Contribution of the parafascicular nucleus in the spontaneous object recognition task

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1. Introduction

The parafascicular nucleus (PF) in rats and the centromedian parafascicular complex (CM–PF) in primates and other mammals are the so-called posterior intralaminar nuclei (pIL) of the thalamus. These nuclei are a critical component of the ascending reticular activating system (ARAS) and the basal ganglia–thalamocortical circuit (Groenewegen & Berendse, 1994; Parent & Parent, 2005; Van der Werf, Witter, & Groenewegen, 2002). In general, damage to intralaminar nuclei has been associated with signs of amnesia (Bailey & Mair, 2005; Mitchell & Dalrymple-Alford, 2005; Newman & Burk, 2005; Quiroz-Padilla, Marti-Nicolovius, & Guillazo-Blanch, 2010; Savage, Castillo, & Langlais, 1998; Van der Werf, Jolles, Witter, & Uylings, 2003), and functions as arousal (Mancia & Marini, 1995; Marini, Tredici, & Mancia, 1998; Shirvalker, Seth, Schiff, & Herrera, 2006; Steriade & Deschenes, 1984; Van der Werf et al., 2002), attention (Bailey & Mair, 2005; Burk & Mair, 2001; Kinomura, Larsson, Gulyas, & Roland, 1996; Minamimoto & Kimura, 2002; Newman & Burk, 2005; Newman & Mair, 2007), and pain (Cheng et al., 2009; Dupouy & Zajac, 1997; Gao et al., 2010; Liu, Qiao, & Dafny, 1993; Vogt, Hof, Friedman, Sikes, & Vogt, 2008), in humans and other animals.

Single-axon tracing studies have indicated that virtually all PF neurons project to both cerebral cortex and striatum (Deschenes, Bourassa, Doan, & Parent, 1996). Anatomically, the PF is a major source of excitatory projections to striatum and prefrontal cortices (PFC), mainly prelimbic, and less abundantly to cingulate regions (Berendse & Groenewegen, 1991; Deschenes et al., 1996; Marini, Pianca, & Tredici, 1996; Parent & Parent, 2005; Smith, Raju, Pare, & Sidibe, 2004; Vercelli, Marini, & Tredici, 2003). In relation to striatal projections, the lateral PF projects to the putamen, the lateral globus pallidus and more diffusely to dorsolateral caudate, areas that are related to sensory-motor function. The medial PF projects to the ventral pallidus and in lesser amounts to the accumbens and olfactory tubercle, regions both related to associative-limbic functions (Otake & Nakamura, 1998; Smith et al., 2004; Van der Werf et al., 2002). The cognitive deficits observed after PF lesions are thought to arise from the combined deafferentation of PFC and striatum targets (Van der Werf et al., 2003). The effect of PF manipulations on memory functions should be specifically related to the neural systems innerved. The PF has a strategic location to be considered an excellent candidate for investigating memory processes. However, before concluding PF participation in non-spatial relational memory it is necessary to rule out any possible deficits in locomotion induced by the excitotoxic lesion. So an open field locomotion assessment was carried out before the spontaneous object recognition (SOR).

The link between PF and cognitive processes has traditionally been investigated through rat studies of radiofrequency (Nyakas, 2002).
Veldhuis, & De Wied, 1985; v Wimerdma Greidanus, Bohus, & de Wied, 1974) or electrolytic (Cardo & Valade, 1965; Guillazo-Blanch et al., 1995; Massanes-Rotger, Alavert-Vera, Segura-Torres, Marti-Nicolovius, & Morgado-Bernal, 1998; Redolari-Ripoll et al., 2003; Shapovalova, Pominova, & Dyubkacheva, 1997; Thompson, Kao, & Yang, 1981; Tikhonravov, 2000) lesions. There are only three studies (M’Harzi, Jarrard, Willig, Palacios & Delacour, 1991; Quiroz-Padilla, Guillazo-Blanch, Vale-Martinez, & Marti-Nicolovius, 2006; Quiroz-Padilla, Guillazo-Blanch, Vale-Martinez, Torras-Garcia, & Marti-Nicolovius, 2007) evaluating the effects of excitotoxic lesions restricted to PF area in four different memory tasks: two of procedural memory (the appetitively motivated odor discrimination and the aversively motivated two-way active avoidance tasks) (Quiroz-Padilla et al., 2007), and two of relational memory (the object recognition and the social transmission of food preference (M’Harzi et al., 1991; Quiroz-Padilla et al., 2006). The lack of knowledge of the specific participation of PF in memory processes urges the need to continue researching on its role in cognitive function.

