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Research report

Effects of dorsal striatum lesions in tone fear conditioning and contextual fear conditioning

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Abstract

It has been suggested that the striatum mediates hippocampus-independent memory tasks. Classical fear conditioning to a discrete stimulus such as a tone is not affected by hippocampal lesion, whereas contextual fear conditioning is an hippocampus dependent task. The purpose of the present study was to verify the effect of dorsal striatal lesions on tone and contextual fear conditioning. The lesioned rats were not impaired in contextual fear conditioning but in tone fear conditioning both electrolytically and neurotoxically lesioned animals showed less freezing compared with controls. The lesion effect was observed after a postoperative recovery period of 14 days but not after 2 months. The results support the hypothesis that the dorsal striatum is involved in hippocampus-independent memory tasks, but, in spite of this involvement, it does not seem to be a critical structure.
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Theme: Neural basis of behavior

Topic: Learning and memory: systems and functions

Keywords: Striatum; Caudate-putamen; Contextual conditioning; Tone conditioning; Classical fear conditioning; Memory

1. Introduction

Although several studies have shown selective memory impairment after hippocampal lesions [36,4,19], relatively few have attempted to identify the neural basis for non-hippocampal memory systems. Some studies have suggested that the hippocampal system and the caudate nucleus may mediate the acquisition of different types of learning and memory (for a review see [41]). The involvement of the dorsal striatum in some learning and memory processes has been proposed [5,32,33,40]. Animals with dorsal striatal lesion were not able to learn the reward position in the radial maze, when the reward was placed in a constant direction from the animal at the radial maze start point (a task that depends on an egocentric orientation strategy) [32]. Double dissociation between dorsal striatal lesion and hippocampal lesion was obtained in some studies. For instance, lesions of fimbria-fornix, but not lesions of the caudate nucleus, impaired the acquisition of a win-shift task in the radial maze. This task requires the animal to remember the arms of the radial maze previously visited in the trial. On the other hand, lesions of the caudate nucleus, but not fimbria-fornix lesions, disrupted the acquisition of the win-stay simultaneous visual discriminative response—a response that does not require the animal to remember the spatial location of the arms previously visited [22]. Double dissociation was also observed in other memory tasks. While the fornix lesion impaired the acquisition of a spatial task in the water maze, the caudate lesion impaired the acquisition of a visual discriminative response, having no effect on the acquisition of the spatial task [24]. These data indicate that the striatum could be one of the neural structures that mediate those learning abilities that are preserved after hippocampal lesions although some conflicting results exist [21,31].

Dissociation between tasks that are hippocampus-dependent, and those that are not also occurs in tasks that involve emotional memory. Hippocampal lesion before

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training, or even 24 h after training, disrupts the contextual fear conditioning task. In this task, the animal receives an aversive unconditioned stimulus (US), such as a footshock, in a specific context, and when the animal is returned to this context it displays conditioned fear responses in the absence of the US (evaluated by the suppression of operant responses, freezing behavior or alterations in autonomic activity). This same lesion does not affect classical fear conditioning to a discrete stimulus, a task quite similar to the previous one, in which the US is associated to a discrete neutral conditioned stimulus (CS) such as a tone or light. After a few pairings, the CS elicits conditioned fear responses, even if the CS is presented in a different environmental context [13,30]. The same kind of dissociation has been observed after experimental manipulations other than hippocampal lesion, such as electroconvulsive shock [3], REM sleep-deprivation [2] and anti-cholinergic drugs administration [7]. It is possible, therefore, that the dorsal striatum may be involved in light or tone fear conditioning, but not in contextual fear conditioning. However, the dorsal striatum is not usually considered part of the neural circuitry mediating tone fear conditioning [15,16]. Nonetheless, the dorso-medial striatum receives projections from the visual cortex, whereas the medial striatum receives projections from auditory cues, and the dorso-lateral striatum from motor areas [18], which makes involvement of this structure in classical conditioning feasible. In fact, caudate lesion impaired acquisition of Pavlovian conditioned eyelid reflex in the rabbit, although conditioned heart rate was unaffected [29]. This result shows an involvement of the caudate nucleus in classical conditioning to a discrete stimulus. Also dorsolateral striatum appears to be involved in the expression of conditioned orienting response but not in the acquisition of this learned behavior [10].

