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Research report

REM sleep deprivation and dopaminergic D2 receptors modulation increase recognition memory in an animal model of Parkinson's disease

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ABSTRACT

Cognitive impairment is an important non-motor symptom of Parkinson's disease (PD). The neuronal death in nigrostriatal pathway is the main factor for motor symptoms and recent studies indicate a possible influence in non-motor symptoms as well. The pedunculopontine tegmental nucleus (PPT) and basal ganglia are closely related anatomically and functionally and, since they are affected by neurodegeneration in PD, they might be involved in recognition memory. To investigate this, we promoted an ibotenic acid lesion within the PPT or a rotenone lesion within substantia nigra pars compacta (SNpc) of Wistar rats, followed by 24 h of REM sleep deprivation (REMSD). Then, we administered a dopaminergic D2 receptor agonist (piribedil, 3 μg/μl), antagonist (raclopride, 10 μg/μl) or vehicle (dimethylsulfoxide) directly in the striatum and the animals were submitted to the object recognition test (ORT). We observed that raclopride administration impaired object recognition memory as well as rotenone and ibotenic acid lesion. Interestingly, REMSD reversed the deleterious effects induced by these drugs. Also, raclopride administration after rotenone lesion allowed the animal to explore the new object for a longer time compared to the familiar object, suggesting that raclopride has a dual effect, dependent of the treatments. These findings suggest a role for PPT, SNpc and striatum in recognition memory and points the D2 receptors modulation and REMSD as possible targets for cognitive deficits in Parkinson's disease.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a loss of dopaminergic neurons in substantia nigra pars compacta (SNpc). In consequence, there is a decrease of dopaminergic tone, leading to the so-called motor signs, represented by rest tremor, disturbances in balance, bradykinesia, among others [1,2]. Although the motor alterations are the hallmark of the disease, several non-motor disturbances also affect the quality of life of PD patients. Complaints of sleep disturbances, olfactory dysfunctions, anxiety, depression and cognitive deficits are very frequent and normally appear before the onset of the motor symptoms [3].

Cognitive deficits observed in PD are mainly represented by executive function impairments, memory dysfunctions and visuospatial disturbances [4]. Different studies suggest that recognition memory is impaired in both PD patients and animal models of Parkinsonism [5–8]. [9] observed impaired long-term, but not short-term, object recognition memory in a mouse model of Parkinsonism, reversed by dopamine D1 receptor agonist administration [9]. Also, Sy and colleagues [10] demonstrated an impairment in recognition memory of rats that received 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [10]. However, clinical studies for cognitive deficits in PD are controversial, considering the types (working memory, recognition memory, among others) and the processes (encoding, consolidation and/or retrieval) of memory affected [11–14].

Several brain structures are associated with the recognition memory such as the perirhinal cortex and the hippocampus [15–19]. In fact, some neurons within the medial temporal lobe are likely the major contributors to this process. Studies report that these neurons have a reduced response to a familiar visual stimulus compared to a novel visual stimulus [20]. Synaptic plasticity mechanisms by means of long-term potentiation (LTP) and long-term depression (LTD) are supposedly associated to this neuronal response [21,22]. In addition, these processes appear to be largely dependent on NMDA receptors [23].

Abbreviations: DA, Dopamine; NA, Noradrenaline; OF, Open field test; ORT, Object recognition test; PD, Parkinson's disease; PPT, Pedunculopontine tegmental nucleus; REB, Sleep rebound period; REMSD, REM sleep deprivation; SNpc, Substantia nigra pars compacta

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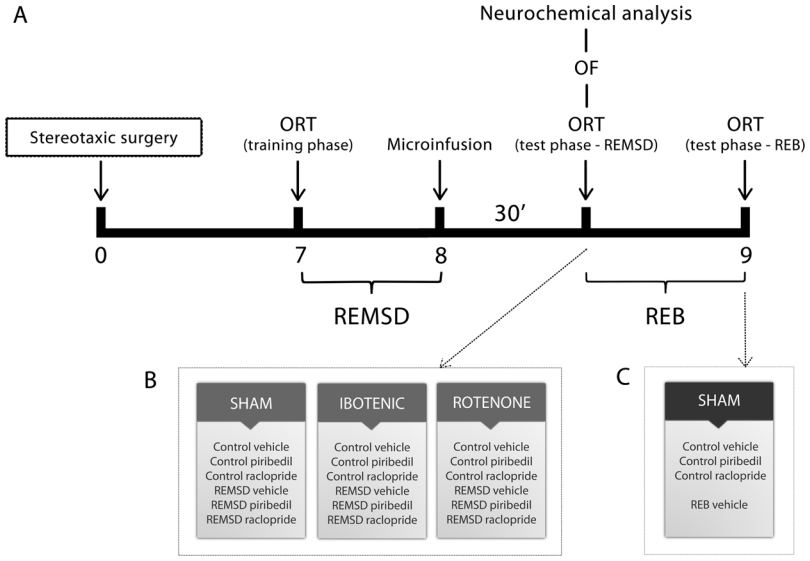

Fig. 1. Experimental design. Experimental design (A), groups after REMSD (B), groups after REB period (C). OF, open field test; ORT, object recognition test; REMSD, REM sleep deprivation; REB, rebound period.

However, how synaptic plasticity mediates this neuronal response remains to be determined [19]. Along with that, the dopaminergic system seems to play an important role [17,24]. In fact, [25] observed that D1 receptor antagonist SCH23390 impaired the long-term object recognition memory when infused in the perirhinal cortex, but not when infused in the hippocampus, while D1 receptor agonist SKF38393 increased this memory when infused in perirhinal cortex, but not in the hippocampus [25]. Conversely, [26] demonstrated a role for dopaminergic receptors within the hippocampus in modulating the recognition memory while the role of these receptors within the nigrostriatal pathway are not completely understood [26].