The main purpose of the present study is to identify the contribution of the PF nuclei to non-spatial relational memory by using the SOR task. Ennaceur and Delacour (1988) proposed differential patterns of exploration for familiar and novel objects maybe as a result of the natural tendency to explore novel objects. An important advantage of SOR is that no aversive/stressful stimuli are needed. Other feature of the task is the requirement of perirhinal (PRh) cortex integrity to discriminate novel objects (Aggleton, Alhasser, Aggleton, Poirier, & Pearce, 2010; Brown & Aggleton, 2001; Clark & Squire 2010; Murray & Bussey, 1999; Winters, Saksida, & Bussey, 2008). Previous studies (Bussey, Duck, Muir, and Aggleton, 2000; Ennaceur, Neave, & Aggleton, 1996) reported impaired object recognition memory in the SOR task following neurotoxic PRh damage in rat. The PRh cortex is responsible for familiarity discrimination however, this kind of memory involves interaction with other structures outside the medial temporal lobe as PFC. According to this idea we can speculate that PF lesions decreased the cortical activation required to discriminate significant events in the SOR task, therefore memory can be affected. This could presumably be a result of PF deafferentation of important system components of basal ganglia–thalamic-cortex circuit, particularly PFC (Berendse & Groenewegen, 1991; Deschenes et al., 1996; Heidbreder & Groenewegen, 2003; Hsu & Price, 2007; Macchi & Bentivoglio, 1986; Marini et al., 1996; Otake & Nakamura, 1998; Parent & Parent, 2005; Sadikot & Rymar, 2009; Smith et al., 2004; Van der Werf et al., 2002; Vercelli et al., 2003; Vertes, 2004).

The finding of impairments in two different retention delays: immediately and/or 24 h after training, in rats submitted to bilateral lesion with N-methyl-D-aspartate (NMDA) should support the contribution of PF in the memory process of the SOR task.

2. Materials and methods

2.1. General methods: Experiments 1 and 2

Both experiments were performed taking into account the ethical and legal standards required for laboratory animal research in Colombia (Estatuto Nacional de Protección Animal – Law 84 of 1989 and Resolution Number 008430 of 1993 of the Ministerio de la Salud).

2.1.1. Apparatus

A cylindrical open field (55 × 60 cm; diameter and height) was used to assess locomotion before and 6 days after surgery. The SOR task was carried out in an open box made of wood (60 × 60 × 40 cm high) with the floor covered with an acrylic surface. The objects were made of plastic, aluminum or glass with differences in color, height (between 8 and 15 cm), weight (between 55 and 226 g), shape and texture (Fig. 1). After each session, the objects and surface of the open box were cleaned with acetic acid (10%) to avoid olfactory cues.

2.1.2. Analysis of behavior

The animals were videotaped while performing both the locomotion tests and the SOR task. Object exploration was operationally defined as physical contact with the object through forepaws or snout. Distances >2 cm, as well as sitting or standing on the object with the nose facing the ceiling were not considered exploratory behavior. For the SOR task training the dependent variables were: the mean time spent exploring the objects and the mean average frequency of contact with the objects. For the SOR task test, a discrimination ratio was used (discrimination ratio = novel object exploration/total interaction with all the objects) (see Bevins & Besheer, 2006).

