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Research report

Activity modulation of the globus pallidus and the nucleus entopeduncularis affects compulsive checking in rats

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ABSTRACT

Deep brain stimulation at high frequencies (HFS) is currently studied in the treatment of therapy-refractory obsessive–compulsive disorder (OCD). The diversity of targeted brain areas and the discrepancy in demonstrating beneficial effects, highlight the need for better mapping of brain regions in which HFS may yield anti-compulsive effects. This goal may be achieved by investigating the effects of HFS in appropriate animal models of OCD. The present study tested the effect of bilateral HFS or pharmacological inactivation (as induced by intracerebral administration of the GABA-agonist muscimol) of both the Globus pallidus (GP; rodent equivalent to human GP externus) and the Nucleus entopeduncularis (EP; rodent equivalent to human GP internus) on checking behaviour in the quinpirole rat model of OCD. We demonstrate that HFS of the GP does not and HFS of the EP only partially reduces OCD-like behaviour in rats. In contrast, pharmacological inactivation of both GP and EP significantly reduces OCD-like behaviour in the model. These data contrast previously derived data on the effectiveness of HFS of the subthalamic nucleus, nucleus accumbens, GP and EP in the same and other rat models of OCD. We conclude that (i) although GP and EP play an important role in the pathophysiology of OCD, these areas may not represent first choice target structures for HFS, (ii) the effectiveness of HFS may depend on different subtypes of OCD, represented in different animal models, and (iii) differential net mechanisms may subserve the effectiveness of HFS and pharmacological inactivation.

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1. Introduction

Obsessive–compulsive disorder (OCD) is a frequent and chronic psychiatric disorder which is often associated with significant distress and disability. With a lifetime prevalence of up to 3.5% [1], OCD comprises recurrent intrusive thoughts (obsessions) and repetitive time-consuming behaviours (compulsions). Standard treatments for OCD include selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioural therapy [2,3]. However, up to 30% of the patients remain refractory to pharmaco- and psychotherapy [4]. Functional and structural imaging studies implicate the involvement of basal ganglia-thalamocortical circuits in terms of increased activity of the orbitofrontal–subcortical system in the pathophysiology of OCD [5,6]. Consequently, lesions to structures and pathways within these circuits can reverse clinical symptoms [7]. Ablation has recently been replaced by the reversible and adjustable deep brain stimulation (DBS) at high frequencies (HFS) in the treatment of several basal ganglia related neurological disorders [8–10].

Meanwhile several attempts have been made to establish HFS also for the treatment of therapy-resistant psychiatric disorders [11–13], including OCD: Beneficial effects of HFS have been shown for the anterior limb of the internal capsule [14,15], the ventral caudate nucleus [16,17], the nucleus accumbens (NAcc) and ventral capsule/ventral striatum [18–20] the subthalamic nucleus as well as the inferior thalamic peduncle [21]. Yet, not all patients responded to these treatments, most responders experienced only partial alleviation of symptoms, and a substantial risk of serious

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adverse events was reported following HFS of the STN [22]. In this context it is of note that pathophysiological considerations suggest even further brain areas of the basal ganglia-thalamocortical circuitry as potential target structure for HFS in the treatment of OCD. Systematically mapping brain regions, at which HFS has therapeutic effects on obsessive–compulsive behaviour and those areas at which DBS lacks such effects or is deleterious is mandatory and will also allow drawing implications regarding the relevance of the investigated brain sites and functional circuits in the manifestation of OCD. Given the clinical and methodological challenges as well as the ethical limitations of human studies such endeavor may benefit from the use of appropriate animal models that closely mimic the behavioural and neural manifestations of OCD.

We have recently found that HFS of the STN alleviates compulsive behaviour in two rat models of OCD, the quinpirole [23] and the signal attenuation [24] model, while rats sustaining ablative lesions to the STN display increased levels of compulsive behaviour [25]. The STN is highly connected with the internal and external segments of the globus pallidus (GP) [29]. Furthermore, bilateral GP lesions have been shown to induce OC symptoms [27], and the GP has been shown to be hyperintense [28] or of altered volume [29–32] in OCD patients compared to healthy controls. Together, these reports implicate the pathophysiological relevance of the GP in OCD. In line with this, we could recently demonstrate that HFS of either the GP (rodent equivalent to human GP externus) or the Nucleus entopeduncularis (EP; rodent equivalent to human GP internus) reduced compulsive behaviour in the signal attenuation rat model of OCD [33]. The replication of any such data in several rat models which differ in terms of the manipulation used to induce compulsive-like behaviour as well as the nature and therapeutic responsiveness of the induced behaviour, makes it more likely that if an anti-compulsive effect of HFS of a specific brain region is found, such an effect reflects a genuine therapeutic effect, rather than being specific to some parameter of a particular model that is not necessarily related to the modeled disorder. Consequently, the present study investigated the effects of HFS of both, the EP and the GP on OC-like behaviour in the quinpirole (QNP) rat model of OCD: Rats treated chronically with the dopamine D2/D3 receptor agonist QNP develop compulsive-like behaviours that resemble compulsive checking behaviour of OCD patients [34–37]. The QNP rat model of OCD has recently been shown to have high predictive validity for mapping brain regions for HFS in the treatment of OCD [26,41]. In the present study, HFS was tested at different current intensities, i.e. 75, 100, and 150 μA, which have previously been proven effective in ameliorating OC symptoms when HFS was performed in the STN, NAcc, GP and EP in the QNP and/or the signal attenuation rat model of OCD [23,24,33,38]. Furthermore, the effect of pharmacological inactivation (as induced by intracerebral microinjections of the GABA-agonist muscimol) of both, the EP and the GP on compulsive checking in QNP-treated rats was tested. This experimental set up aimed at assessing (i) the EP and the GP as potential neurosurgical targets in the treatment of OCD and (ii) further elucidating overall mechanisms underlying the effectiveness of HFS on compulsive-like behaviour in the QNP rat model of OCD.

2. Methods and materials

2.1. 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 used. 120 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 6 a.m.–6 p.m.). All experiments were performed during day time. Food and water were available ad libitum.

