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High but not low frequency stimulation of both the globus pallidus and the entopeduncular nucleus reduces 'compulsive' lever-pressing in rats

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ABSTRACT

The anti-compulsive effects of high and low frequency stimulation (LFS, HFS) of the entopeduncular nucleus and globus pallidus (the rat's equivalent, respectively, of the primate's internal and external segments of the globus pallidus) were assessed in the signal attenuation rat model of obsessive-compulsive disorder (OCD). HFS, but not LFS, of the two nuclei exerted an anti-compulsive effect, suggesting that HFS of either segment of the globus pallidus may provide an additional therapeutic strategy for OCD.

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1. Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric affliction with a lifetime prevalence of 1–3% [51,55]. To date, the most effective treatments for OCD are pharmacological treatment, using serotonin reuptake inhibitors (SRIs [e.g. 43,49,50,59,75]), and behavioral treatment, using the response exposure and prevention technique [e.g. 57]. Yet there are roughly 30% of treated OCD patients who remain treatment resistant [15]. In patients refractory to pharmaco- and behavioral therapy, lesions to structures and pathways within basal ganglia-thalamo-cortical circuits can reverse clinical symptoms (for review see: [39]). Following the replacement of ablative lesions by deep brain high frequency stimulation (HFS) in the treatment of several basal ganglia-related disorders [13,34,63,64,67], there have been attempts to establish HFS also for the treatment of OCD. Recent studies suggest that HFS of the ventral striatum region [5,6,18,19,52,60] and of the subthalamic nucleus (STN) [41], may be particularly effective in alleviating symptoms in OCD. Yet, not all patients responded to these treatments, most responders experienced only partial alleviation of symptoms, and a substantial risk of serious adverse events was reported following HFS of the STN [41, for a recent review see: 18]. The shortcomings of current stimulation sites highlight the need for identifying additional brain regions whose stimulation may produce beneficial effects in OCD patients.

An important source of information for such a mapping attempt is the assessment of the effects of stimulation in appropriate animal models that closely mimic the behavioral and if possible the neural manifestations of OCD. We have recently found that HFS of the STN alleviates compulsive behavior in the signal attenuation rat model of OCD [32, for a recent review of the model see: 23], in line with evidence that bilateral HFS of the STN alleviates symptoms in OCD patients [41].

In the signal attenuation model, a deficient response feedback, assumed to underlie compulsions in patients (for review, see [47,61]), is simulated by attenuating a signal indicating that a lever-press response was effective in producing food. Signal attenuation leads, in a subsequent extinction test, to excessive lever-pressing that is not accompanied by an attempt to collect a reward. This behavior, which we have named 'compulsive' lever-pressing because it may be analogous to the excessive and unreasonable behavior seen in OCD, is abolished by the SSRIs fluoxetine, paroxetine and fluvoxamine, but not by the anxiolytic drug, diazepam, the antipsychotic, haloperidol, or the tricyclic antidepressant, desipramine [24,27,26], in accordance with the differential efficacy of these drugs in alleviating obsessions and compulsions in OCD patients [e.g. 14,49,75]. Compulsive lever-pressing is also sensitive to manipulations of the orbitofrontal cortex [28,29,30] and of the dopaminergic system [25,27], in line with different lines of evidence implicating these systems in the pathophysiology of OCD (for review see [5,58]).
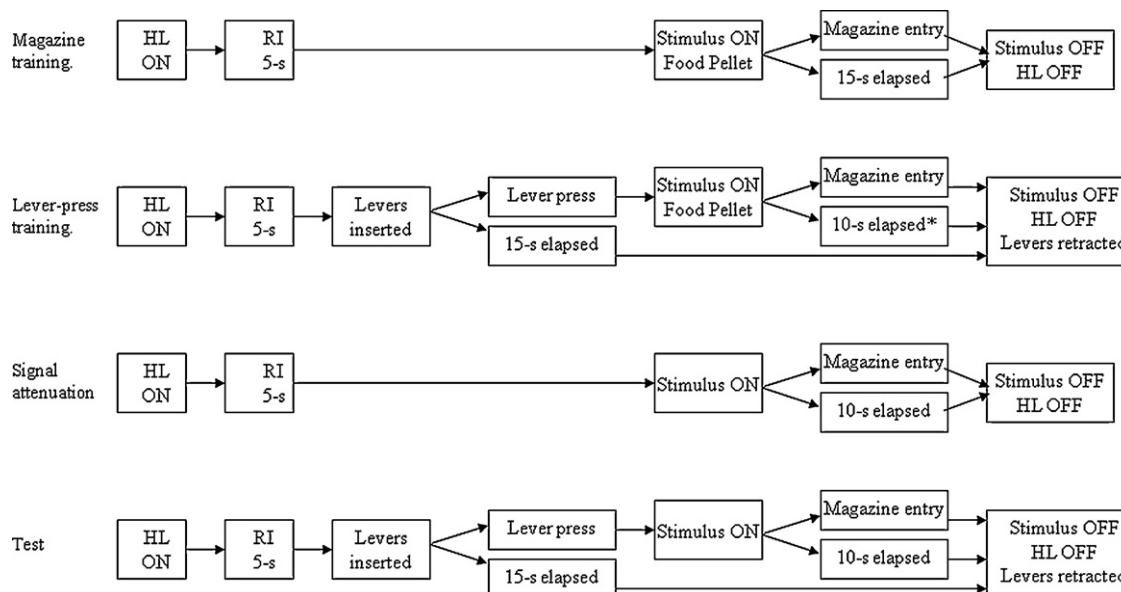
Fig. 1. A schematic diagram of the organization of a trial in each of the different training stages of the post-training signal attenuation procedure. HL, houselight; RI, random interval; (*) on the first day of lever-press training (Day 5) this time limit was 15 s.