The dopaminergic system also plays a significant role in rapid eye movement (REM) sleep regulation. In a previous study, we demonstrated that striatal D2 receptors activation increased the time spent in REM sleep after REM sleep deprivation (REMSD) in animals with a lesion in the pedunculopontine tegmental nucleus (PPT), which is classically associated with REM sleep regulation [27]. In addition, [28] observed that the blockade of D2 receptors decreased the time spent in REM sleep after REMSD [28]. However, other structures and neurotransmitter systems are associated with REM sleep regulation, for example, the so-called “REM-on” neurons from the sublaterodorsal nucleus and mesopontine tegmentum, which inhibits the “REM-off” neurons from the ventrolateral periaqueductal gray matter and lateral pontine tegmentum. The REM-off also inhibits the REM-on neurons, producing a “flip-flop” switch, that represents the abrupt transitions between NREM and REM sleep [29]. This REM switch is modulated by the cholinergic neurons from PPT (promoting REM sleep) and noradrenergic and serotoninergic neurons from the locus coeruleus and dorsal raphe nucleus, respectively (inhibiting REM sleep) [30,31]. Along with that, REM sleep and, consequently, REMSD are known to affect memory processes [32,33]. Studies showed that recognition memory was impaired by both D2 receptors blockade and REMSD and that D2 receptors activation reversed this impairment [33,34]. This highlights the complex relationship among recognition memory, REM sleep and dopaminergic system.

The PPT, SNpc and striatum are affected in PD and have a similar pattern of inputs and outputs, including the cortex, thalamus, amygdala and brainstem [35]. Forster and Blaha [36] demonstrated that electrical stimulation of the PPT evokes an efflux of striatal dopamine that seems to be accomplished via cholinergic and glutamatergic afferents to dopaminergic cells of SNpc [36]. In addition, striatal dopaminergic stimulation affects the PPT, demonstrated by an increase in c-Fos expression [37]. Functionally, these structures are also related, being associated with motricity, sleep regulation and memory processes [27,35,38]. Considering this, we aimed to investigate the role of PPT, SNpc and striatum in recognition memory in a context of Parkinsonism. We used REMSD to mimic sleep disturbances that occurs in individuals with PD and modulated the striatal D2 receptors to investigate a possible counteracting effect over the expected cognitive deficits produced by PPT lesion, SNpc lesion or REMSD.

2. Materials and methods

2.1. Subjects

The experiments performed in this study were approved by the ethics committee of Federal University of Paraná (approval ID #655) and conducted according to the guidelines of ethics and experimental care and use of laboratory animals (SBCAL). All efforts were made to minimize animal suffering and to reduce the number of animals used. The male Wistar rats, weighing 280–330 g, were maintained in a temperature controlled room (22 °C ± 2 °C) with a 12-h light-dark cycle (lights on at 7:00 AM). The housing consisted in polypropylene cages, where the animals were maintained in groups of 5 animals per cage. Bottles of water and pellets of food were available throughout the entire experiment.

2.2. Experimental design

The experimental design is represented in Fig. 1. Initially, the animals underwent stereotaxic surgery for ibotenic acid infusion within the PPT or rotenone infusion within the SNpc. In addition, bilateral guide cannulas were implanted within the dorsal striatum. After an interval of 7 days for recovery purposes, the animals performed the training phase of the object recognition test (ORT), followed by 24 h of REMSD. Afterwards, the animals received a bilateral striatal infusion of D2 receptor agonist piribedil (3 μg/μl), D2 receptor antagonist raclopride (10 μg/μl) or vehicle (Dimethylsulfoxide [DMSO]) [27]. Thirty minutes later, the rats were submitted to the test phase of ORT and to the open field test (OF). A group of animals were decapitated and their brains were removed for neurochemical analysis, while the other group were re-tested in the ORT (24 h after striatal infusion) to evaluate the effect of sleep rebound period (REB) and possible reminiscent effects of the drugs.

2.3. Stereotaxic surgery

The animals were initially sedated with intraperitoneal xylazine

(10 mg/kg; Syntec do Brasil Ltda, Brazil) and anesthetized with intraperitoneal ketamine (90 mg/kg; Syntec do Brasil Ltda, Brazil). For ibotenic acid infusion within the PPT or rotenone infusion within the SNpc, the following coordinates were used, bregma as a reference: PPT (AP) = − 7.8 mm, (ML) = ± 2.0 mm and (DV) = − 7.4 mm; SNpc (AP) = − 5.0 mm, (ML)= ± 2.1 mm e (DV) = − 8.0 mm [39]. Ibotenic acid (0.12 M; Tocris Bioscience®, United Kingdom) or saline infusions of 0.2 µl in each hemisphere were made in steps, separated by intervals of 10 s, totalizing 200 s of injection [40]. Rotenone (12 µg/µl; Sigma-Aldrich®, United States) or DMSO 10% v/v (Sigma-Aldrich®, United States) infusions of 1 µl in each hemisphere were made at a rate of 0.33 µl/min for 3 min [41]. These infusions were made using an electronic infusion pump (Insight Instruments, Ribeirão Preto, Brazil). For bilateral guide cannulas implantation, the following coordinates were used, bregma as a reference: Striatum (AP) = − 1.0 mm, (ML) = ± 3.0 mm and (DV) = − 6.0 mm [39].

2.4. REM sleep deprivation (REMSD) procedure

The single platform method was used for REMSD procedure. Briefly, the animals were individually placed in a circular platform (6.5 cm in diameter) inside of a tank (23 × 23 × 35 cm) filled with water up 1 cm below the platform surface for 24 h. Once the animal experiences a REM sleep episode, it loses its muscular tonus and falls into the water, being awakened. A detailed description of the procedure is present in previous studies [41,42].

2.5. Striatal infusions

The awake animals were gently immobilized for striatal infusions of 1 µl of piribedil (3 µg/µl; Tocris Bioscience®, United Kingdom), raclopride (10 µg/µl; Sigma-Aldrich®, United States) or DMSO (10% v/v; Sigma-Aldrich®, United States). The infusions were made at the bilateral guide cannulas (implanted during stereotaxic surgery), at a rate of 0.33 µl/min for 3 min, with the assistance of an electronic infusion pump (Insight Instruments, Ribeirão Preto, Brazil).