2.2. Apparatus and behavioural procedure

Prior to the beginning of the experimental procedure, 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 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 behaviour was videotaped continuously throughout a 30 min session. The open field consisted of a glass table (140 × 140 and 20 cm height) 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 behaviour 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) frequency of stops at each open field locale; (3) mean duration of return time to a given locale; (4) mean stop duration at a given locale; (5) total duration of stops at a given locale. For each rat the locale with the highest total duration of stops was defined as the home base and compulsive checking behaviour was analyzed with reference to the home base. According to Szechtman et al. [39] 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 analyzed: the total number of visits to the home base; the mean time to return to the home base; and the mean number of stops before returning to the home base. In addition, because repeated administration of QNP increases locomotion [39,40] and since checking behaviour requires locomotion, an arithmetic was applied allowing the assessment of changes in checking behaviour while controlling for 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 by 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 by the expected rate of return to a locale [23,36,41].

2.3. 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 ($n = 64$) or saline (controls, $n = 56$), followed by behavioural testing in the open field. Previous work has shown that the effects of chronic treatment with QNP reach a plateau after 8–10 drug injections as well as reliable checking behaviour [39,41,42]. After the 10th behavioural testing, QNP-treated and control rats were each randomly assigned to six groups, depending on the targeted brain region (EP, GP, each $n = 60$) and the treatment (HFS, pharmacological inactivation, no treatment, i.e. electrode placement only; for allocation to the respective groups, see Table 1). Rats in the HFS ($n = 44$) and the no treatment experiment ($n = 32$) underwent bilateral implantation of concentric bipolar electrodes with an outer diameter of 250 and an inner diameter of 125 μm (platinum-iridium, we-sense LTD, Nazareth, Israel) and rats in the pharmacological inactivation experiment ($n = 44$) underwent bilateral implantation of guide cannulae. In *phase II* the effects of HFS of either the EP or the GP, of muscimol microinjections into either the EP or the GP or of no treatment intervention to either the EP or GP were investigated using a within-subjects design. The effects of the manipulation were assessed 1 week following electrodes/cannulae implantation, to allow recovery from the micro-trauma induced by implantation [22,37,43]. Specifically, control and QNP rats in the HFS experiment underwent five additional saline or QNP (respectively) injections (2 injections per week), each followed by behavioural testing (sessions 11–15). During each of these sessions, electrodes were connected to the stimulator via an isolated cable system: HFS was applied on the 12th–14th session at varying current intensities in random order. Control and QNP rats in the pharmacological inactivation experiment likewise underwent five additional saline or QNP injections (2 injections per week), each followed by behavioural testing (sessions 11–15). Muscimol was applied in varying dosages dissolved in 0.5 μl per side in a random order on the 12th–14th sessions. On the 15th session, saline (0.5 μl per side) was applied. The last test session in both, the HFS and the pharmacological inactivation experiments, served to assess reversibility of treatment manipulation, as 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

Table 1
Number of rats included into the study. Total number of animals operated (second number) and included (first number) into final statistical analysis for the respective groups following exclusion due to inappropriate localization or dysfunction/occlusion of electrode or cannula.

	HFS	Muscimol	No treatment	
GP QNP	10/12	10/12	6/8	26/32
GP NaCl	10/10	10/10	6/8	26/28
EP QNP	10/12	12/12	7/8	29/32
EP NaCl	8/10	10/10	8/8	26/28
	38/44	42/44	27/32	107/120

[23,24,38,45]. Control and QNP rats in the no treatment group underwent five additional saline or QNP (respectively) injections (2 injections per week), each followed by behavioural testing (sessions 11–15). During the test sessions no treatment intervention, i.e. HFS or pharmacological inactivation, was applied. This group was inserted to control unspecific lesion effect following surgery and included animals with electrodes placed in the targeted areas only.

2.4. 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 concentric bipolar electrodes with connector (platinum–iridium, Nano-biosensors Nazareth, Israel) were implanted bilaterally into the GP at −1.0 mm posterior and 2.8 mm lateral from bregma as well as −6.4 mm ventral from dura or the EP at −2.6 mm posterior, 2.6 mm lateral and 7.4 mm ventral from the dura [46]. Cannula implantation: Two guide cannulae were implanted bilaterally at the same coordinates but above the GP or EP, respectively (5 mm dorsal) so that the injector would protrude 5 mm below the cannula. Wire stylets were inserted into the guide cannula to prevent occlusion. Electrodes and cannulae were fixed to the skull surface with stainless steel screws and dental acrylic cement (Technovit®, Heraeus-Kulzer, Hanau, Germany).

2.5. 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 0.0005, 0.001 and 0.005 μg per 0.5 μl. Saline and muscimol were applied right before systemic QNP or saline injection. These dosages were chosen based on what has been proven behaviourally effective [22,23], and on pilot studies that showed reduced motor activity at higher dosages. 25 gauge stainless steel injection needles were inserted into the guide cannulae to protrude 5 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.

2.6. Stimulation

HFS was performed with an isolated stimulator (Coulbourn Instruments, Allentown, PA, USA) as previously described [23,24,38]. Implanted electrodes were connected to the stimulator via an isolated cable system hanging from the ceiling of the behavioural 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 μs, current intensities 75, 100 or 150 μA. Current intensities were chosen according to what has been proven effective in ameliorating OC symptoms following HFS of the STN, NAcc, EP and GP in the QNP and the signal attenuation rat model of OCD [23,24,33,38] in order to allow direct comparability of potential beneficial effects and according to what has been demonstrated safe in terms of unspecific lesion effect induced by prolonged HFS [47]. Frequency 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 [44,48–50] and are in proximity to the clinical situation [51,52]. HFS was started right after the rat was connected to the cable system and placed on the open field scenario for behavioural testing and lasted throughout the testing.

2.7. Histology

Rats were decapitated after the 15th testing under deep anesthesia (chloral hydrate 50 mg/kg, Merck, Darmstadt, Germany) and their brains were removed within seconds and stored at −80 °C for further analysis. The brains were sectioned in the coronal plane at 40-μm thickness and every second section was stained with cresyl violet. Verification of placements was performed using the atlas of Paxinos and Watson [46]. Only animals with the electrodes or cannulae placed correctly in the target areas were included in the statistical analysis of the results.

