treatment of Parkinson's disease. Previous studies have shown that HFS of these structures reduces the overall activity of targeted neurons (Salin *et al.*, 2002; Tai *et al.*, 2003; Benazzouz *et al.*, 2004; Filali *et al.*, 2004; Welter *et al.*, 2004; Meissner *et al.*, 2005), which has been discussed to be the result of an excitation of inhibitory afferents (Salin *et al.*, 2002; Tai *et al.*, 2003; Bacci *et al.*, 2004; Benazzouz *et al.*, 2004; Meissner *et al.*, 2007), a direct inhibition of targeted cell bodies (Benabid *et al.*, 2005) or modulation of efferent projections of the stimulated region (Windels *et al.*, 2000; Hashimoto *et al.*, 2003; Maurice *et al.*, 2003; McIntyre *et al.*, 2004; Stefani *et al.*, 2005).

We may consequently speculate that the differential effects of HFS of the NAc core and shell may result from modulations of different subregions and subregion-specific efferents (Heimer *et al.*, 1997; Groenewegen *et al.*, 1999; Zahm, 1999, 2000). The NAc shell is reciprocally connected with the ventral to dorsal prefrontocortical areas via the ventromedial pallidum and the NAc core is reciprocally connected to the more conventional basal ganglia circuitry via the ventrolateral pallidum (for review see Zahm, 2000). These circuitries are probably differentially involved in locomotive behavior as well as OCD pathophysiology, both induced by QNP sensitization.

Taken together, differential findings of HFS of the NAc core and shell on both compulsive checking behavior and locomotion highlight the functional differentiation of the NAc into two subregions (Kelly & Roberts, 1983; Jongen-Relo *et al.*, 2002, 2003; Sturm *et al.*, 2003) potentially associated with different anatomical systems that subserve different functions (Zahm & Brog, 1992; Groenewegen *et al.*, 1999) and may thus suggest that the locus of the anti-compulsive effect following HFS of the NAc is the shell. The demonstration of such an anti-compulsive effect following HFS of the NAc is in line with a recent publication on NAc-HFS in rats with schedule-induced polydipsia (Kuyck *et al.*, 2008) but contrasts a previous finding by the same group that electrical stimulation of the NAc increased compulsive responding in another rat model of OCD (8-OH-DPAT-induced perseveration in a T-maze) (van Kuyck *et al.*, 2003). One plausible reason for the contrasting results may be the difference in stimulation frequency, as the present study used high frequency (130 Hz), whereas van Kuyck *et al.* (2003) used low frequencies close to 10 Hz (pulse pairs with a 10 ms interpulse interval, given at 5 Hz), a frequency that is ineffective for most deep brain stimulation indications in the clinic (Benabid *et al.*, 1991; Limousin *et al.*, 1995; Ushe *et al.*, 2006; Kuyck *et al.*, 2008).

As there are very few studies on the physiological and biochemical effects of HFS of the NAc we can only speculate on the mechanism by which this manipulation exerts its anti-compulsive effect. So far, it has been found that HFS of the NAc reduces firing rates of neurons in the orbitofrontal cortex (McCracken & Grace, 2007). These authors speculate that HFS of the NAc region may reduce OCD symptoms by reducing activity in orbitofrontal cortex neurons. This hypothesis is in line with several *in-vivo* microdialysis studies showing altered neurotransmission and consequently activity under HFS in projection areas of the stimulated region (Hiller *et al.*, 2007; Winter *et al.*, 2008a).

Repeated QNP administration has been shown to decrease basal dopamine levels in the striatum (Koeltzow *et al.*, 2003) and the NAc projects densely to the dopaminergic neurons that innervate the striatum (Joel & Weiner, 2000). It is possible that HFS of the NAc counteracted the altered functioning of the dopaminergic system brought about by repeated QNP administration. Another structure that may be involved in mediating the anti-compulsive effect of NAc-HFS is the ventral pallidum, another projection target of the NAc whose functioning has been shown to be altered following repeated administration of QNP (Carpenter *et al.*, 2003; Richards *et al.*, 2007). Furthermore, it is of interest to note that we have recently found that HFS of the subthalamic nucleus (which also projects to the ventral pallidum) also exerts an anti-compulsive effect in the QNP model (Winter *et al.*, 2008b).

Conclusions

The present study demonstrated that acute HFS of the NAc core and shell selectively reduces compulsive checking behavior in the QNP rat model of OCD. Equivalently, HFS of the NAc has been found to reduce obsessive compulsive behavior in patients (Sturm *et al.*, 2003; Greenberg *et al.*, 2006; Rauch *et al.*, 2006; Okun *et al.*, 2007). The present study consequently supports the predictive validity of the QNP model for mapping regions for HFS for the treatment of OCD. In addition, although the extrapolation from an animal model to the clinical condition is problematic, the present findings demonstrate that the exact electrode placement, even within a single brain region, has a crucial impact on the therapeutic outcome.

Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix S1. Analysis of generalized estimating equations (GENMOD procedure (SAS 9.1.3)).

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Abbreviations

GEE, generalized estimating equation; HFS, high-frequency stimulation; NAc, nucleus accumbens; OCD, obsessive compulsive disorder; QNP, quinpirole.

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