The aim of the present study was to test the effects of HFS of the entopeduncular nucleus (EP, which corresponds to the internal segment of the globus pallidus in primates) and of the globus pallidus (GP, which corresponds to the external segment of the globus pallidus in primates) in the signal attenuation rat model of OCD. These two nuclei were chosen because they are highly interconnected with the STN, and because imaging studies in OCD patients (for review see [22]) and case reports of acquired OCD following lesions to the globus pallidus implicate this structure in the pathophysiology of OCD [2,3,12]. In addition to HFS, low frequency stimulation (LFS) was also tested in each region because LFS has been shown effective in other models of psychiatric disorders [17,53] as well as in the clinic [46].

Because the effects of signal attenuation are assessed under extinction conditions, the effects of HFS and LFS of both the GP and EP were assessed in rats undergoing an extinction test of lever-press responding that was preceded by signal attenuation (i.e., the post-training signal attenuation [PTSA] procedure), and in rats undergoing a control procedure in which the extinction test was not preceded by signal attenuation (the 'regular extinction' procedure). This design enables the differentiation between the effects of signal attenuation and of extinction per se (for a detailed discussion see [23]).

2. Experimental procedures

2.1. Subjects

Sprague–Dawley (Tel Aviv University, Israel) male rats approximately 3–4 months old, were housed individually under a reversed 12-h light–dark cycle (lights on 19:00–07:00 h) and maintained on a 22-h food restriction schedule, with water freely available. All experimental protocols were carried out according to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University.

2.2. Surgery

Rats received 3-mg diazepam, and 20 min later were anesthetized with i.p. injection of Avertin (10-ml/kg). *HFS and LFS groups*: two platinum–iridium concentric bipolar electrodes (Nano-biosensors Nazareth, Israel) were stereotaxically implanted bilaterally into GP: 1 mm posterior to bregma, 2.8 mm lateral to the midline, and 6.2 ventral to the dura. EP: 2.4 mm posterior to bregma, 2.6 mm lateral to the midline, and 7.2 ventral to the dura [48]. *Control group*: Rats underwent the same surgical procedure as GP/EP-HFS rats, but were implanted with stainless steel dummy electrodes with connector (exposed at the tip), approximately the gage of the electrodes used in the *HFS* and *LFS* group, at the same coordinates. The electrodes

were fixed to the skull surface with stainless steel screws and dental acrylic cement (Popco dental, Israel).

2.3. Apparatus and behavioral procedure

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

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

2.4. Post-training signal attenuation

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

Table 1
Summary of experiments.

Exp no.	Region	Procedure	Stimulation	Num of rats	Num of rats excluded	Final n per group
1	GP	PTSA and RE	HFS	54	1 - freezing 2 - illness 8-technical problems 2 - statistical	PTSA-HFS -8 PTSA-sham - 13 RE-HFS - 8 RE-sham - 12
2	EP	PTSA and RE	HFS	39	2 - technical problems 1 - statistical	PTSA-HFS - 10 PTSA-sham - 11 RE-HFS - 7 RE-sham - 8
3	GP and EP	PTSA	LFS	33	1 - illness 3 - freezing 3 - statistical	GP-LFS - 7 EP-LFS - 8 control - 11
4	GP and EP	RE	LFS	23	None	GP-LFS - 7 EP-LFS - 7 control - 9

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

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

2.5. Regular extinction

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

2.6. High frequency and low frequency stimulations

Electrical stimulation was conducted only during the test stage. Stimulation was maintained for the whole duration of the test and was performed using an isolated stimulator (STG1004; Multichannel Systems, Germany) in a constant current and balanced biphasic pulse mode: GP - high frequency, 130 Hz; low frequency, 10 Hz; pulse width, 100 μs; current intensity, 75 μA; EP - high frequency, 130 Hz; low frequency, 10 Hz; pulse width, 100 μs; current intensity, 100 μA. These stimulation parameters were chosen on the basis of preliminary results obtained in Winter's laboratory suggesting that at these parameters HFS of the EP and GP exerts an anti-compulsive effect in the quinpirole model. The pattern of stimulation was supervised throughout the test via an analog oscilloscope, in order to ensure that a stable and continuous stimulation was applied. A wire long enough to allow rats to freely move inside the skinner-box, was threaded through a hole in the ceiling of the chamber and attached to a home made swivel via a rubber band to prevent wire entanglement and allow maximum flexibility of movement. Rats were observed during the entire period of stimulation in order to ensure that no motor symptoms or impairments were visible, and that free access to the levers and magazine panel and recess was available.

2.7. Histology

Rats were lightly anesthetized with CO_2, decapitated and their brains removed within seconds and stored at $-80\,°C$ for further analysis. The brains were sectioned in the coronal plane at 30-μm thickness and stained with cresyl violet.