2.6. Object recognition test (ORT)

The apparatus consists of an open box (width × length × height = 80 cm × 80 cm × 50 cm) made of wood and covered with a black opaque plastic film. The objects to be discriminated were available in triplicate copies and were made of a biologically neutral material such as glass, plastic or metal. Also, they are not known to have any ethological significance for the rats. This test is based in the tendency of the animals to explore new things instead of familiar things. Thus, when an animal remembers a familiar object and does not know a new object, there is a tendency of this animal to explore the new object for a longer time when compared to the familiar object [43]. The object recognition test in this study consisted of two phases: a sample/training phase and a choice/test phase [43–45]. In the training phase, two identical objects were exposed in the back corners of the open box, 10 cm away from the sidewall. The rat was placed in the open box facing away from the objects and after 3 min of exploration, the rat was removed from the open box and returned to its cage. After a delay of 15 min, the rat was reintroduced to the open box and the training phase was started again for further 3 min. This situation was repeated for one more time. After REMSD, there was a training phase, followed by a test phase after an interval of 15 min. In the test phase, two objects were presented in the same locations that were occupied by the previous sample objects. One of the objects was identical to the object seen in the training phase and the other one was different. The same procedure was replicated after the REB period. The tests were video recorded and analyzed by a blind experimenter. It was considered as exploration only when the rat touched the object with its nose or when the rat's nose was directed toward an object at a distance ≤2 cm.

2.7. Open field test (OF)

The apparatus consists of a circular arena (1 m of diameter) limited by a 40-cm-high wall and illuminated by four 60-W lamps situated 100 cm above the arena floor, providing illumination around 300 lx. The animals were gently placed in the center of the arena and could freely explore the area for 5 min. During the experiments, the OF was video recorded and the measure for ambulatory distance was computed online by an image analyzer (Smart Junior, PanLab, Harvard Apparatus, Spain).

2.8. Neurochemical analysis

For neurochemical analysis, the brains were removed from skulls after decapitation and the hippocampus were dissected. The endogenous concentrations of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxytryptamine/serotonin (5-HT), noradrenaline (NA) and 3, 4-dihydroxyphenylethyleneglycol (DHPG) were assayed by reverse phase HPLC (High performance liquid chromatography) with electrochemical detection. A detailed description of the procedure is present in other studies [46].

2.9. Statistical analysis

The normal distribution of the data was assessed by the Kolmogorov-Smirnov test. Differences between groups were assessed by three-way ANOVA (open field test and neurochemical analysis), repeated measures three-way ANOVA (object recognition test), repeated measures one-way ANOVA (object recognition test for reminiscent effects of drugs in REB), paired *t*-test (object recognition test for reminiscent effects of REMSD in REB). Fisher's post hoc test was carried when necessary. Values were expressed as mean ± standard error of mean (SEM). The level of significance was set at $P < 0.05$.

3. Results

3.1. Object recognition test (ORT)

3.1.1. REMSD period effects

Fig. 2A shows that the sham control vehicle group ($P < 0.05$), sham control piribedil group ($P < 0.05$) and the sham REMSD groups ($P < 0.001$, for all) spent more time exploring the new object compared to the familiar object, demonstrating that these animals differentiated the objects. Also, the sham REMSD raclopride group spent more time exploring the new object compared to its control group ($P < 0.01$). In fact, we found an influence of the objects [$F(1,173) = 99.25$, $P < 0.001$], REMSD [$F(1,173) = 8.76$, $P < 0.01$] and the interactions objects × REMSD [$F(1,173) = 11.63$, $P < 0.001$] and objects × REMSD × D2 receptors modulation [$F(2,173) = 3.69$, $P < 0.05$] in our results.

Surprisingly, REMSD reversed the impairment induced by ibotenic acid infusion (Fig. 2B), since the ibotenic acid REMSD groups explored the new object for a longer time compared to the exploration of the familiar one ($P < 0.001$ for vehicle and piribedil, $P < 0.01$ for raclopride group). Also, the ibotenic acid REMSD vehicle and piribedil groups spent more time exploring the new objects compared to its respective controls ($P < 0.05$ for vehicle and $P < 0.01$ for piribedil group).

The animals that received rotenone within the SNpc (Fig. 2C) showed increased exploration of the new object, compared to the familiar one, only when raclopride was administered ($P < 0.01$). Similarly to the previous result with ibotenic acid lesion, REMSD reversed the deleterious effects of rotenone administration, demonstrated by an increased exploration of the new object in rotenone REMSD groups compared to its respective controls ($P < 0.05$ for vehicle, $P < 0.001$