2.8. Statistical analysis

Statistical analysis was performed to allow direct comparability to previously derived data on the effectiveness of HFS and pharmacological inhibition of the STN and the NAcc core and shell on OCD-like behaviour in rats [23,38]. Phase I: For comparisons between the performance of the two groups (QNP and control) on the last session (10th) t-tests were performed. Phase II: For comparisons between treatment conditions within a group, one way repeated measure 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 to be statistically significant. This statistical procedure has previously been shown appropriate to sufficiently depict specific and significant effects [38].

3. Results

3.1. Electrode/cannula placement

Fig. 1(1 and 2) presents photomicrographs of coronal sections taken from representative rats implanted with electrodes into either the GP or the EP. The only visible damage in these rats was the electrode tracks toward the GP/EP. Fig. 1(3 and 4) presents schematic reconstructions of electrodes and cannulae tips in the GP (Fig. 1(3)) or the EP (Fig. 1(4)) of all QNP-treated rats which underwent HFS or pharmacological inactivation and which 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). Table 1 summarizes the number of rats which were initially included into the study and the final number of animals which were included into statistical analysis after exclusion due to inappropriate localization or dysfunction/occlusion of the electrode/cannula in the respective groups.

3.2. Phase I

3.2.1. QNP-induced compulsive checking behaviour

QNP treatment over a total of 10 injections induced compulsive checking behaviour as demonstrated with three performance measures of compulsive checking previously introduced by Szechtman et al. [34]. In particular: (1) QNP-treated rats visited their home base (HB) significantly more often than did saline-treated animals (Fig. 2(1), $P < 0.001$). This was also true when taking into account the higher total number of visits to all locales in QNP-treated rats compared to control rats. Thus, the ratio of observed to expected visits to the home base (Fig. 2(2)) was significantly higher in QNP compared to control rats ($P < 0.001$). (2) The mean return time to the home base (Fig. 2(3)) was significantly shorter in QNP-treated than in control rats ($P < 0.001$). (3) QNP-treated rats visited fewer places than control rats before returning to their home base (Fig. 2(4), $P < 0.001$). In addition, chronic intermittent application of QNP led to locomotor sensitization, evident in a significantly higher total distance traveled by QNP compared to control rats during the 10th session (Fig. 2(5), $P < 0.001$).

3.3. Phase II

3.3.1. High frequency stimulation

HFS of the GP did neither affect QNP-induced compulsive checking behaviour as measured in the total number of returns to the home base ($F_{4,49} = 0.99$, $P = 0.426$, Fig. 3(2)), the ratio of observed to expected home base visits ($F_{4,49} = 0.72$, $P = 0.584$, Fig. 3(3)), the return time to the home base ($F_{4,49} = 1.19$, $P = 0.335$, Fig. 3(4)) as well as visits to other places before revisiting the home base ($F_{4,49} = 0.96$, $P = 0.444$, Fig. 3(5)) nor did it affect locomotion in QNP-treated rats ($F_{4,49} = 2.02$, $P = 0.117$, Fig. 3(1)). HFS of the EP, in contrast, significantly reduced one out of four measures of compulsive checking behaviour, i.e. the ratio of observed to expected home base visits ($F_{4,49} = 13.18$, $P < 0.001$, Fig. 3(3)). The remaining measures, i.e. returns to the home base ($F_{4,49} = 1.51$, $P = 0.22$, Fig. 3(2)), return time to the home base ($F_{4,49} = 1.35$, $P = 0.271$, Fig. 3(4)) and visits to other places before revisiting the home base ($F_{4,49} = 2.58$, $P = 0.054$, Fig. 3(5)) as well as locomotion ($F_{4,49} = 1.19$, $P = 0.337$, Fig. 3(1)) were not affected.

In control rats, HFS of neither the GP nor the EP did affect compulsive checking behaviour as measured in the total number of returns to the home base (GP: $F_{4,49} = 1.56$, $P = 0.21$; EP: $F_{4,39} = 0.35$,