2.8. Statistical analysis

As there were no differences between the behavior of EP-sham and GP-sham rats in the LFS experiments (Exps. 3 and 4) data from these groups were combined into one Control group. Rats' performance on the Test was analyzed using analysis of variance (ANOVA) (main factors of Stimulation and Procedure in Experiments 1 and 2, and Region in Experiments 3 and 4) performed on the number of ELP-C and ELP-U as well as on the number of completed, uncompleted and unpressed trials, and the number of nose-pokes and of lever-presses on the non-reinforced lever. Although rats were stimulated only during the test stage, rats' performance on the lever-press training and signal attenuation stages was also analyzed, to ensure that differences in performance at the test stage were not a result of an earlier difference. For the former, the number of ELP-C and unpressed trials on the last day of lever-press training were analyzed (as all rats had 40 completed trials and almost no uncompleted trials, the variability of all other variables was too low to enable statistical analysis). Performance on the signal attenuation stage was analyzed using a mixed ANOVA performed on the number of collected trials on the three sessions of the signal attenuation stage.

3. Results

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

3.1. Experiment 1: the effects of bilateral HFS of the GP in the PTSA and RE procedures

3.1.1. Anatomical

Fig. 2a presents a photomicrograph of a coronal section taken from a representative GP-HFS rat. The only visible damage in these rats was the electrode tracks toward the target area. Fig. 2b presents a schematic reconstruction of electrode placement in the GP. In all the rats, electrode tips were located within the GP.

3.1.2. Behavioral

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown, ps > 0.14). Fig. 3a and b presents the mean number of ELP-C and ELP-U, respectively, in GP-HFS and sham rats undergoing the test stage of the PTSA or regular extinction procedures. As can be seen, HFS of the GP decreased the number of ELP-C in the two procedures (Two-way ANOVA yielded a significant main effect of Stimulation only, $F(1,37) = 12.584$, $p < 0.0012$; Procedure $F(1,37) = 0.16$, $p = 0.691$, Procedure $\times$ Stimulation interaction, $F(1,37) = 0.493$, $p = 0.487$). In contrast, HFS of the GP reduced the
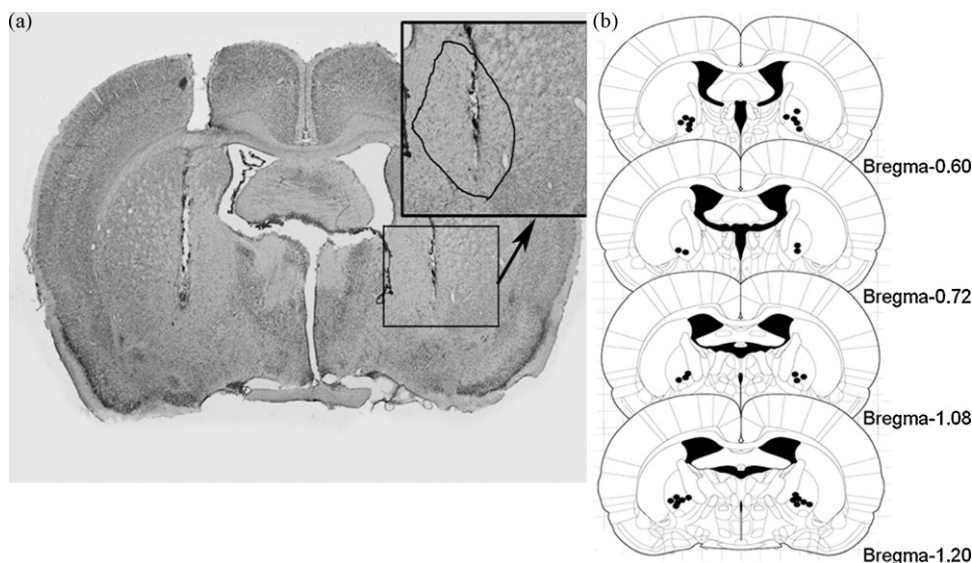
Fig. 2. (a) A photomicrograph of a coronal section taken through the GP in a representative GP-HFS rat. (b) A reconstruction of electrode placement in GP-HFS rats. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson [47] (Experiment 1).

number of ELP-U in rats undergoing PTSA, but had no effect in rats undergoing regular extinction (Two-way ANOVA yielded significant effects of Procedure $F(1,37)=4.711$, $p<0.037$; Stimulation $F(1,37)=12.300$, $p<0.0013$; and Procedure $\times$ Stimulation interaction, $F(1,37)=4.427$, $p<0.043$. Post hoc least significant difference (LSD) comparisons between GP stimulated and sham rats within each procedure yielded a significant difference in the PTSA procedure only, $p<0.0003$). In addition, in the two procedures, HFS of the GP decreased the number of completed trials, lever-presses on the non-reinforced lever (NRL) and nose pokes, and increased the number of unpressed trials, compared to control rats (Table 2). In addition, HFS of the GP decreased the number of uncompleted trials, only in rats undergoing the PTSA procedure (LSD post hoc comparison, $p<0.0061$) (see Table 2 for the full results of the statistical analyses).

3.2. Experiment 2: the effects of bilateral HFS of the EP in the PTSA and RE procedures

3.2.1. Anatomical

Fig. 4a presents a photomicrograph of a coronal section taken from a representative EP-HFS rat. The only visible damage in these rats was the electrode tracks toward the target areas. Fig. 4b presents a schematic reconstruction of electrode placement in the GP. In all the rats, electrode tips were located within the EP.