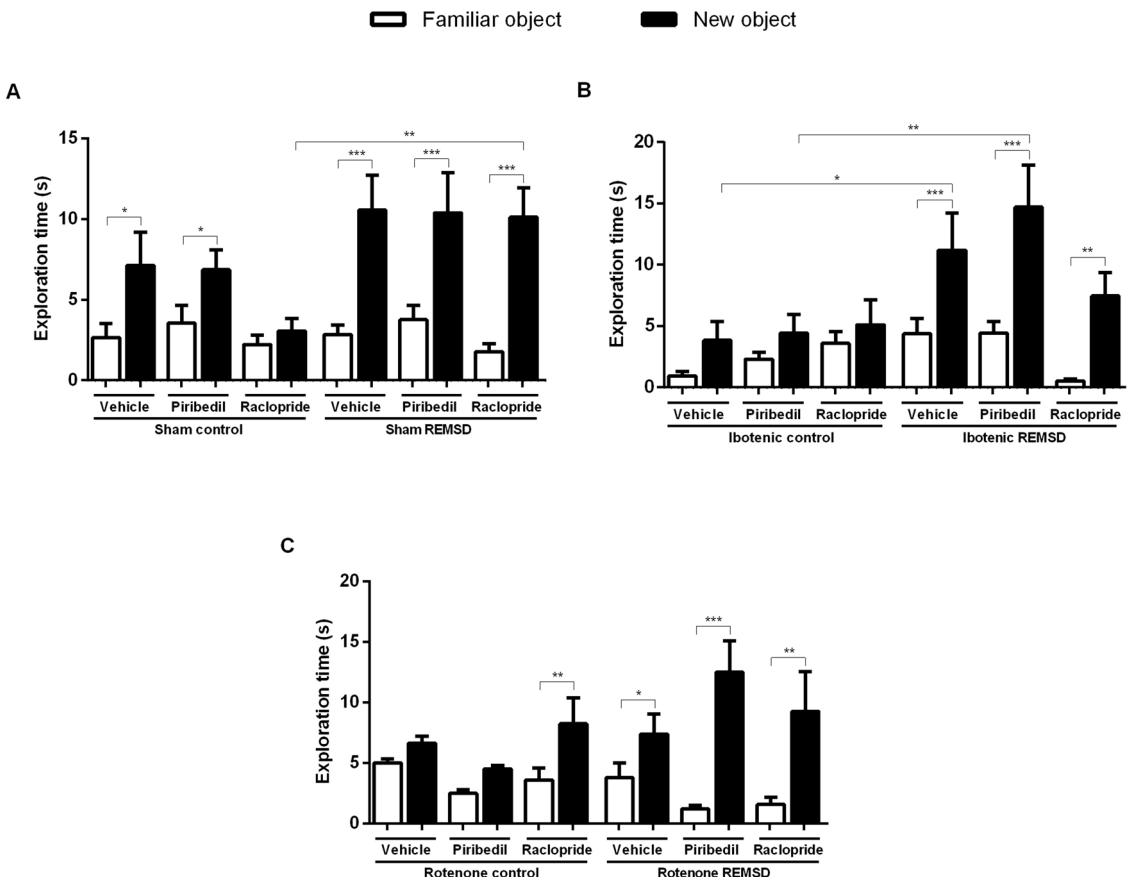

Fig. 2. Object recognition test. Time spent exploring the objects in sham groups (A), ibotenic acid groups (B) and rotenone groups (C). Values are expressed as mean ± SEM. *P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001. Repeated measures three-way ANOVA followed by the Fisher's post hoc test. n = 10-12 animals/group.

for piribedil and $P < 0.01$ for raclopride group).

3.1.2. Rebound period effects

Complementarily, we investigated if D2 receptors modulation effects would persist 24 h after striatal infusions (Fig. 3A). As expected, the sham control raclopride group recovered its cognitive ability, demonstrated by the longer time exploring the new object compared to the familiar one ($P < 0.05$). Also, we aimed to investigate if the ability to recognize the new object would change after REB for the animals that were REM sleep deprived (Fig. 3B). We did not see any changes regarding this aspect, since the sham REB vehicle group demonstrated a similar behavior compared to the sham REMSD vehicle group, exploring the new object for a longer period compared to the familiar one ($P < 0.001$).

3.1.3. Open field test (OF)

We did not find effects of the treatments in sham groups (Fig. 4A) and ibotenic acid groups (Fig. 4B). However, a treatment effect was observed in rotenone groups (Fig. 4C), demonstrated by a decreased distance in the rotenone control raclopride group and rotenone REMSD raclopride group compared to its respective rotenone piribedil groups ($P < 0.05$ for rotenone control raclopride and $P < 0.01$ for rotenone

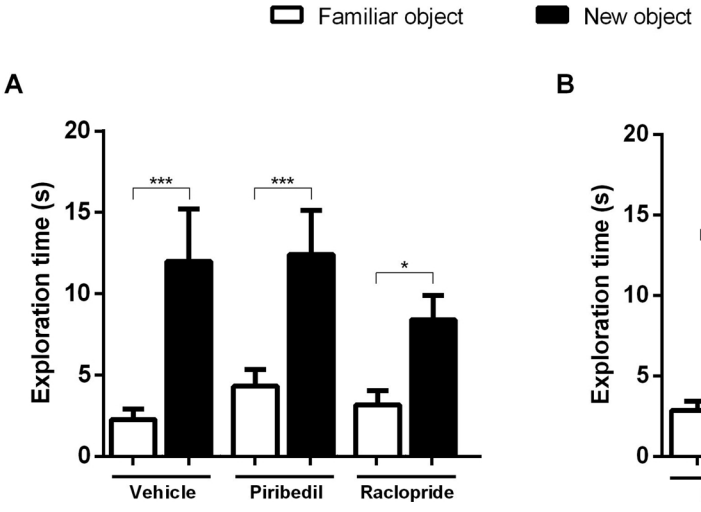

Fig. 3. Rebound period effects. Time spent exploring the objects 24 h after drugs administration in sham control groups (A) and 24 h after REMSD has ended (REB) in sham vehicle groups. Values are expressed as mean ± SEM. *P ≤ 0.05, ***P ≤ 0.001. Repeated measures one-way ANOVA followed by the Fisher's post hoc test (A), paired *t*-test (B). n = 10-12 animals/group. REB, sleep rebound period.

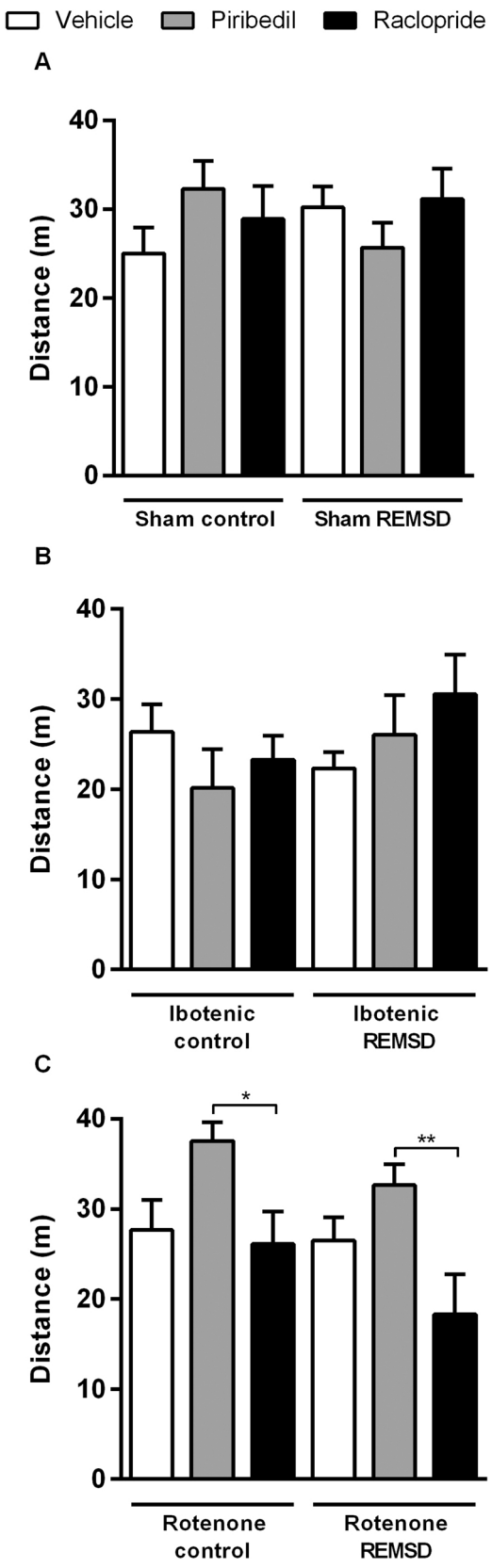

Fig. 4. Open field. Distance travelled in sham groups (A), ibotenic acid groups (B) and rotenone groups (C). Values are expressed as mean ± SEM. *P ≤ 0.05, **P ≤ 0.01. Three-way ANOVA followed by the Fisher's post hoc test. n = 10-12 animals/group.