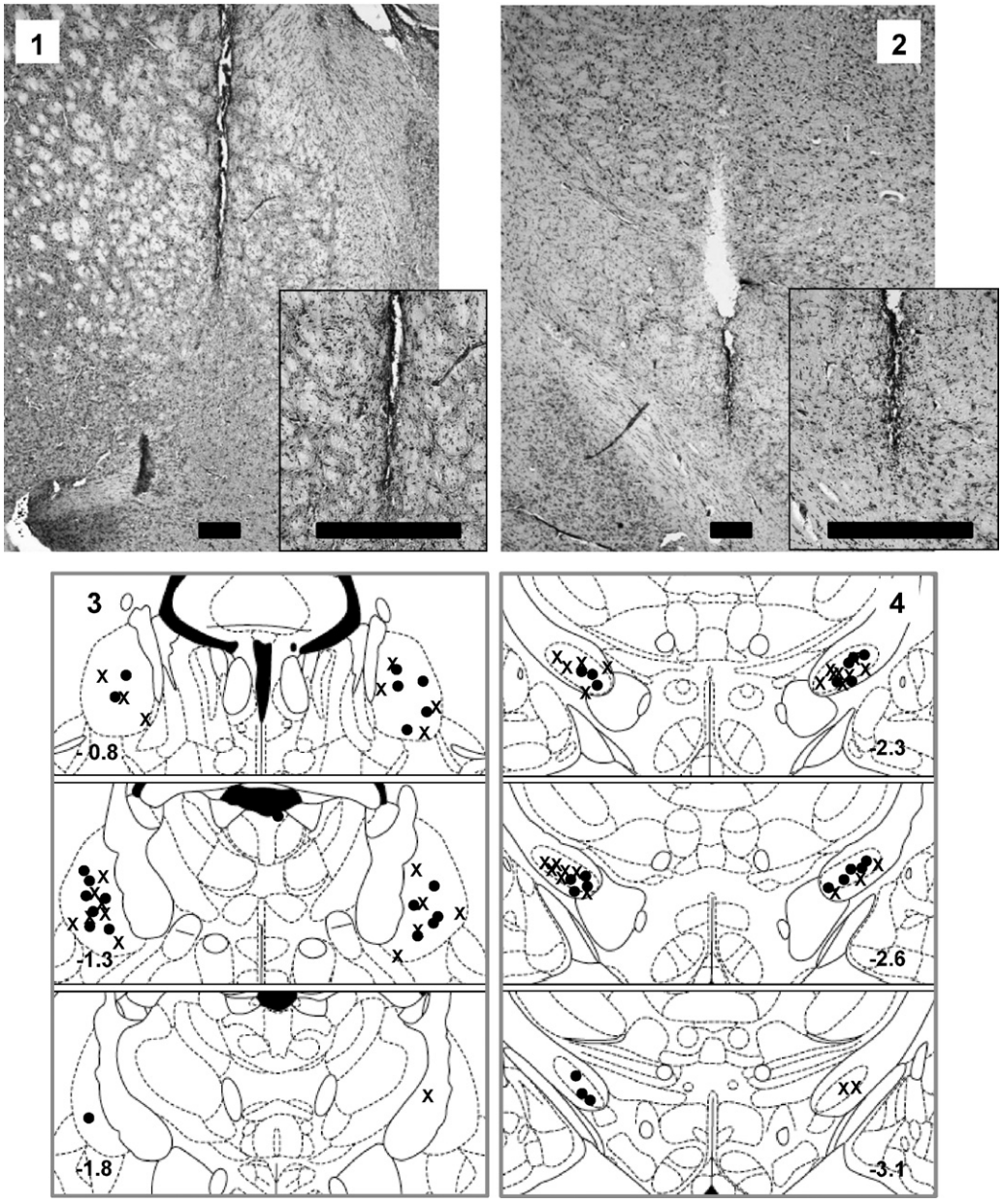

Fig. 1. Post mortem histology. (1 and 2) Photomicrographs of a coronal section stained with cresyl violet and taken from representative rats showing the tip of the electrode in the GP (1) or the EP (2). (3 and 4) Schematic reconstructions of electrode (●) and cannula (×) tip placement in the GP (3) or EP (4) of QNP-treated stimulated rats. Equivalent distribution patterns of electrode/cannula tip placements were found in NaCl treated controls subjected to HFS or pharmacological inactivation as well as QNP or NaCl-treated sham treated rats. Schematic reconstruction of these finding was left out in order to avoid confusion of the relevant data.

$P = 0.84$, Fig. 3(2)), the ratio of observed to expected home base visits (GP: $F_{4,49} = 0.64$, $P = 0.64$; EP: $F_{4,39} = 0.1$, $P = 0.98$, Fig. 3(3)), the return time to the home base (GP: $F_{4,49} = 1.61$, $P = 0.2$; EP: $F_{4,39} = 0.27$, $P = 0.9$, Fig. 3(4)) and visits to other places before revisiting the home base (GP: $F_{4,49} = 0.51$, $P = 0.73$; EP: $F_{4,39} = 0.92$, $P = 0.47$, Fig. 3(5)). HFS of the EP did likewise not affect locomotion ($F_{4,39} = 1.79$, $P = 0.2$, Fig. 3(1)), whereas HFS of the GP lead to a significant reduction in locomotion in control rats ($F_{4,49} = 3.89$, $P = 0.01$, Fig. 3(1)).

3.4. Pharmacological inactivation

Pharmacological inactivation of both, the GP and the EP significantly attenuated QNP-induced compulsive checking: rats visited their home base significantly less often than they did under control conditions (sessions 10 and 15; GP: $F_{4,49} = 19.75$, $P < 0.001$, EP: $F_{4,59} = 9.79$, $P < 0.001$, Fig. 4(2)). Also, after adjusting for the total number of visits, returns to the home base were significantly reduced in QNP rats under pharmacological inactivation. Thus, the ratio of observed to expected visits to the home base was significantly lower under pharmacological inactivation than under control conditions (sessions 10 and 15; GP: $F_{4,49} = 26.4$, $P < 0.001$; EP: $F_{4,59} = 16.245$, $P < 0.001$, Fig. 4(3)). The mean return time to the home base was two- (EP) to eightfold (GP) longer in QNP-treated rats under pharmacological inactivation than in the same QNP-treated rats under control conditions (sessions 10 and 15; GP: $F_{4,49} = 9.69$, $P < 0.001$; EP: $F_{4,59} = 20.70$, $P < 0.001$, Fig. 4(4)). QNP-treated rats under pharmacological inhibition visited significantly more locales before returning to their home base than they did under control conditions (sessions 10 and 15; GP: $F_{4,49} = 3.114$, $P = 0.28$; EP: $F_{4,59} = 23.8$, $P < 0.001$, Fig. 4(5)). Whereas locomotion was also reduced by pharmacological inactivation of the GP at a muscimol dosage of 0.005 μg ($F_{4,49} = 10.29$, $P < 0.001$, Fig. 4(1))