The frequency of following behaviors were analyzed in the locomotion tests: crossing the lines that divided the cylindrical open field bearing in mind that the animal’s hind paws crossed the line between each quadrant; standing on their hind paws in the field (rearing); licking or scratching themselves (grooming); elongation of the head and shoulders followed by retraction to its original position (stretching); and remaining stationary showing piloerection (freezing). Each of these behaviors was measured before and after of the surgery, and a delta score was obtained; this delta score is defined as: frequency of the behavior before surgery - frequency of the behavior after surgery. These dates were collected with the software X-Plo-Rat 2005 1.1. (Taverna-Chaim & Morato, 2008).

2.1.3. Measurements and statistical analysis

All statistical analyses were carried out by using SPSS for Windows, version 17.0. The comparison of the averages of the groups for all SOR task measures was done using Student t test for independent samples. In order to compare the results in locomotion tests, a Student t test for independent samples was done using delta scores for each behavior (crossing, rearing, grooming and stretching). Other analyses were carried out to assess the effect of bilateral PF lesions on object exploratory behaviors and therefore discard any effect of lesion on the SOR task. In this regard, General Lineal Model for repeated measures was used with corresponding contrasts (simple for between-groups effects and polynomial and repeated for within-group effects), in which the independent variables were Group (Lesion and Vehicle) and the
dependent variables were: approaches ≤2 cm, contact with forepaws, and snout. In the statistical procedures used in this study an alpha of \( p \leq 0.05 \) were assumed, with a reliability of 95%.

2.2. Experiment 1

2.2.1. Subjects

Twenty-four male Wistar rats obtained from Immunopharmos laboratories were used in the experiment. At the beginning of the study the mean age of the animals was 98 days (SE = 3.87) and mean weight of 291.48 g (SE = 8.09). Throughout the period of the experiment the animals were housed individually in plastic-bottomed cages (48 × 38 × 20 cm) with sawdust bedding. During all stages of the investigation the animals were kept under controlled temperature settings (20–24 °C), humidity (40–70%) and a 12 h light–dark cycle (lights on at 8:00 a.m.). All experimental procedures were performed during artificial light cycle. During the experiment the animals were supplied with food and water ad libitum, and their weight and cleanliness were monitored.

2.2.2. Surgical procedure

Before surgical procedure, the animals were randomly assigned to Lesion or Vehicle groups. Rats were anaesthetized with intraperitoneal injection of ketamine hydrochloride (ketamine 50°, Holliday-Scott SA, 75 mg/kg) and xylazine (Seton®, Calier; 10 mg/kg), and placed in a stereotaxic instrument (Stoelting Co., Model 51725) with the incisor bar set 3.3 mm below the interaural line. Before the skin incisions, local anesthesia was administered by subcutaneous application of lidocaine (Roxicaina 1%, Rospoh Therapeutics Ltda). The skull was exposed through a midline incision and leveled along the bregma-lambda axis. Two holes were drilled in the cranium of the animals and a 26-gauge needle Hamilton syringe was lowered to the targets according to the following stereotaxic coordinates (Paxinos & Watson, 1997): anteroposterior (AP) = -4.1 mm from bregma, lateral (L) ± 0.6 mm from midline, and dorsoventral (DV) = 6.1 mm and 5.6 mm from the skull surface. Before the infusion, the needle was left in place for 30 s. Animals belonging to the lesion group were infused bilaterally at the PF nucleus the excitotoxin NMDA (Sigma-Aldrich®, 0.15 M in sterile phosphate-buffered, saline, pH 7.4). A digital microinjector (Stoeling Quintessential Injector, model 5331) was used for all infusions. The total volume of infusion for each hemisphere was 1.2 µl. At the first depth 0.8 at a rate of 0.133 µl per minute were infused. While 0.4 at a rate of 0.1 µl per minute were infused at the second depth. The first infusion was made in the DV deeper coordinate (DV = 0.61 mm). The needle was allowed to sit for 10 min before being raised to avoid the spread of NMDA up the needle tract. The scalp was then sutured and a topical antiseptic (Iodosine®, Boehringer Ingelheim S.A.). Throughout the procedure, the animals body temperature was kept constant with a thermal blanket. Vehicle rats underwent the same procedure, except that sterile phosphate-buffered saline was infused.