REMSD raclopride group). In fact, we observed an effect of lesion × striatal D2 modulation receptors interaction [$F(4,221) = 3.41$, $P < 0.01$].

3.1.4. Neurochemical analysis

Neurochemical analysis regarding noradrenergic system are presented in Table 1. Concerning DHPG levels in the hippocampus, we observed a lesion effect [$F(2,99) = 14.82$, $P < 0.001$], a REMSD effect [$F(1,99) = 13.30$, $P < 0.001$], a striatal D2 receptors modulation effect [$F(2,99) = 8.80$, $P < 0.001$], and interactions between lesion and REMSD [$F(2,99) = 9.79$, $P < 0.001$], lesion and D2 receptors modulation [$F(4,99) = 6.47$, $P < 0.001$], REMSD and D2 receptors modulation [$F(2,99) = 6.77$, $P < 0.001$], lesion × REMSD × D2 receptors modulation [$F(4,99) = 6.95$, $P < 0.001$]. The rotenone REMSD raclopride group presented an increase of this metabolite compared to the sham REMSD raclopride, rotenone control raclopride, rotenone REMSD vehicle and rotenone REMSD piribedil group ($P < 0.001$). Regarding NA, we observed significant effects of the lesion [$F(2,99) = 3.90$, $P < 0.05$], D2 receptors modulation [$F(2,99) = 7.49$, $P < 0.001$] and interactions between lesion and REMSD [$F(2,99) = 4.24$, $P < 0.01$], REMSD and D2 receptors modulation [$F(2,99) = 4.04$, $P < 0.05$] and lesion × REMSD × D2 receptors modulation [$F(4,99) = 4.52$, $P < 0.01$]. In fact, this is demonstrated by an increase of NA levels in the ibotenic acid control raclopride group compared to piribedil ($P < 0.01$) and in the ibotenic acid REMSD piribedil group compared to its control ($P < 0.05$) and vehicle group ($P < 0.01$). The rotenone REMSD raclopride group presented the same differences found previously for DHPG levels ($P < 0.001$). We also found significant effects related to all of the treatments concerning NA turnover: lesion effect [$F(2,99) = 21.82$, $P < 0.001$], demonstrated by decreases in ibotenic acid control raclopride ($P < 0.01$), rotenone control raclopride ($P < 0.05$), rotenone REMSD vehicle group ($P < 0.01$) compared to its sham groups; REMSD effect [$F(1,99) = 10.97$, $P < 0.01$], demonstrated by an increased turnover in rotenone REMSD vehicle group compared to its control group ($P < 0.001$); D2 receptors modulation [$F(2,99) = 6.85$, $P < 0.01$], demonstrated by a decrease in the rotenone REMSD piribedil group and an increase in the rotenone REMSD raclopride group compared to its vehicle ($P < 0.001$); interactions between lesion and REMSD [$F(2,99) = 8.80$, $P < 0.001$], lesion and D2 receptors modulation [$F(4,99) = 2.96$, $P < 0.05$], lesion × REMSD × D2 receptors modulation [$F(2,99) = 3.38$, $P < 0.01$].

The treatments promoted relevant effects to the dopaminergic neurotransmission as well (Table 2). In this regard, DOPAC levels were affected as indicated by the lesion effect [$F(2.94) = 3.86$, $P < 0.05$], demonstrated by a decrease in ibotenic acid control raclopride and rotenone control raclopride groups compared to its sham groups ($P < 0.01$). Also, we observed interactions among lesion × REMSD × D2 receptors modulation [$F(4,94) = 4.90$, $P < 0.001$]. For HVA levels, we detected a lesion effect [$F(2,94) = 5.40$, $P < 0.01$], demonstrated by a decrease in ibotenic acid REMSD piribedil and rotenone REMSD piribedil groups compared to the sham REMSD piribedil group ($P < 0.001$ and $P < 0.01$, respectively). Likewise, we found a REMSD effect [$F(1,94) = 4.72$, $P < 0.05$], demonstrated by a decrease in sham REMSD piribedil group compared to its control ($P < 0.01$) and a D2 receptors modulation effect [$F(2,94) = 4.52$, $P < 0.01$], demonstrated by a decrease in sham REMSD raclopride compared to sham REMSD piribedil group ($P < 0.001$). Furthermore, we found significant interactions between lesion and D2 receptors modulation [$F(4,94) = 8.47$, $P < 0.001$] and lesion × REMSD × D2 receptors modulation [$F(4,94) = 2.85$, $P < 0.05$]. The DA levels were only influenced by the lesion [$F(2,95) = 5.11$, $P < 0.01$] and by the interaction between REMSD and D2 receptors modulation [$F(2,95) = 7.06$, $P < 0.001$]. We observed decreased DA levels in ibotenic acid and rotenone REMSD piribedil groups compared to its sham group ($P < 0.01$). Regarding DA turnover, only

Table 1
Endogenous concentrations of noradrenaline and DHPG in hippocampus.

Groups	DHPG	NA	Turnover
Sham control vehicle	1013 (199.6)	339.3 (82.7)	3.5 (0.81)
Sham control piribedil	841.3 (119)	300.5 (39.64)	2.836 (0.32)
Sham control raclopride	1266 (476.2)	329.6 (140.7)	6.955^{d} (3.65)
Sham REMSD vehicle	1440 (348.6)	331.3 (31.9)	4.222 (0.73)
Sham REMSD piribedil	1602 (491.1)	332.8 (33.43)	4.69 (1.33)
Sham REMSD raclopride	2181 (526.5)	390.2 (46.76)	5.684 (1.17)
Ibotenic control vehicle	511.3 (127.9)	346.8 (8.66)	1.454 (0.33)
Ibotenic control piribedil	657.2 (46.67)	281.9 (16.19)	2.419 (0.22)
Ibotenic control raclopride	855.4 (35.97)	444.3^{dd} (48.39)	2.022^{aa} (0.20)
Ibotenic REMSD vehicle	419.5 (36.19)	212.6 (38.61)	2.171 (0.27)
Ibotenic REMSD piribedil	679.3 (55.54)	400.8^{bcc} (27.59)	1.846^{a} (0.27)
Ibotenic REMSD raclopride	595.9 (78.67)	313.4 (47.49)	1.988^{aa} (0.21)
Rotenone control vehicle	1445 (364.5)	351.1 (42.66)	3.84 (0.54)
Rotenone control piribedil	905.6 (26.7)	326.2 (45.72)	3.055 (0.39)
Rotenone control raclopride	1232 (122.7)	365.1 (17.34)	3.428^{a} (0.36)
Rotenone REMSD vehicle	2341 (507.4)	295.4 (31.53)	$7.97^{aaabbbeee}$ (1.48)
Rotenone REMSD piribedil	1246 (38.39)	372.9 (47.61)	3.704^{ccc} (0.57)
Rotenone REMSD raclopride	11700^{dddfff} (5622)	736.3^{dddfff} (225.4)	12.35^{dddfff} (3.85)