3.2.2. Behavioral

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown, $ps>0.39$). Fig. 3c and d presents the mean number of ELP-C and ELP-U, respectively, in EP-HFS and sham rats undergoing the test stage of the
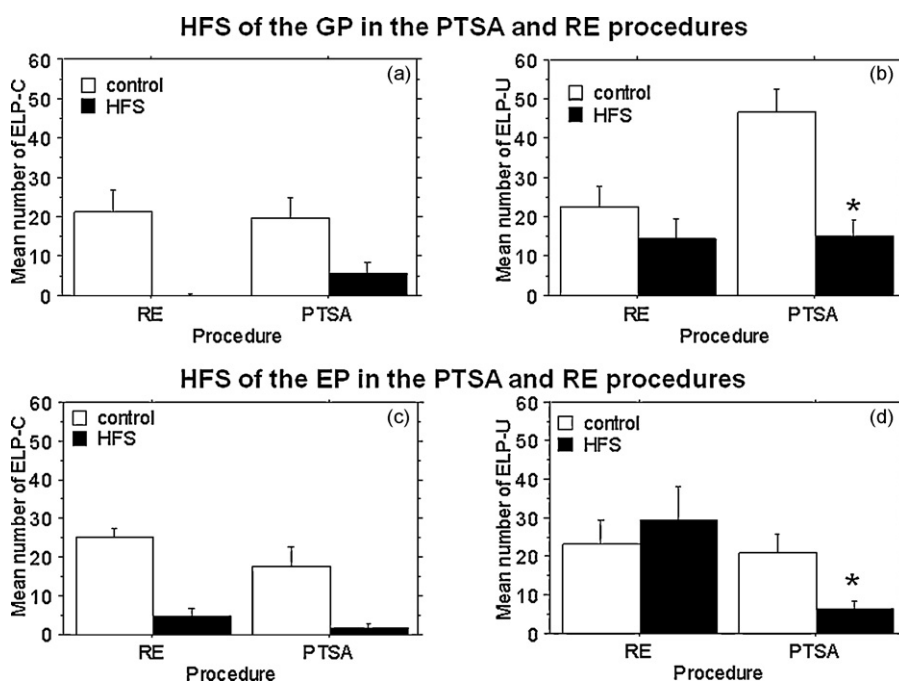

Fig. 3. The mean and standard error of the mean number of (a and c) ELP-C and (b and d) ELP-U in sham and GP-HFS (a and b) or EP-HFS (c and d) rats undergoing the Test stage of the regular extinction (RE) or post-training signal attenuation (PTSA) procedure (Experiments 1 and 2). Asterisk marks a significant difference from the sham group.
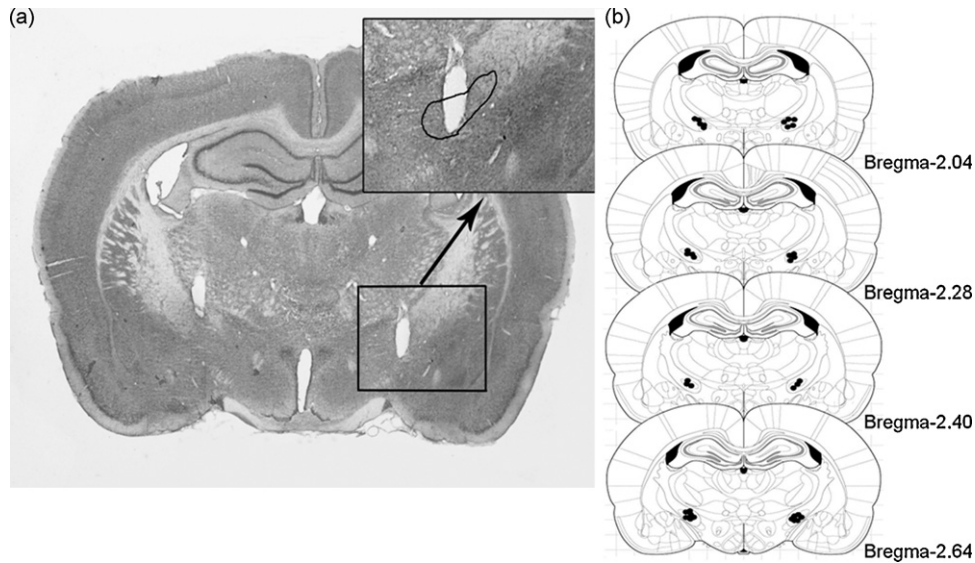
Fig. 4. (a) A photomicrograph of a coronal section taken through the EP in a representative EP-HFS rat. (b) A reconstruction of electrode placement in EP-HFS rats. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson [47] (Experiment 2).

PTSA or regular extinction procedures. As can be seen, HFS of the EP decreased the number of ELP-C in the two procedures (Two-way ANOVA yielded a significant main effect of Stimulation only, $F(1,32)=25.783$, $p<0.0001$; Procedure $F(1,32)=2.276$, $p=0.141$; Procedure × Stimulation interaction, $F(1,32)=0.385$, $p=0.539$). However, HFS of the EP reduced the number of ELP-U in rats undergoing PTSA, but had no effect in rats undergoing regular extinction (Two-way ANOVA yielded a significant effect of Procedure $F(1,32)=5.148$, $p<0.0302$, and a nearly significant Procedure × Stimulation interaction, $F(1,32)=3.605$, $p=0.0667$; [the effect of Stimulation was non-significant, $F(1,32)=0.603, p=0.443$]. Post hoc LSD comparisons between EP stimulated and sham rats within each procedure yielded a significant difference in the PTSA

procedure only, $p<0.047$). In addition, in the two procedures, HFS of the EP decreased the number of completed trials, lever-presses on the non-reinforced lever ($p=0.0513$) and nose pokes, and increased the number of unpressed trials, compared to control rats (Table 3, see Table for the full results of the statistical analyses).