2.2.3. Behavioral tasks

In the first phase of the experiment, each rat was kept in individual plastic cages. In order to animals get familiarized to the investigator, all rats were handled for 5-min each day for a period of 4 days. On the fifth day the locomotion pre surgery test was done by placing the animals in the cylindrical open field for 5 min. Then the rats had 2 days without treatment before the surgery. All animals were allowed to recover for 7 days previous to locomotion post surgery test, which was performed for 5 min in the same cylindrical open field used in the pre surgery tests. Next day, the SOR task was applied to the animals. First, each rat had a habituation session for five minutes in the open field (above described) without objects. Then, three 5-min training trials were done, with inter-trial intervals of 2 min. In each trial, the animals were placed in the corner of the open field where there was not object, looking at the vertex of the walls. All other three corners had a different object. These three objects were the same in all three trials for each subject, but among trials the objects were rotated taking care of do not to repeat the location, to reduce place preferences. The test session took place two minutes after completion of training trials and lasted five minutes. In this session, one of the three objects previously used (familiar objects) was replaced by a new object with which the animal had never had contact.

2.2.4. Histology

After the behavioral procedures, all animals were deeply anaesthetized with an overdose of sodium pentobarbital (Euthanex®, Invet s.a., 200 mg/kg) and were perfused transcardially with 0.9% saline followed by 10% formalin-saline. Brains were extracted and post-fixed in formalin for at least 24 h and then submerged in a 30% sucrose solution prior to sectioning. Coronal 40-μm sections were cut out on a cryostat (Leica Microsystems®, model CM1850), mounted and stained with Cresyl violet. The sections were examined under a light microscope (Nikon® Eclipse 80i) and microphotographs were taken with a digital camera (Nikon Ds-Fi1). The tissue evaluation was done using a blind strategy: two observers who were not aware of the behavioral results independently examined the brain sections. The lesions were reconstructed on standardized sections of the rat brain (Paxinos & Watson, 1997).

3. Results

3.1. Histology

Fig. 2A and B shows the maximum and minimum extents of successful PF lesions for each plate (figures modified from Paxinos & Watson, 1997). Final sample included only rats with bilateral lesions ≥40% in the PF, damage that extended from −3.80 mm to −4.52 mm posterior to bregma (Paxinos & Watson, 1997). The lesions were characterized by loss of neurons, glycosis and traces of necrosis adjacent to the tracks made by the needle (Fig. 3A-D). The axons in the fasciculus retroflexus remained visible in all
subjects included in the final sample. For both experiments, histo-
logical analyses were performed by two independent blind
observers.

3.2. Behavior

3.2.1. Experiment 1

The final sample was made up of 18 rats distributed into LESION
(n = 8) and VEHICLE (n = 10) groups.

3.2.1.1. Locomotion test. In order to assess any possible effect of sur-
gery upon locomotion and motility, Student $t$ tests were conducted
on delta scores (differences between data at the pre and post surgery
sessions) (see page 8 for description) for crossings, grooming, rear-
ing, stretching and freezing. Independent samples $t$-test analysis
showed that there were not differences between the groups in delta
scores for crossings ($t_{(16)} = -0.563; p = 0.581$), rearing ($t_{(16)} = -0.07;
p = 0.945$), grooming ($t_{(16)} = -0.989; p = 0.337$) and stretching
($t_{(16)} = 0.243; p = 0.811$). None of the subjects regardless of the
group showed immobility or piloerection (freezing). These results indicate
that lesions did not affect the locomotor activity of animals.