Endogenous concentrations of noradrenaline and DHPG in hippocampus. Values are expressed as mean ± SEM (ng/mg). $^{a}P < 0.05$; $^{aa}P < 0.01$; $^{aaa}P < 0.001$, compared to its respective Sham group. $^{b}P < 0.05$; $^{bb}P < 0.01$; $^{bbb}P < 0.001$, compared to its respective control group. $^{c}P < 0.05$; $^{cc}P < 0.01$; $^{ccc}P < 0.001$, compared to its respective vehicle group. $^{d}P < 0.05$; $^{dd}P < 0.01$; $^{ddd}P < 0.001$, compared to its respective piribedil group. $^{e}P < 0.05$ $^{ee}P < 0.01$ $^{eee}P < 0.001$, compared to its respective ibotenic group. $^{f}P < 0.05$; $^{ff}P < 0.01$; $^{fff}P < 0.001$, compared to all of its respective control groups. Three-way ANOVA followed by the Fisher's test. n = 4-5 animals/group.

the interaction lesion × REMSD × D2 receptors modulation is observed [$F(4,95) = 2.67$, $P < 0.05$].

Finally, on 5-HT levels (Table S1), there was an influence of the lesion × REMSD interaction [$F(2,103) = 3.19$, $P < 0.05$] and the lesion × REMSD × D2 receptor modulation interaction [$F(4,103) = 3.20$, $P < 0.01$].

4. Discussion

We observed that lesioning PPT (with ibotenic acid), SNpc (with rotenone) or blocking striatal D2 receptors in healthy animals, consistently impaired the object recognition memory. Surprisingly, REMSD prevented the raclopride-induced cognitive impairment and reversed the ibotenic acid and rotenone lesion effects. A previous study, employing systemic raclopride and quinpirole administration, did not demonstrate effects in object recognition memory [47]. Interestingly, we observed that intrastriatal raclopride infusion impaired this type of memory, apparently contradicting the above-mentioned study. One possible explanation for this discrepancy is that, in our study, raclopride was administered directly in the striatum. Also, we did the administration just before the test phase, while in the cited study the authors administered the drug before the training phase, which probably affected the encoding process. In addition, it has been recently reported that object recognition is optimal at intermediate levels of D2 receptor activity, which suggests that any disturbance in dopaminergic transmission is sufficient to promote behavioral changes [48].

We observed that ibotenic acid lesion in PPT impaired the object recognition memory since the animals could not differentiate the new object from the familiar one. In fact, several studies discuss a role for PPT in cognition, despite contradictory findings [49–51]. Excitotoxic lesions of this structure apparently affect only encoding of acquired avoidance behaviors, not affecting consolidation and retrieval [52]. [51] demonstrated a deficit in sustained attention after selective lesions of cholinergic neurons within the PPT. Other studies reported

Table 2
Endogenous concentrations of dopamine and metabolites in hippocampus.

Groups	DOPAC	HVA	DA	Turnover
Sham control vehicle	2.934 (2.9)	0.06422 (0.03)	9.368 (8.24)	6.577 (5.40)
Sham control piribedil	0.01982 (0.01)	0.003372 (0.001)	14.27 (10.09)	0.06511^{ccc} (0.06)
Sham control raclopride	11.44^{cdd} (11.44)	0.03785 (0.03)	13.14 (13.12)	1.336^{cc} (0.78)
Sham REMSD vehicle	0.01461 (0.006)	0.03069 (0.01)	8.38 (5.86)	0.4072^{bbb} (0.35)
Sham REMSD piribedil	8.873^{bbcc} (5.61)	8.129^{bbcc} (3.68)	24.15^{c} (8.3)	0.6138 (0.17)
Sham REMSD raclopride	0.02062^{bbdd} (0.01)	0.02962^{ddd} (0.01)	19.45 (8.26)	0.3238 (0.32)
Ibotenic control vehicle	0.04955 (0.02)	0.003803 (0.001)	20.94 (2.17)	0.003303^{aaa} (0.001)
Ibotenic control piribedil	0.01603 (0.006)	0.002473 (0.001)	14.12 (3.05)	0.04005 (0.02)
Ibotenic control raclopride	0.003857^{aa} (0.002)	0.01066 (0.004)	0.05811^{ccd} (0.02)	1.374 (0.71)
Ibotenic REMSD vehicle	0.01598 (0.007)	0.01523 (0.004)	5.937^{b} (3.68)	0.0914 (0.04)
Ibotenic REMSD piribedil	0.01066^{aa} (0.005)	0.008174^{aaa} (0.003)	4.095^{aa} (2.7)	0.07252 (0.04)
Ibotenic REMSD raclopride	0.03726 (0.01)	0.01662 (0.01)	$24.28^{bbbccdd}$ (5.05)	0.00232 (0.0005)
Rotenone control vehicle	0.02185 (0.01)	0.03836 (0.007)	6.26^{e} (3.91)	0.3212^{aaa} (0.10)
Rotenone control piribedil	0.02703 (0.003)	0.05148 (0.01)	5.492 (3.42)	0.4883 (0.24)
Rotenone control raclopride	0.01165^{aa} (0.006)	5.311^{cde} (3.47)	1.37 (0.87)	1.112 (0.62)
Rotenone REMSD vehicle	0.01411 (0.006)	0.03611 (0.009)	0.04175 (0.009)	2.396 (0.95)
Rotenone REMSD piribedil	0^{aa} (0)	0.007343^{aa} (0.002)	5.78^{aa} (3.65)	0 (0)
Rotenone REMSD raclopride	$9.545^{ddeeefff}$ (6.03)	$14.6^{ddeeefff}$ (5.32)	15.42^{bc} (6.24)	0.4275 (0.26)