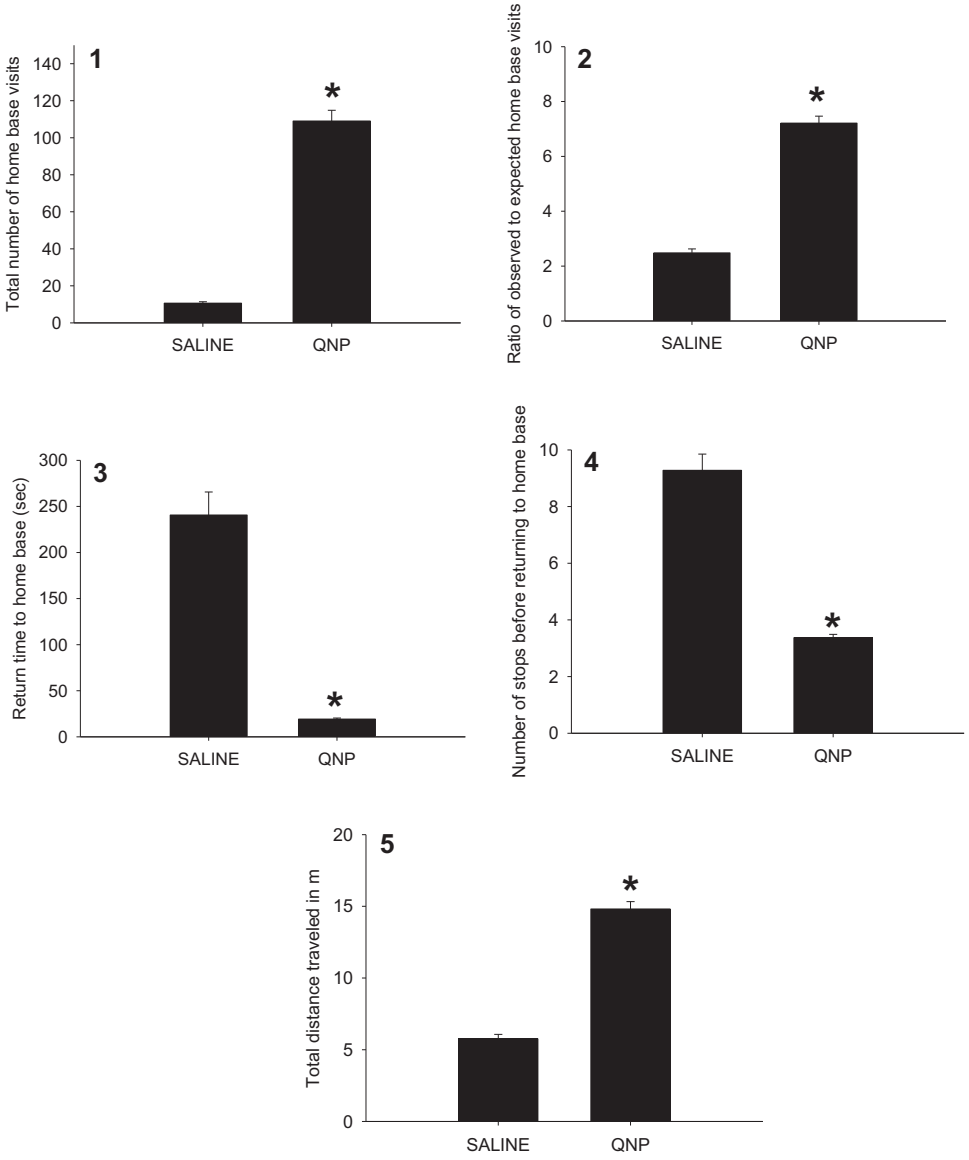

Fig. 2. Induction of compulsive checking behaviour. Checking behaviour is analyzed with reference to the home base (HB) established by each rat during the 10th session, and recognized as the locale with the longest total duration of stops. QNP-treated animals met compulsive checking criteria and displayed (1) more frequent returns to the home base, (2) a higher than an expected rate of returning to the home base, (3) reduced return time to home base, and (4) fewer visits to other places before revisiting home base compared to saline-treated controls. Additionally, QNP treated rats displayed an increased locomotion as measured in the mean and standard error of the mean total distance traveled over the 30 min observation period (5). $^{*}P < 0.05$, *t*-test. Values are expressed as mean ± SEM.

it remained unaffected by pharmacological inactivation of the EP ($F_{4,59} = 0.11$, $P = 0.977$, Fig. 4(1)).

Interestingly, pharmacological inactivation of the GP also significantly affected 3 out of 4 measures of checking behaviour in control rats, i.e. the total number of returns to the home base ($F_{4,49} = 24.26$, $P < 0.001$, Fig. 4(2)), the ratio of observed to expected home base visits ($F_{4,49} = 3.02$, $P = 0.031$, Fig. 4(3)) and the return time to the home base ($F_{4,49} = 4.92$, $P = 0.004$, Fig. 4(4)) but not the number of visits to other places before revisiting the home base ($F_{4,49} = 1.5$, $P = 0.23$, Fig. 4(5)) and significantly reduced locomotion in control rats ($F_{4,49} = 19.67$, $P = <0.001$, Fig. 4(1)). In contrast, pharmacological inactivation of the EP did neither affect checking behaviour, as measured in the total number of returns to the home base ($F_{4,49} = 1.95$, $P = 0.12$, Fig. 4(2)), the ratio of observed to expected home base visits ($F_{4,49} = 2.11$, $P = 0.1$, Fig. 4(3)), the return time to the home base ($F_{4,49} = 0.61$, $P = 0.66$, Fig. 4(4)) and visits to other places before revisiting the home base ($F_{4,49} = 0.99$, $P = 0.43$, Fig. 4(5)) nor locomotion ($F_{4,49} = 1.97$, $P = 0.15$, Fig. 4(1)) in control rat.

Electrode implantation into either the GP or EP and sham HFS of both regions did not affect locomotion and parameters used for quantification of compulsive checking behaviour in QNP and saline-treated control rats (data not shown). If not indicated differently in text of figures, all observed effects were independent of stimulation parameter or muscimol dosage.

4. Discussion

The present study assessed the effects of HFS and pharmacological inactivation of the GP and the EP in the QNP rat model of OCD. The basis of the quinpirole model is the behavioural similarity between the behaviour of rats treated chronically with the dopamine D2/D3 agonist quinpirole and compulsive behaviours in OCD patients [34] supporting the face validity of the model [37]. The fact that compulsive checking is induced by a dopaminergic manipulation is congruent with several lines of evidence implicating abnormalities of the dopaminergic system in OCD [53–55] and