3.3. Experiment 3: the effects of bilateral LFS of the GP and EP in the PTSA procedure

3.3.1. Anatomical

Fig. 5a and b presents a schematic reconstruction of electrode placement in the GP and EP (in matching order). In all the rats,
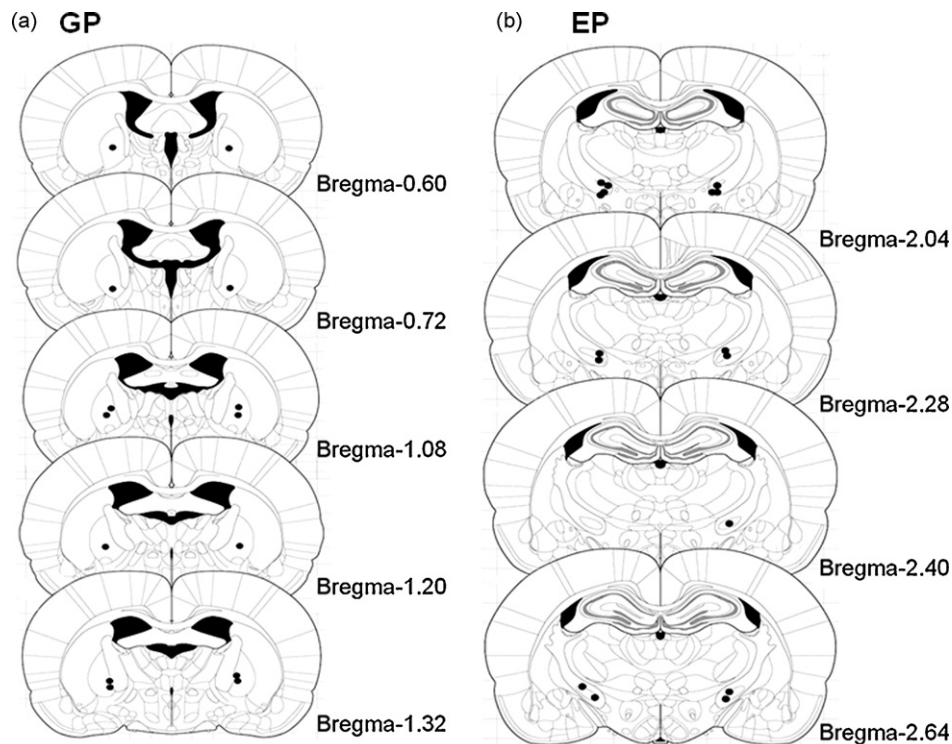

Fig. 5. A reconstruction of electrode placement (a) in the GP in GP-LFS rats and (b) in the EP in EP-LFS rats. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson [47] (Experiment 3).

Table 2
Performance in the Test under bilateral HFS of the GP in the PTSA and RE procedures (Experiment 1, mean (SE)).

	Completed trials	Uncompleted trials	Unpressed trials	Lever-presses on NRL	Nose pokes
PTSA - Sham	7.846 (1.764)	8.692 (1.015)	33.385 (2.286)	18.000 (6.207)	59.462 (20.185)
PTSA- HFS	1.875 (0.953)	4.000 (0.779)	40.000 (1.524)	4.000 (2.252)	11.000 (4.145)
RE - Sham	16.833 (3.468)	4.833 (1.014)	28.333 (3.702)	13.250 (2.568)	108.417 (15.959)
RE- HFS	1.250 (0.620)	5.250 (1.612)	43.500 (1.592)	2.375 (0.596)	10.875 (6.963)
Procedure × Stimulation ANOVA					
Procedure	$F_{(1,37)} = 2.939$, $p = 0.0948$	$F_{(1,37)} = 1.290$, $p = 0.2634$	$F_{(1,37)} = 0.960$, $p = 0.3336$	$F_{(1,37)} = 0.510$, $p = 0.4795$	$F_{(1,37)} = 2.132$, $p = 0.1527$
Stimulation	$F_{(1,37)} = 19.527$, $p < 0.0001$	$F_{(1,37)} = 3.464$, $p = 0.0707$	$F_{(1,37)} = 20.702$, $p < 0.0001$	$F_{(1,37)} = 7.768$, $p < 0.0084$	$F_{(1,37)} = 19.063$, $p < 0.0001$
Procedure × Stimulations	$F_{(1,37)} = 3.883$, $p = 0.0536$	$F_{(1,37)} = 4.946$, $p < 0.0324$	$F_{(1,37)} = 0.645$, $p = 0.4270$	$F_{(1,37)} = 0.123$, $p = 0.7282$	$F_{(1,37)} = 2.154$, $p = 0.1506$

Table 3
Performance in the Test under bilateral HFS of the EP in the PTSA and RE procedures (Experiment 2, mean (SE)).