3.2.1.2. Spontaneous object recognition task. Fig. 4A shows the
discrimination ratio of the novel object for all the groups in the
test. Student $t$-test showed significant differences between the
groups in the discrimination ratio ($t_{(16)} = -2.162; p = 0.0461
< 0.05$). This finding suggests that lesions in PF change the normal
functioning of object recognition memory when performing the
test 2 min. after training. There were no significant differences be-
tween groups in the total time exploring objects during the trial
sessions ($t_{(16)} = 1.983; p = 0.085$), in the total frequency of contact
with objects in the trial sessions ($t_{(16)} = 0.587; p = 0.566$) and in
the total time exploring objects during the test session
($t_{(16)} = -1.277; p = 0.220$) (Fig. 4B). General lineal model for re-
peated measures showed no significant differences in the explora-
tion time ($F_{(1,16)} = 3.935, P = 0.056$), as well as the frequencies of
approaches $\leq 2$ cm ($F_{(1,16)} = 0.136, P = 0.717$), and contacts with
forepaws ($F_{(1,16)} = 0.397, P = 0.505$), and the snout ($F_{(1,16)} = 0.390,
P = 0.574$).

3.2.2. Experiment 2

The final sample was made up of 17 rats distributed into LESION
(n = 7) and VEHICLE (n = 10) groups.

3.2.2.1. Locomotion test. Independent samples $t$-test analysis
showed that there were not differences between the groups in delta
scores for crossings ($t_{(15)} = 0.245; p = 0.810$), rearing ($t_{(15)} = -0.095;
p = 0.926$), grooming ($t_{(15)} = -0.373; p = 0.715$) and stretching
($t_{(15)} = -0.967; p = 0.349$). None of the subjects regardless of the
group showed immobility or piloerection (freezing). The findings
are consistent with those found in Experiment 1, confirming that

Fig. 2. Schematic drawing of the smallest (gray area) and the largest (striped area) PF lesions in successive anterior/posterior coronal sections in Experiment 1 (A) and
Experiment 2 (B). The extent of the lesions is superimposed on figures modified from Paxinos and Watson (1997).
the PF nucleus lesions did not affect the locomotor activity of the experimental subjects.

3.2.2.2. Spontaneous object recognition task. Analysis of the discrimination ratio revealed that there are significant differences between the control group and lesion group \((t_{15}) = -4.890; p < 0.001\) (Fig. 5 A). This result suggests that lesions in PF produce a deficit in object recognition memory at 24 h. Moreover, there were no significant differences between groups in the total time exploring objects during the trial sessions \((t_{15}) = 0.0238; p = 0.815\), in the total frequency of contact with objects in the trial sessions \((t_{15}) = 0.091; p = 0.929\) and in the total time exploring objects during the test session \((t_{15}) = 1.707; p = 0.0108\) (Fig. 5 B).

To complement the analysis of exploratory behavior, general lineal model for repeated measures was conducted for the trial sessions. There were no significant differences between groups \((F_{1,15}) = 0.057, p = 0.815\). This result supports the evidence that the PF nucleus lesion did not affect exploratory behavior. In the analysis of object exploration during the trial phases there were no differences groups for the frequency of approaches \((F_{1,15}) = 0.31, p = 0.863\), the frequency of contacts with snout \((F_{1,15}) = 0.41, p = 0.842\), and with forepaws \((F_{1,15}) = 1.282, p = 0.275\). These results, together with those obtained in Experiment 1, suggest that bilateral lesions of the PF nucleus did not affect object exploration and, therefore, did not influence animal performance in SOR task.

Fig. 3. Photomicrographs of Cresyl violet-stained coronal sections (40 µm thick), about 4.30 mm posterior to bregma, showing the appearance of a typical NMDA bilateral PF lesion (A) and (B) compared to a vehicle-infused subject (C) and (D). Scale bar = 1.00 mm in (A), (B), (C) and (D). PF, parafascicular; fr, fasciculus retroflexus.