To test the hypothesis that the striatum may mediate tone- but not contextual-fear conditioning, the same stereotaxic coordinates used by Packard and McGaugh [24] were used, since this lesion was shown to be effective in producing deficits in hippocampus-independent memory tasks.

In the present study we sought to verify the effect of dorsal striatum lesion in tone fear conditioning (a task not affected by hippocampal lesion) and in contextual fear conditioning (which is dependent on hippocampal function), aiming to extend the range of hippocampus-independent tasks that are susceptible to striatal lesion.

2. Material and methods

Subjects were male Wistar rats aged 3–4 months and bred and raised in the animal facility of the Department of Psychobiology at UNIFESP/EPM. They were maintained under controlled temperature (23±2 °C) and 12:12-h light–dark cycle (lights on at 7:00 a.m.) conditions. Rat chow and tapwater were provided ad libitum. The animals were allocated to four different experiments and each behavioral test was conducted on different groups of animals.

2.1. Surgery

The rats were pretreated with 10 mg/kg of Diazepam (Valium®, Roche) and were anesthetized with 15 mg/kg of Ketamina® (Agener). Both drugs were administered i.p. Stereotaxic bilateral lesion were made with bregma and lambda in the same horizontal plane. An incision was made along the sagital midline of the scalp and holes were drilled in the skull.

In Experiments 1, 2 and 3, bilateral dorsal striatum lesions were carried out by passing an anodic current of 5 mA for 10 s through a stainless-steel electrode insulated except for about 0.5 mm at the tip. Control groups underwent the same surgical procedure, except that no current was delivered. The following coordinates were used: 0.7 mm anterior to bregma, 2.5 mm lateral to the central sinus, and 4.5 mm ventral from the skull surface [27,28].

In Experiment 4, bilateral dorsal striatum lesions were carried out by infusion of 0.6 μl of ibotenic acid (10 mg/ml) dissolved into phosphate buffered saline (pH 7.2). The solution was infused through a drawn glass pipette attached to the needle of a 5.0-μl Hamilton syringe (Reno, NV, USA) at the rate of 1 μl/min. The pipette was left in place for 5 min and then slowly withdrawn. In control animals the holes were drilled in the skull but the pipette was not lowered. The coordinates used in Experiment 4 were the same as those described for the electrolytic lesions.

The postsurgical recovery period was 14 days in Experiments 1, 2 and 4, and 2 months in Experiment 3.

2.2. Apparatus

The conditioning apparatus consisted of an acrylic box, measuring 30×21×30 cm. The walls were black with some visual white patterns (two squares measuring 5.5×5.5 cm and 3 4.0×4.0 cm made of white cardboard). The top was covered with transparent acrylic. The floor consisted of a metal grid (0.4 cm diameter rods placed 1.2 cm apart) connected to a shock generator and a control module (Ugo Basile model cat. 7551), through which footshocks could be delivered. The tone conditioning test used a white cylindrical chamber, 35 cm in diameter and 60 cm in height, and covered by a transparent acrylic top. The apparatuses were kept in different rooms. A buzzer placed outside the conditioning apparatus and outside the cylindri-

cal chamber produced the 90-dB tone used as conditional stimulus (CS).

2.3. Behavioral procedures

Each behavioral procedure was conducted in a different set of animals.