|	Completed trials	Uncompleted trials	Unpressed trials	Lever-presses on NRL	Nose pokes
PTSA - Sham	10.455 (2.038)	4.455 (0.705)	35.091 (2.034)	10.273 (3.778)	47.818 (9.658)
PTSA- HFS	2.100 (0.752)	3.400 (0.980)	44.500 (1.522)	5.500 (2.531)	11.900 (3.863)
RE - Sham	27.125 (3.014)	6.000 (1.363)	16.875 (1.865)	8.500 (2.686)	127.000 (29.185)
RE- HFS	4.143 (1.370)	7.857 (1.143)	38.000 (1.431)	1.000 (0.535)	36.714 (15.562)
Procedure × Stimulation ANOVA					
Procedure	$F_{(1,32)} = 22.300$, $p < 0.0001$	$F_{(1,32)} = 8.378$, $p < 0.0069$	$F_{(1,32)} = 45.124$, $p < 0.0001$	$F_{(1,32)} = 1.071$, $p = 0.3085$	$F_{(1,32)} = 10.859$, $p < 0.0025$
Stimulation	$F_{(1,32)} = 62.533$, $p < 0.0001$	$F_{(1,32)} = 0.150$, $p = 0.7013$	$F_{(1,32)} = 68.869$, $p < 0.0001$	$F_{(1,32)} = 4.100$, $p = 0.0513$	$F_{(1,32)} = 15.991$, $p < 0.0005$
Procedure × Stimulations	$F_{(1,32)} = 13.625$, $p < 0.0009$	$F_{(1,32)} = 1.971$, $p = 0.1699$	$F_{(1,32)} = 10.139$, $p < 0.0033$	$F_{(1,32)} = 0.202$, $p < 0.6558$	$F_{(1,32)} = 2.968$, $p = 0.0946$
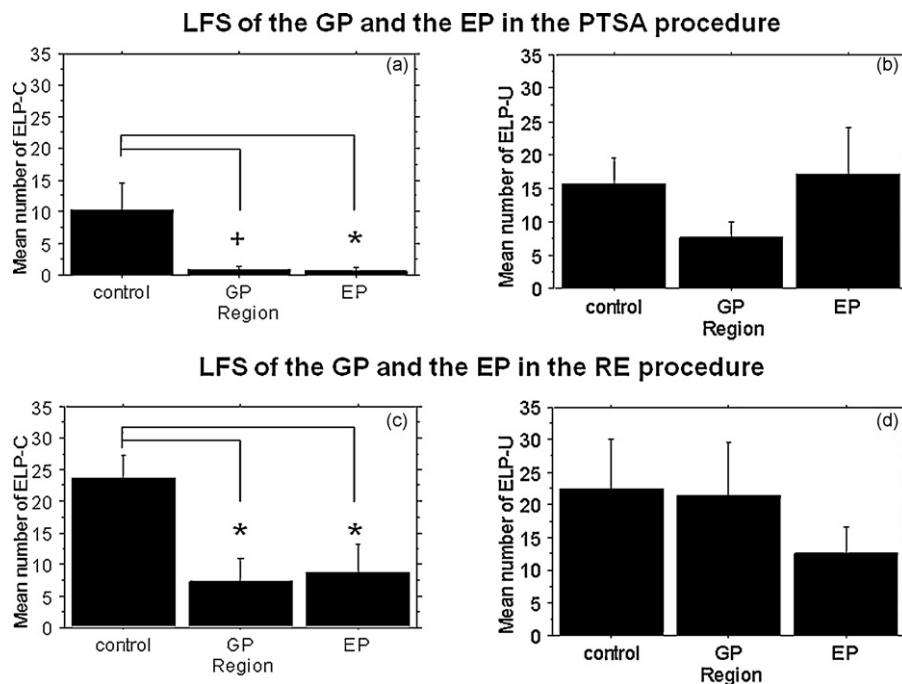
Fig. 6. The mean and standard error of the mean number of (a and c) ELP-C and (b and d) ELP-U in sham, GP-LFS and EP-LFS rats undergoing the Test stage of the post-training signal attenuation procedure (a and b, Experiment 3) or regular extinction procedure (c and d, Experiment 4). Asterisk marks a significant difference from the sham group. + marks a near significant difference from the sham group.

electrode tips were located within the proper region and the only visible damage was the electrode tracks toward the target areas.

3.3.2. Behavioral

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown, $ps > 0.24$). Fig. 6a and b presents the mean number of ELP-C and ELP-U, respectively, in GP-LFS, EP-LFS and sham rats undergoing the test stage of the PTSA procedure. As can be seen, LFS of the two regions tended to decrease the number of ELP-C, $F(2,23) = 2.951$, $p = 0.072$ (post hoc LSD comparisons revealed a significant difference between the EP-LFS and sham groups, $p < 0.0485$, and a nearly significant difference between the GP-LFS and sham groups, $p = 0.0592$), without affecting the number of ELP-U ($F(2,23) = 1.014$, $p = 0.378$). In addition, LFS of both regions decreased the number of completed trials and nose pokes, and increased the number of unpressed trial, compared to sham rats (Table 4, see Table for the full results of the statistical analyses).

3.4. Experiment 4: the effects of bilateral LFS of the GP and EP in the RE procedure

3.4.1. Anatomical

Fig. 7a and b presents a schematic reconstruction of electrode placement in the GP and EP (in matching order). In all the rats, electrode tips were located within the proper region and the only visible damage was the electrode tracks toward the target areas.

3.4.2. Behavioral

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown, $ps > 0.9$). Fig. 6c and d presents the mean number of ELP-C and ELP-U, respectively, in GP-LFS, EP-LFS and sham rats undergoing the test stage of the RE procedure. As can be seen, in both regions LFS decreased the number of ELP-C, $F(2,20) = 5.784$, $p < 0.011$ (post hoc LSD comparisons between GP or EP stimulated and sham rats revealed both to be significant $p < 0.008$ and $p < 0.0126$). In both regions, LFS had no significant effect on ELP-U, $F(2,20) = 0.561$, $p = 0.579$. In addition, LFS

Table 4
Performance in the Test under bilateral LFS of the GP or the EP in the PTSA procedure (Experiment 3, Mean (SE)).