Endogenous concentrations of dopamine and metabolites in hippocampus. Values are expressed as mean ± SEM (ng/mg). $^{a}P < 0.05$; $^{aa}P < 0.01$; $^{aaa}P < 0.001$, compared to its respective Sham group. $^{b}P < 0.05$; $^{bb}P < 0.01$; $^{bbb}P < 0.001$, compared to its respective control group. $^{c}P < 0.05$; $^{cc}P < 0.01$; $^{ccc}P < 0.001$, compared to its respective vehicle group. $^{d}P < 0.05$; $^{dd}P < 0.01$; $^{ddd}P < 0.001$, compared to its respective piribedil group. $^{e}P < 0.05$ $^{ee}P < 0.01$ $^{eee}P < 0.001$, compared to its respective ibotenic group. $^{f}P < 0.05$; $^{ff}P < 0.01$; $^{fff}P < 0.001$, compared to all of its respective control groups. Three-way ANOVA followed by the Fisher's test. n = 4-5 animals/group.

modulation of cognition after deep brain stimulation of PPT [50,53]. To our knowledge, this is the first time that an association between recognition memory and PPT is directly investigated. It is important to address that ibotenic acid lesion affects cholinergic neurons and the cholinergic system, in general, is classically associated to learning, memory and attention. In fact, decreased acetylcholine release is related to impairment in consolidation of the object recognition memory [54]. Thus, the results found in our study, after ibotenic acid lesion, may be a consequence of a decreased cholinergic tone.

We also found significant differences in some of the ibotenic acid groups compared to the sham groups regarding dopamine and noradrenaline turnovers within the hippocampus. Such results may suggest that disturbances in aminergic neurotransmission, triggered by PPT lesioning, can negatively impact the recognition memory. In fact, dopamine seems to be an important neurotransmitter for the hippocampus-based memories and SNpc seems to be an important source of the dopaminergic efflux in the hippocampus, along with the ventral tegmental area [55]. Also, Borgkvist and colleagues [56] demonstrated a considerable interaction between the dopaminergic and noradrenergic systems, showing that the noradrenaline transporter is responsible for dopamine clearance in hippocampus [56]. Corroborating these findings, we observed that the ibotenic acid groups that received raclopride, whether REM sleep deprived or not, presented differences in noradrenaline turnover. This demonstrates that our treatments influenced also noradrenergic neurotransmission.

The nigrostriatal pathway is of remarkable importance for memory and other non-motor symptoms of PD [57–59]. Regarding recognition memory, different studies demonstrate that SNpc lesioning leads to impairment in this type of memory, corroborating our results [8,10]. Dos Santos and colleagues [33] reported impaired object recognition memory 22 days after nigral rotenone infusion, which leads us to believe that this model promotes a somewhat long-term cognitive decline [33]. Regarding the neurochemical data, we observed that SNpc lesion influenced both noradrenergic and dopaminergic hippocampal neurotransmission, reflecting an association of these structures [56].

Intriguingly, the animals that were REM sleep deprived recognized the new object. In an attempt to explain these results, we investigated the possibility of a late effect of REMSD. Thus, we observed the animals 24 h after the REMSD has ended (after REB period) and we failed to see any harmful effect of REMSD. This is in apparent discordance to most of studies in the literature which demonstrate deleterious effects in cognition after REMSD. However, concerning REMSD and object recognition test, the findings in the literature are contradictory [34]. Proença and colleagues [34] observed an impairment in object recognition memory after REMSD, which was also observed by other authors [33,34,60]. Conversely, some authors found no influence of sleep deprivation in this type of test [61]. It is important to address that there are considerable methodological differences among these studies that should account for such discrepancies. Considering this, we believe that three major points were fundamental: (i) the method we chose to quantify the object exploration − time of exploration and not the frequency [62,63]; (ii) residual dopaminergic supersensitivity effect due to REMSD, generating a ceiling novelty-motivational effect [28]; (iii) the method chosen for REMSD procedure, which is known to induce variable levels of stress and affect sleep in variable intensities [64].

REMSD not only allowed the animals to recognize the new object but reversed the deleterious effects promoted by ibotenic acid and rotenone lesions. This procedure is known to induce supersensitivity of dopaminergic receptors [65], which could counteracted the decreased dopaminergic tone promoted by rotenone or ibotenic acid lesion. In relation to the raclopride deleterious effect in sham animals, the ratio receptor/drug may have increased after REMSD and, consequently, masked the effects of the drug. An important observation regarding REMSD must be made at this point. The single platform method abolishes REM sleep episodes completely, however, it partially affects NREM sleep and the total sleep structure aswell. Although controversy exists regarding the significance of NREM sleep deprivation in this context since the REB effect is not observed after the procedure, our findings might be, at least in part, consequence of alterations in other aspects of sleep [64].

Raclopride induced a contradictory behavior when we compare sham and rotenone animals. An inverted U-shape activity, in which a specific activity level is necessary for an expected performance, is described for D1 receptors activation [66,67]. Also, it was demonstrated that the modulation of D2 receptors activity exerts a nonlinear dose-dependent effect on neuroplasticity in the human motor cortex [68]. D2 activation seems to induce an inverted U-shape performance in mice related to object recognition memory, since both high and low D2 receptor activation led to memory impairment [69]. In the light of our study, we have two different scenarios: one without SNpc lesion, in which the neurotransmission is normal and the other with a SNpc lesion by rotenone, in which there is reduced dopamine levels. Thus, we believe that the dopaminergic system within the nigrostriatal pathway present an invert U-shaped activity, in which a modulation of this activity whether increasing or decreasing dopaminergic tone, leads to impairment of memory. Also, it is important to address that raclopride has affinity for D3 (Ki = 7.5) and D4 (Ki = 5.7) receptors besides the discussed D2 receptors affinity (Ki = 7.7–9.3), which could be contributing for the observed effects [70,71].