Fig. 4. Experiment 1. (A) Discrimination ratio of the novel object two minutes after training trials for both groups. (B) Differences between groups in the total time exploring objects during the trial sessions (*P < 0.05).
4. Discussion

The present study evaluated the effects of bilateral NMDA lesions of the PF nucleus on a SOR task. In this paradigm, rats were required to remember familiar objects immediately or 24 h after. The main results showed that PF lesions impair SOR at both retention delays. These findings suggest that PF is involved in the object recognition memory.

Regarding to exploration or motor behavior in both experiments, there were no significant differences between groups in crossing, rearing and stretching frequency in the open field. There were no significant differences between groups in both frequency or time spent exploring the sample objects in the SOR task or in other exploratory behaviors (approaches < 2 cm, contact with fore-paws and snout). No significant changes were observed in the overall exploration time in the test session.

Altogether, these findings dismiss the incidence of variables other than memory and maybe learning on the performance of lesioned animals in the SOR task. The explanations for the results obtained in this investigation are based on the fact that the PF nucleus participates in the ARAS, as well as in the basal ganglia–thalamic-cortex circuit; both systems related to generalized activation or arousal (Jones, 2003; Quiroz-Padilla et al., 2010), attention (Heidbreder & Groenewegen, 2003; Hulme, Whiteley, & Shipp, 2010; Matsumoto, Minamimoto, Graybiel, & Kimura, 2001; Minamimoto, Hori, & Kimura, 2005; Minamimoto & Kimura, 2002; Raeva, 2006; Smith et al., 2004), learning and memory (Guillazo-Blanch et al., 1995; Massanes-Rotger et al., 1998; Quiroz-Padilla et al., 2006; Quiroz-Padilla et al., 2007).

According to this evidence it is hypothesized that the PF lesions decreased the cortical activation required to discriminate significant events in the SOR task, therefore memory can be affected. This could presumably be a result of PF deafferentation of important system components of basal ganglia–thalamic-cortex circuit, particularly PFC (Berendse & Groenewegen, 1991; Deschenes et al., 1996; Heidbreder & Groenewegen, 2003; Hsu & Price, 2007; Macchi & Bentivoglio, 1986; Marinelli et al., 1996; Otake & Nakamura, 1998; Parent & Parent, 2005; Sadikot & Rymar, 2009; Smith et al., 2004; Van der Werf et al., 2002; Vercelli et al., 2003; Vertes, 2004).

There are some reports on memory impairment after lesions in the intralaminar nuclei, including the PF nucleus, very similar to those caused by hypofunction of PFC (Burk & Mair, 1998; Van der Werf et al., 2003). Indeed, there have been reported deficits in working memory after thalamic damage, including the PF nucleus, in different animal models used to evaluate this kind of memory (Burk & Mair, 1999; Langlais & Savage, 1995; Porter, Koch, & Mair, 2001; Savage et al., 1998). Furthermore, Smith, Countryman, Sahuque, and Colombo (2007) found that the acquisition and remembering in the socially transmitted food preference task (model of non-spatial relational memory) induces activation of the medial prefrontal cortices (PFCm), specifically in the prelimbic and infralimbic cortex.

Concerning to object recognition memory, there are studies showing connection between this kind of memory and PFCm cortex, especially with the prefrontal area (Barker, Bird, Alexander, & Warburton, 2007; Christoffersen et al., 2008; DeVito & Eichenbaum, 2010; Levallet, Hotte, Boulouard, & Dauphin, 2009). Barker et al. (2007), suggest that object recognition memory in rats requires judgments on the previous occurrence of stimuli made on the basis of the relative familiarity with each object. It has been proposed that PFCm may be related to the discrimination required for object recognition test in order to establish an order or timing of the objects presentation (Dere, Huston, & De Souza Silva, 2007).