|	Completed trials	Uncompleted trials	Unpressed trials	Lever-presses on NRL	Nose pokes
GP- LFS	0.857 (0.404)	3.000 (0.690)	46.143 (0.962)	3.143 (1.487)	8.714 (3.428)
EP-LFS	0.750 (0.313)	4.375 (1.194)	44.875 (1.274)	1.875 (0.718)	19.625 (3.746)
Control	6.909 (2.380)	4.727 (0.875)	38.364 (2.495)	5.091 (1.734)	62.545 (12.154)
One-way ANOVA					
Region (GP, EP and control)	$F(2,23) = 4.288$, $p < 0.0262$	$F(2,23) = 0.833$, $p = 0.4476$	$F(2,23) = 4.607$, $p < 0.0209$	$F(2,23) = 1.263$, $p = 0.3017$	$F(2,23) = 9.890$, $p < 0.0009$
Significant Fisher PLSD Post hoc	Control, GP: $p < 0.0260$; control, EP: $p < 0.0191$		Control, GP: $p < 0.0128$; control, EP: $p < 0.0275$		Control, GP: $p < 0.0006$; control, EP: $p < 0.0029$
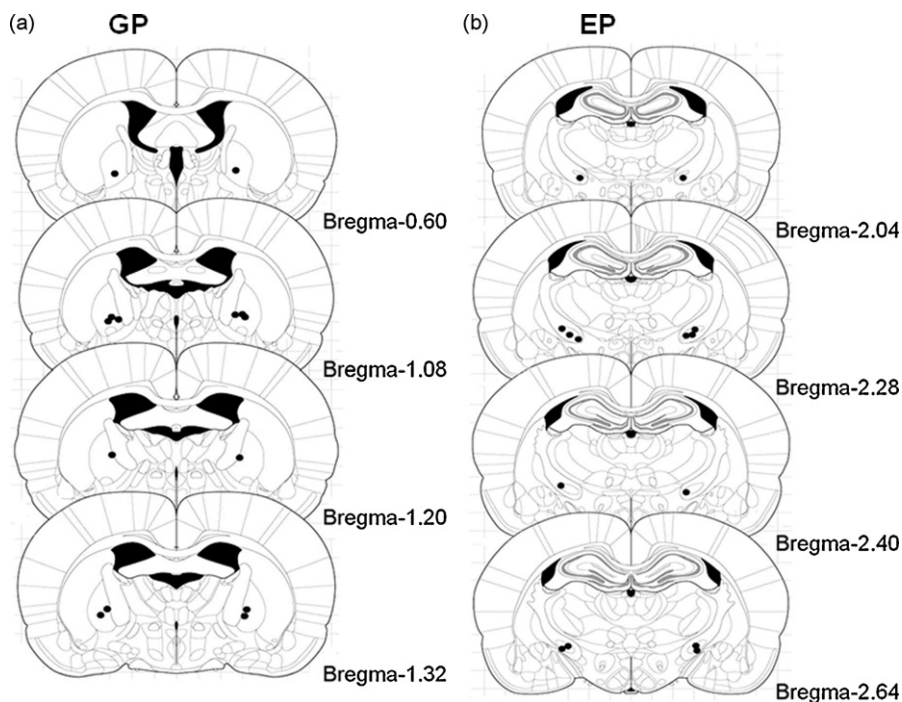
Fig. 7. A reconstruction of electrode placement (a) in the GP in GP-LFS rats and (b) in the EP in EP-LFS rats. Coordinates of the coronal sections are indicated with reference to Bregma according to the stereotaxic atlas of Paxinos and Watson [47] (Experiment 4).

of both regions decreased the number of completed trials and nose pokes, and increased the number of unpressed trials compared to sham rats. In addition, LFS of the EP tended to decrease the number of NRL (Table 5, see Table for the full results of the statistical analyses).

4. Discussion

The present study tested the effects of HFS and LFS of the GP and EP on compulsive lever-pressing, assessed in the signal attenuation rat model of OCD. The effects of each of these manipulations were assessed in rats undergoing an extinction test of lever-press responding that was or was not preceded by signal attenuation (the PTSA and 'regular extinction' procedures, respectively). This design allows the differentiation between the effects of signal attenuation and of extinction per se. Briefly, a manipulation-induced effect on compulsive responding is evidenced in a change in the number of excessive lever-presses that are not followed by magazine entry (ELP-U) in the PTSA procedure but not in the regular extinction procedure, whereas a manipulation-induced effect on extinction is manifested in a change in the number of excessive lever-presses that are followed by magazine entry (ELP-C) in both the PTSA and regular extinction procedures (for a detailed discussion see [23]).

It should be noted that although typically the number of ELP-U is higher in rats undergoing the PTSA procedure compared to rats undergoing the regular extinction procedure, this is not always the case, especially in Sprague–Dawley rats, used in the present study [7]. Whereas the reason for this strain difference is not known, the fact that also in Sprague–Dawley rats SSRIs reduce ELP-U in PTSA but not in regular extinction [7] indicates that only signal attenuation-induced ELP-U are a form of compulsive behavior.

The main finding of the present study is that HFS, but not LFS, of the GP and EP exerted an anti-compulsive effect, although stimulation of the two nuclei at both low and high frequency exerted a similar effect on other behavioral measures. More specifically, HFS, but not LFS, of both the GP and EP decreased ELP-U in the PTSA but not in the regular extinction procedure, that is, selectively decreased the number of compulsive lever-presses. In contrast, HFS and LFS of the GP and EP decreased the number of ELP-C, completed trials and nose pokes, and increased the number of unpressed trials, in both the PTSA and regular extinction procedures. These effects may reflect facilitation of extinction, but may also be the result of a general decrease in behavioral output. In addition, HFS of the GP and EP decreased the number of lever presses on the NRL in the two procedures, and LFS of the EP tended to decrease this behavioral measure in the regular extinction procedure.