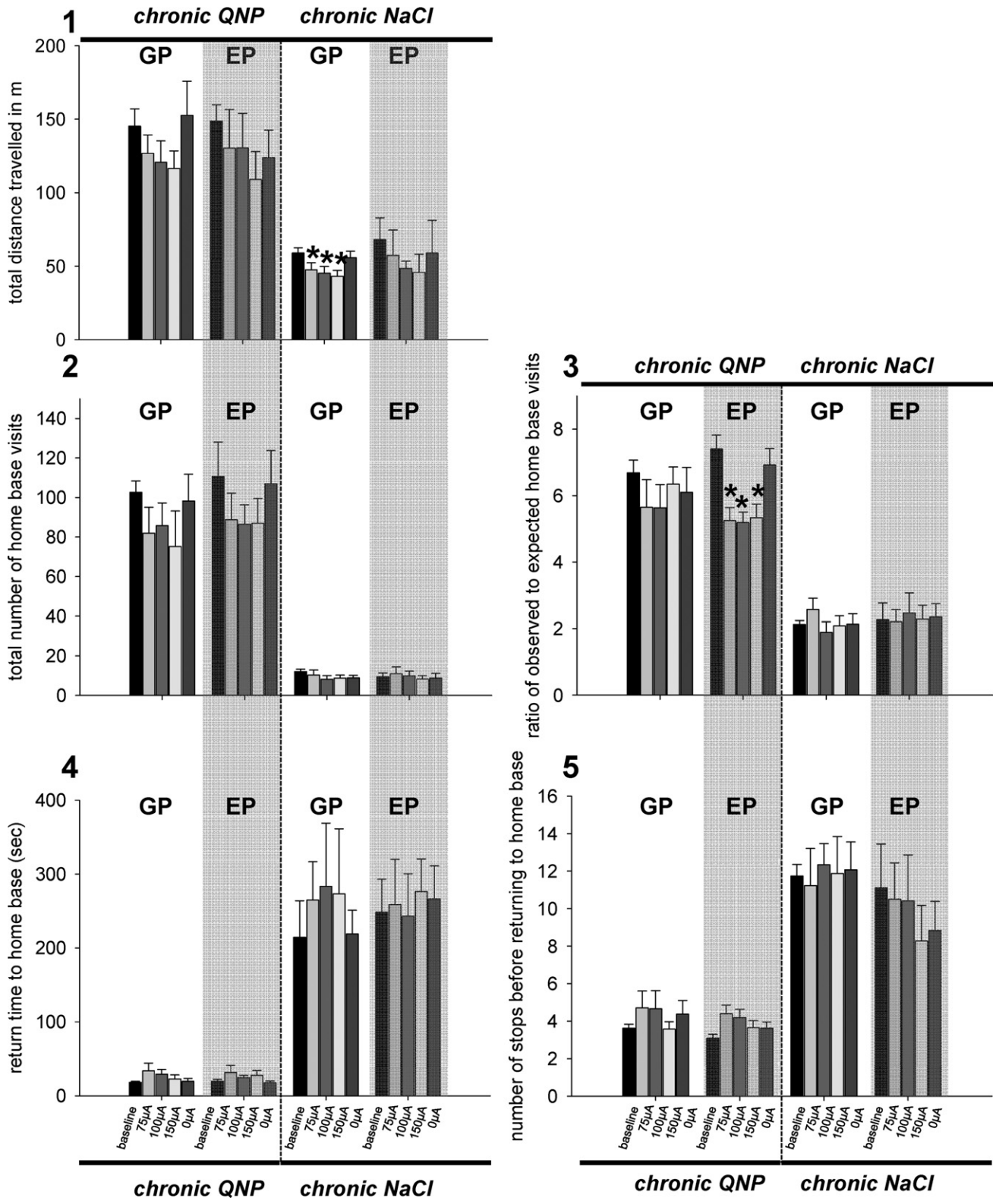

Fig. 3. The effects of HFS of the GP and EP on locomotion and compulsive checking behaviour in QNP-treated and control rats. *QNP treated rats*: HFS of neither the GP nor the EP did affect locomotion as measured in the mean and standard error of the mean total distance traveled over the 30 min observation period (1). HFS of the GP did not affect QNP-induced checking behaviour when compared to 10th (baseline) and 15th (remission, 0 μA) as measured in the mean and standard error of the mean (2) number of returns to the home base; (3) ratio of expected to observed home base visits; (4) return time to the home base, and (5) visits to other places before revisiting the home base. HFS of the EP reduced checking behaviour when compared to 10th (baseline) and 15th (remission, 0 μA) as measured in the mean and standard error of the mean (3) ratio of expected to observed home base visits, but not in the mean and standard error of the mean (2) number of returns to the home base; (4) return time to the home base, and (5) visits to other places before revisiting the home base. *Control rats*: HFS of the GP significantly decreased locomotion (1) but did not affect behavioural parameters specific for checking behaviour (1–4). HFS of the EP did neither affect locomotion (1) nor behavioural parameters specific for checking behaviour (4). *Denotes significant difference vs. 10th and 15th session (remission), $P < 0.05$, repeated measures ANOVA, followed by Holm–Sidak post hoc test. Values are expressed as mean ± SEM.