These considerations, in association with the notion of a unified circuitry, composed by PPT, SNpc and striatum [27], explains the findings of this study in an integrative manner (Fig. 5). Thus, in the absence of neurotoxic disruption (sham animals), raclopride blocked nigral D2 receptors, which are mainly pre-synaptic and, consequently, increased dopamine release. According to the U-shaped activity, this increase in dopaminergic tone would lead to memory impairment. However, after SNpc lesion, raclopride does not have the same effect, since there are not sufficient dopamine to increase the dopaminergic tone. In consequence, there is not an impairment in memory. Regarding the raclopride effect in ibotenic acid lesioned animals, the lack of response is probably due to a reduced activation of dopaminergic neurons in SNpc as a consequence of a decreased cholinergic tone from the PPT. Considering the observed effects in the REM sleep deprived groups and the REMSD-induced supersensitivity of D2 receptors (which affects the number of D2 receptors and/or the affinity of dopamine for the D2 receptors), we also hypothesize that a specific ratio between D1/D2 receptors in the post-synaptic striatal GABAergic neurons is also necessary for the consolidation of recognition memory. It is important to address that the interventions used in this study also affect REM sleep regulation as demonstrated by Targa and collaborators [27,72]. Given the influence of sleep on memory consolidation, one could say that the effects observed in this study are a consequence of an altered sleep aswell.

In conclusion, we suggest that both PPT and SNpc are important structures related to object recognition memory processing, expanding the notion of a unified circuitry, composed by PPT, SNpc and striatum [72]. In view of that, the modulation of striatal D2 receptors, especially the blockade, could be a possible target for the cognitive deficits associated to PD. This is of significant importance, considering the absence of a specific drug for this context [73]. In fact, levodopa and dopaminergic agonists demonstrated to improve and impair cognitive performance, depending on the task requirement, the areas with dopamine depletion and the treatment duration [74–76]. Finally, REMSD, at advanced stages of the disease, might be attenuating the cognitive deficits, particularly recognition memory deficits, in the same way that it decreases the depressive-like behaviors [46].

Conflict of interests

The authors have declared that no conflict of interests exists.

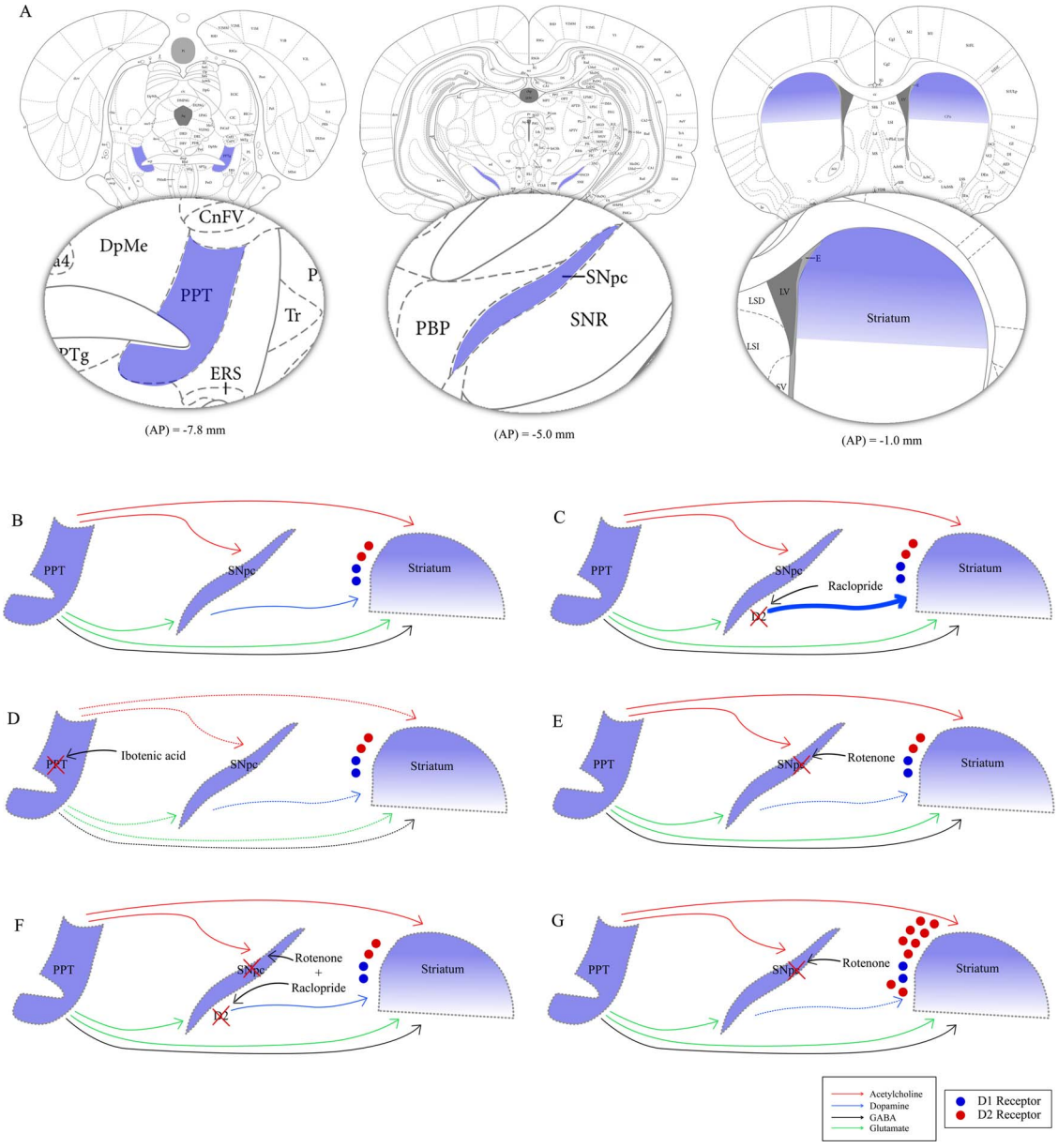

Fig. 5. Integrative scheme of PPT, SNpc and striatum interactions. Representative illustrations of PPT, SNpc and dorsal striatum according to the respective coordinates (AP = −7.8 mm, for PPT; AP = −5.04 mm, for SNpc; AP = 0.96 mm, for striatum) adapted from Paxinos and Watson Atlas (A). The interactions and proposed events in a control situation (B), in Sham control raclopride group (C), in ibotenic acid control vehicle group (D), in rotenone control vehicle group (E), in rotenone control raclopride group (F) and in rotenone REMSD vehicle group (G).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2017.11.008.

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