Our results contrast with those reported by M’Harzi et al. (1991), who found no impairment on object recognition memory after ibotenic acid lesion of PF in rats. This divergence in results may be due to some methodological differences such as the kind of the object recognition task used. In the experiments reported here, three trials before the test session were done using three objects per session, whereas in the study of M’Harzi et al. (1991), there was only one trial before test and two objects per session. Our variation increases the difficulty of the SOR task, demanding so a greater degree of arousal and attention in order to properly acquire and store it. Moreover, this study adds to emerging evidence of the involvement of PF non-spatial relational memory, as was suggested in the study reported by Quiroz-Padilla et al. (2006), and complements the work involving PF with other kinds of relational memory (Bailey & Mair, 2005; Burk & Mair, 1998; Lopez et al., 2009; Porter et al., 2001; Savage, Sweet, Castillo, & Langlais, 1997; Savage et al., 1998; Van der Werf et al., 2003).

Given that an optimal level of alertness is required for learning and behavior to occur, and that the PFCm is critically involved in alertness (Robbins & Everitt, 1995; Valdés & Torrealba, 2006), it is possible that the deficit observed in object recognition test could be the result of alterations in glutamatergic neurons projecting from PF to PFCm, particularly to prelimbic cortex – region directly related to ARAS and relational memory processes. The deafferentation of the prelimbic cortex could have decreased the cortical activation required for encoding information and memory formation. This idea
is consistent with the findings reported by DeCoteau, McElvaine, Smolentzov, and Kesner (2009), according to which the animals with prelimbic/infralimbic cortex lesions displayed a profound and sustained deficit, in a go/no-go visual discrimination task.

According to Minamimoto and Kimura (2002), PF is involved in tasks requiring shifts in response patterns. Differential exploratory behavior on near objects could be understood as a response pattern. It could be the case that PF lesions animal failed to shift the exploratory pattern between new and familiar objects resembling so an attentional failure leading to alterations in memory formation. From this stand, it is possible that the SOL task used here could include some components similar to those found in flexibility tasks (i.e., enhancement of exploration of novel object and decrease of familiar objects exploration) and, as a result of PF lesions, the subject is unable to make a behavioral shift between ongoing behavior and appropriated responses to each kind of object.

The crucial role of PFC has been well documented in this kind of behavioral shifts (Egerton et al., 2008; Floresco, Block & Tse, 2008; Parsegian, Glen, Lavin, & See, 2011). As already stated by Brown, Baker, and Ragozzino (2010), the role of PF on PCC activation could be indirectly mediated by striatal cholinergic neurons related to behavioral flexibility. They found that PFC lesions cause a decrease in acetylcholine release which concomitantly impaired tasks requiring flexibility as reversal learning. This effect could be mediated by the decreased cholinergic activity in the striatal-cortical projection to PFC. In fact, it has been proposed that one of the functions of PFC relates to the processing of stimuli that were previously irrelevant, requiring the selection of different actions (Brown et al., 2010).

It could be also the case that PF lesions lead to a possible attention deficit interfering with the performance in object recognition task and not exactly a failure in cortical arousal. As above mentioned, PF is also related to attentional processes; in fact, some authors have proposed that the preference for novelty (traditionally assessed by SOL tasks) could reflect deficits in attention rather than alterations of relational memory (Desimone & Duncan, 1995; Gaskin et al., 2010). However, as already mentioned, in this study some changes in the SOL task made it more complex and, therefore, demanded greater attention for the acquisition and retention of the task. In addition, the analysis of exploratory behavior during the three trials and the test session did not show any differences between control group and lesioned animals, so, it is possible that PF lesions did not impact attention deficits as the only explanation for the memory deficits observed.

In conclusion, our results suggest that PF may be involved in modulation of object recognition memory. The contribution of PF in memory may be linked to its role in the basal ganglia-thalamic-cortex circuit. Hence, PF damage may have reduced the activation of specific brain regions necessary for helping animals to cope with changing task demands.

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