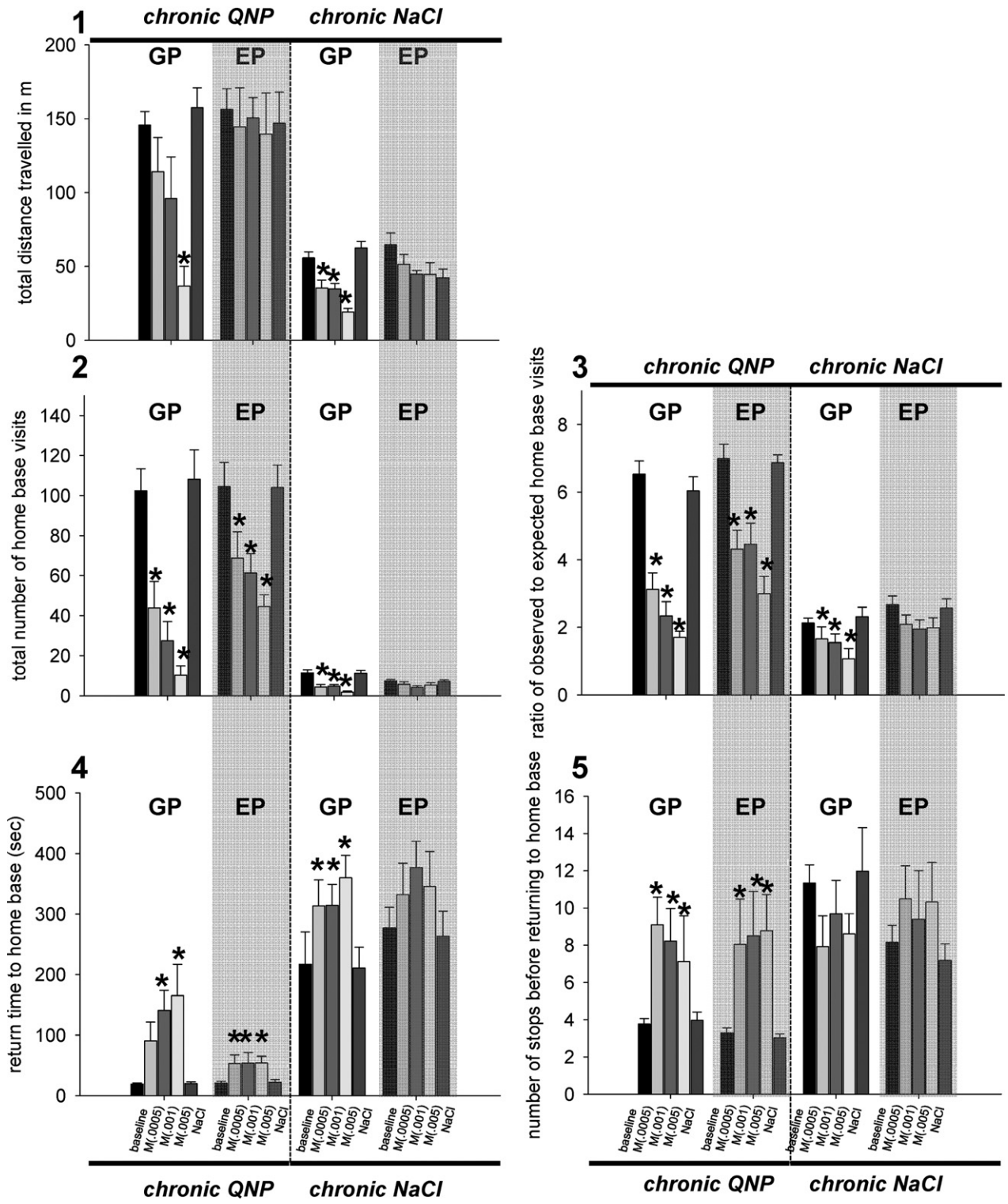

Fig. 4. The effects of pharmacological inactivation of the GP and EP on locomotion and compulsive checking behaviour in QNP-treated and control rats. *QNP-treated rats*: Pharmacological inhibition of the GP reduced locomotion as measured in the mean and standard error of the mean total distance traveled over the 30 min observation period, solely at the highest muscimol dosage tested. Pharmacological inhibition of the EP did not affect locomotion as measured in the mean and standard error of the mean total distance traveled over the 30 min observation period (1). Pharmacological inactivation of the GP and EP reduced QNP-induced checking behaviour when compared to 10th (baseline) and 15th (remission, 0 μA) as measured in the mean and standard error of the mean (2) number of returns to the home base; (3) ratio of expected to observed home base visits; (4) return time to the home base (not applicable for pharmacological inactivation of GP at lowest muscimol dosage), and (5) visits to other places before revisiting the home base. *Control rats*: Pharmacological inactivation of the GP significantly decreased locomotion (1) and three out of four behavioural parameters specific for checking behaviour. (1–4) Pharmacological inactivation of the EP significantly reduced locomotion (1) but did not affect behavioural parameters specific for checking behaviour (1–4). *Denotes significant difference vs. 10th and 15th session (remission), $P < 0.05$, repeated measures ANOVA, followed by Holm–Sidak post hoc test. Values are expressed as mean ± SEM.

provides construct validity [34]. Furthermore, recent studies document high predictive validity of the QNP model for mapping regions for HFS for the treatment of OCD [23,38]. As has been reported before, 10 injections of QNP given twice a week led to the emergence of compulsive checking in QNP-treated rats [23,34,35,38]. QNP-treated rats revisited their home base 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 home base. In addition to compulsive checking, QNP-treated rats developed locomotor sensitization, as reported previously [23,38–40].

The main findings of the present study are that pharmacological inactivation of the EP and the GP and HFS of the EP exerted an anti-compulsive effect. In addition pharmacological inactivation and HFS of the GP reduced locomotion in saline-treated rats, whereas in QNP-treated rats, pharmacological inactivation of the GP reduced the expression of sensitized locomotion. However, pharmacological inactivation and HFS of the EP had no effect on locomotion in saline-treated controls as well as in QNP-sensitized rats.

4.1. Effects on locomotion

The finding that manipulations of the GP affected locomotion in control rats is in line with several studies describing reduced locomotor activity and behavioural output following pharmacological inactivation or ablative lesion of the GP in rats [56–59]. In QNP-treated rats, pharmacological inactivation of the GP at the highest dosage tested antagonized QNP-induced locomotor sensitization and significantly reduced compulsive checking, whereas HFS of the GP had no effect. The differential effects of HFS and muscimol on locomotion in QNP-treated rats suggest that different mechanisms underlie locomotion in saline-treated vs. QNP-treated rats.

The finding that pharmacological inactivation and HFS of the EP had no effect on locomotion in saline-treated controls and in QNP-sensitized rats add to the ongoing controversy regarding the involvement of the EP in locomotion. On the one hand, HFS of the GPi/EP decreased hyperlocomotive aspects of dystonia in humans [9] and in the dt (sz) hamster model of dystonia [60,61]. In addition, ablative lesion of the EP impaired motor initiation and increased mean reaction time in rats [58]. On the other hand, HFS of the GPi in humans has been shown to promote locomotion in Parkinson's disease [62,63]. These oppositional findings suggest that the motor consequences of manipulations of the GPi/EP depend on the pathophysiological configuration [64,65].