Table 5
Performance in the Test under bilateral LFS of the GP or the EP in the regular extinction procedure (Experiment 4, Mean (SE)).

	Completed trials	Uncompleted trials	Unpressed trials	Lever-presses on NRL	Nose pokes
GP- LFS	10.571 (2.680)	7.429 (2.256)	32.000 (3.612)	9.429 (3.030)	93.286 (32.887)
EP-LFS	9.714 (3.469)	6.429 (1.043)	33.714 (3.490)	1.143 (0.857)	83.143 (20.407)
Control	30.889 (2.680)	5.111 (1.611)	14.000 (2.759)	8.000 (2.784)	227.667 (51.579)
One-way ANOVA					
Region (GP, EP and Control)	$F(2,20)=13.691, p<0.0003$	$F(2,20)=0.484, p=0.6234$	$F(2,20)=12.183, p<0.0004$	$F(2,20)=2.880, p=0.0796$	$F(2,20)=4.201, p<0.0301$
Significant Fisher PLSD Post hoc	Control, GP: $p<0.0004$; control, EP: $p<0.0003$	None	Control, GP: $p<0.0008$; control, EP: $p<0.0004$	Control, EP: $p=0.0654$	Control, GP: $p<0.0284$; control, EP: $p<0.0195$

Although HFS of the GP and EP markedly reduced behavioral output, their anti-compulsive effect does not seem to be a result of a non-specific effect, because (i) in both cases there was no effect on the number of ELP-U in regular extinction, and (ii) LFS of the GP and EP, which also markedly decreased behavioral output, did not affect compulsive lever-pressing. The anti-compulsive effect of HFS of the EP and GP also cannot be explained by their effect on the tendency to nose-poke, because a reduction in nose pokes may be expected to increase the number of lever-presses that are not followed by a nose-poke, that is, to increase the number of ELP-U.

Interestingly, another effect which was obtained following high- but not low-frequency stimulation of the GP and EP was a decrease in the number of lever-presses on the NRL which was evident in both the PTSA and regular extinction procedures. While clearly lever-presses on the NRL are a form of inappropriate behavior, they do not seem to reflect compulsive responding because they are not consistently antagonized by SSRI (unpublished data; for further discussion of similarities and differences between compulsive lever-presses and lever-presses on the NRL see [30]).

There are only a few studies on the behavioral effects of electrical stimulation of the EP and GP in rodents. HFS of the GP prolonged reaction time and decreased the number of premature responses in a choice reaction time task [62], supporting the possibility that GP-HFS results in a general decrease in behavioral output. This possibility is in line with the results of lesion studies which found a decrease in behavioral output following GP lesions [10,16,74]. HFS of the EP improved dystonia in a mutant hamster model of idiopathic paroxysmal non-kinesiogenic dystonia [20]. The effect of HFS in the present study does not seem to reflect a general decrease in behavioral output, however, because lesion and inactivation of the EP can either reduce behavioral output [11,54,71] or increase it [4] depending on the task used [8]. Indeed in humans, HFS and lesion of the GPi are used to treat both hypokinetic and hyperkinetic movement disorders, including Parkinson's disease, dystonia, Tourette's syndrome, chorea and hemiballism [1,33,35,36,40,56,68,70,72].

A decrease in compulsive responding in the signal attenuation model combined with the facilitation of extinction has also been found following HFS of the STN [32]. Thus, HFS of these three highly interconnected nuclei exerts a similar behavioral effect. This finding is hard to explain using current views of basal ganglia-thalamo-cortical circuitry, according to which activity in the direct (striatum → EP) and indirect (striatum → GP → STN → EP) pathways exerts opposing effects on behavioral output (e.g. [3]) Therefore, regardless of the precise mechanism of action of HFS, which is still controversial [e.g. 9,21,37,38,44,45], HFS of the three nuclei is not expected to exert the same behavioral effect. One possible explanation to this paradox is that activation of passing fibers contributed to the observed effects. Such a possibility applies especially for the rat EP, whose neurons are embebbed in the internal capsule, where corticofugal fibers travel [48].

We would like to note that the fact that the current results are hard to explain using current models of basal ganglia functioning does not detriment from their possible clinical importance. Indeed, there are several similar paradoxes in basal ganglia research. For example, lesion to both the GPi and thalamus alleviate symptoms in Parkinson's disease, an observation that led Marsden and Obeso [42] to write a paper titled "The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease" [42]. Another possible paradox is the observation that HFS and lesion to the GPi are used to treat both hypokinetic and locomotor dysfunctions [31,66,69]. Similarly, HFS of the STN has been shown to alleviate both obsessive-compulsive and Parkinsonian symptoms, which have been postulated to originate from opposing basal ganglia-thalamocortical network pathologies [31,41].

Although the extrapolation from a rat model to the clinical condition should be made with great caution, the present finding supports the possibility that HFS of the GP and EP may be effective in alleviating symptoms in OCD patients. It is noteworthy that although HFS of the GPe is much less common as a treatment for PD compared to HFS of the GPi and STN [e.g. 34,35,64], there are several reports that HFS of the GPe is also effective in alleviating Parkinsonian symptoms [65,73], providing another demonstration of similar behavioral effects of HFS of these three nuclei.

Acknowledgments

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