4.2. Exerting an anti-compulsive effect

Pharmacological inactivation of the EP and the GP and HFS of the EP exerted an anti-compulsive effect, expressed in reduced QNP-induced compulsive checking without affecting QNP-induced hyperlocomotion (except for the highest dose of muscimol which decreased both compulsive checking and locomotion when administered into the GP). Pharmacological inactivation of the GP and the EP exerted a dose-dependent anti-compulsive effect. Under pharmacological inactivation 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) pharmacological inactivation of the EP did not affect locomotion; (ii) pharmacological inactivation of the GP decreased both locomotion and compulsive checking only at the highest dose tested (0.005 μg per side), but at the intermediate (0.001 μg per side) and lowest dose tested (0.0005 μg per side) it only decreased compulsive checking; (iii) pharmacological inactivation of the GP and the EP significantly decreased the metric ratio of observed to expected visits to the home base that statistically controls for changes in the amount of activity and in this respect permits the inference that the reduced frequency of checking is not solely a function of the amount of locomotion; (iv) pharmacological inactivation of the GP and the EP significantly increased the number of stops before returning to the home base, which, if anything, should be inversely correlated with the general level of locomotion [23,38].

It should be noted that whereas pharmacological inactivation of the EP did not affect checking behaviour in saline-treated rats, pharmacological inactivation of the GP did reduce behavioural measures of checking behaviour. It is not clear how this effect should be interpreted, because the pharmacological and neural basis of checking behaviour in control rats has not been characterized, and it is not clear whether a reduction of this behaviour has predictive validity for an anti-compulsive effect. However, taken together with the hypolocomotive effect of pharmacological inactivation of the GP it may be suggested that pharmacological inactivation of the GP results in a non-selective reduction of behavioural output in saline-treated controls. This needs to be considered when assessing the potential therapeutic relevance of the GP in the treatment of OCD.

HFS of the EP reduced one out of four behavioural measures of OC behaviour in QNP-sensitized rats, namely the ratio of observed to expected visits to the home base. This finding suggests that HFS of the EP at the parameters tested has only a minor beneficial effect as a therapeutic intervention.

Further studies are needed to test whether HFS of the GP and EP with the specific electrodes used at higher current intensities may exert an anti-compulsive effect. Although there are reports of beneficial effects of HFS of different neural targets at higher intensities [66,67] anti-compulsive effects have also been obtained using the stimulation parameters applied here for HFS of the STN [23,24] and the NAcc [38], and there are also reports of beneficial effects of HFS using these parameters in other animal models of neuropsychiatric dysfunctions [60,61,68,69]. Moreover, HFS of the GP at 75 μA and the EP at 100 μA has previously been shown to exert an anti-compulsive effect in the signal attenuation rat model of OCD [33]. As equivalently configured electrodes were used in both studies, the lack of effect of HFS of the GP and the EP in the present study may consequently be due to specific aspects of the model it was tested in. In the QNP model compulsive behaviour is induced by a dopaminergic manipulation (see above). In the signal attenuation model compulsive behaviour is induced by a behavioural manipulation based on the theoretical proposition that compulsive behaviours result from a deficit in the feedback associated with the performance of normal goal-directed responses [70–73]. Whereas compulsive behaviour in the signal attenuation model is alleviated by serotonin reuptake inhibitors [74], compulsive checking in the QNP model is only partially alleviated by such drugs [33]. It is therefore possible that the signal attenuation and the QNP rat models represent different subtypes of OCD which may also differ in their response to HFS.

While HFS of the GP and EP was not effective in producing a clear anti-compulsive effect in the QNP rat model of OCD, pharmacological inactivation of both nuclei was. This is most likely related to the different effects of these manipulations. The underlying mechanism of muscimol-induced pharmacological inhibition is the enhancement of GABAergic input to the targeted nucleus. The mechanisms of action are not clear, but the leading hypotheses are that (i) HFS causes suppression of the neuronal activity in the stimulated brain area as a result of increased inhibitory GABAergic afferences, pre- and postsynaptic suppression of excitatory glutamatergic afferences and/or depolarization block of the somata [75,76], and (ii) HFS leads to initiation of new activity and synaptic plasticity in the associated neuronal network [77–79]. The strength of muscimol-mediated inactivation of the targeted brain area depends on the specific distribution of GABA-A receptors, as

well as the injected volume, its concentration and the speed of injection. Likewise, the effects of HFS depend on numerous factors, including the stimulation parameters, the configuration of the electrode, the geometry of the stimulus field and the stimulated elements, the physiological properties of individual cells as well as the specific arrangements of individual cells to a cellular network [80]. Whether the behavioural effects of HFS and of pharmacological inactivation are similar or different may depend on the specific cellular arrangement of the targeted region. We and others have shown similar behavioural effects following pharmacological inactivation and HFS when applied in the STN [23,24,44], suggesting that the specific cellular arrangement of the STN subserved both interventions to engage the same mechanism, or alternatively, different mechanisms resulting in the same behavioural effect. Furthermore, we may speculate that the cellular arrangement of both the GP and the EP does not promote equivalent behavioural effects of pharmacological inactivation and HFS. However, so far there are no further studies which compare the behavioural effects of HFS and pharmacological inactivation of the GP and EP or which demonstrate contrasting behavioural effects of both manipulations to support this notion.

A surprising finding of the present study is the similar behavioural effects of manipulations of the GP and EP, because these nuclei are thought to have opposing roles in basal ganglia-thalamocortical circuitry with the EP increasing and the GP decreasing behavioural output [5]. At this stage of investigation our data point once again to the crucial role of an imbalance in the activity of the various subunits of the basal ganglia thalamocortical circuits in the pathogenesis of OCD although our data do not entirely support the traditional pathophysiological conception of the basal ganglia thalamocortical circuitry in OCD [5,6,81].

5. Conclusion

We have previously shown that HFS of the STN and the NAcc at stimulation parameters of 100 μA attenuates compulsive behaviour in the QNP rat model of OCD [25,40]. Consolidating the QNP-model of OCD and supporting the notion that the observed effects constitute a real phenomenon and not an artefact of the experimental method, these findings were reproduced in further rat models of OCD [24,66].

Using stimulation parameters in between 75 and 150 μA the present study could not detect a consistent anti-compulsive effect of HFS of the GP or EP, while pharmacological inactivation of the two nuclei did exert an anti-compulsive effect.

Although the extrapolation from an animal model to the clinical condition is problematic, the synopsis of these data suggests that neither GP (GP externus) nor the EP (GP internus) may be first targets options for HFS in the treatment of therapy-refractory OCD.

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