2.3.1. Contextual fear conditioning

The task was carried out during 2 consecutive days. On the first day (training), the animals were individually placed in the black box, where they remained for 5 min. The behavior of each animal was recorded continuously by measuring the seconds it remained in freezing (defined as complete immobility and absence of vibrissae movements and sniffing [1]) minute by minute for 5 min. After this period, rats received 5 footshocks (1 mA, 1-s duration) at 30-s intervals and were removed from the apparatus 1 min after the last footshock. Contextual conditioning tests were performed on the second day, 24 h after training. All rats were placed in the same training context, and no footshocks were delivered. The time in freezing was recorded minute by minute for 5 min. The freezing/min ratio was taken as a measure of contextual conditioning.

2.3.2. Tone fear conditioning:

This task was carried out during 3 consecutive days. On the first day (familiarization), rats were individually placed in the black box, where they remained for 5 min. After this period, they were removed from the apparatus and returned to their homecage. On the second day (training), they were again placed in the black box and after 30 s were given a series of 5 tone-footshock pairings at 30 s intervals. The tone (CS) sounded for 5 s and in the last second a footshock (US) was delivered, which ended together with the tone. Rats were removed from the apparatus 30 s after the last footshock. The tone conditioning test was performed on the third day, 24 h after training. Rats were placed in the cylindrical chamber (new context) for 6 min in Experiments 1, 3 and 4, but not in Experiment 2, in which they remained in the test chamber for 8 min. During the 4th minute of exposure to the apparatus, the CS was presented five times at 30-s intervals, beginning at the end of the 3rd minute. The freezing time was measured, minute by minute, before and after the tone.

2.4. Histology

Following the behavioral experiments, the rats were sacrificed by a lethal dose of chloral hydrate and their brains were removed and stored at −80 °C. The brains were cut into 20-μm coronal sections. The sections were slide mounted, stained with cresyl violet, and examined microscopically.

2.5. Statistical analysis:

Data from the classical fear conditioning were analyzed by a three or two-way ANOVA (for contextual and tone conditioning, respectively) with Group and Minute (and Session for the contextual fear conditioning) as main factors. When applied, the analysis was followed by the post-hoc Duncan test.

3. Results

3.1. Histology

Placement of the striatal electrolytic lesions is represented in Fig. 1A. The lesioned area was the anterodorsal striatum. A schematic representation of the neurotoxic lesions is shown in Fig. 1B. These lesions were larger and their placement was more caudal than the electrolytic lesions. Rats with unilateral lesions were not considered for the analysis of the results. For contextual fear conditioning task of Experiment 1, 16 control animals and 15 lesioned animals were used for the analysis of the data. For the tone fear conditioning 1 (Experiment 1), 11 control animals and 11 lesioned animals were used. In Experiment 2 we used 13 control and 15 lesioned animals, in Experiment 3, 31 control and 23 lesioned and in Experiment 4, 15 control and 13 lesioned animals.

3.2. Behavioral results

3.2.1. Experiment 1

3.2.1.1. Tone fear conditioning 1. The lesioned animals were impaired in the acquisition of tone fear conditioning (Fig. 2). There was a significant Minute effect [$F_{(5,100)}$= 57.4; $P<0.0001$] and a significant interaction between Minute and Group [$F_{(5,100)}=2.4$; $P=0.04$]. Posthoc (Duncan $P<0.05$) test showed that both groups increased freezing after tone presentation but the lesioned animals showed less freezing than the control animals during the last 2 min of the test. The main effect of Group was not significant [$F_{(1,20)}=1.45$; $P=0.24$].

3.2.1.2. Contextual fear conditioning.. Dorsal striatum lesion did not affect contextual fear conditioning (Fig. 3). Three-way ANOVA showed that the main Group effect was not significant [$F_{(1,29)}=0.24$; $P=0.67$]. In addition, there were no statistically significant Group×Session [$F_{(1,29)}=0.21$; $P=0.65$], Group×Minute [$F_{(4,116)}=0.35$; $P=0.84$] or Group×Minute×Session [$F_{(4,116)}=0.31$; $P=$

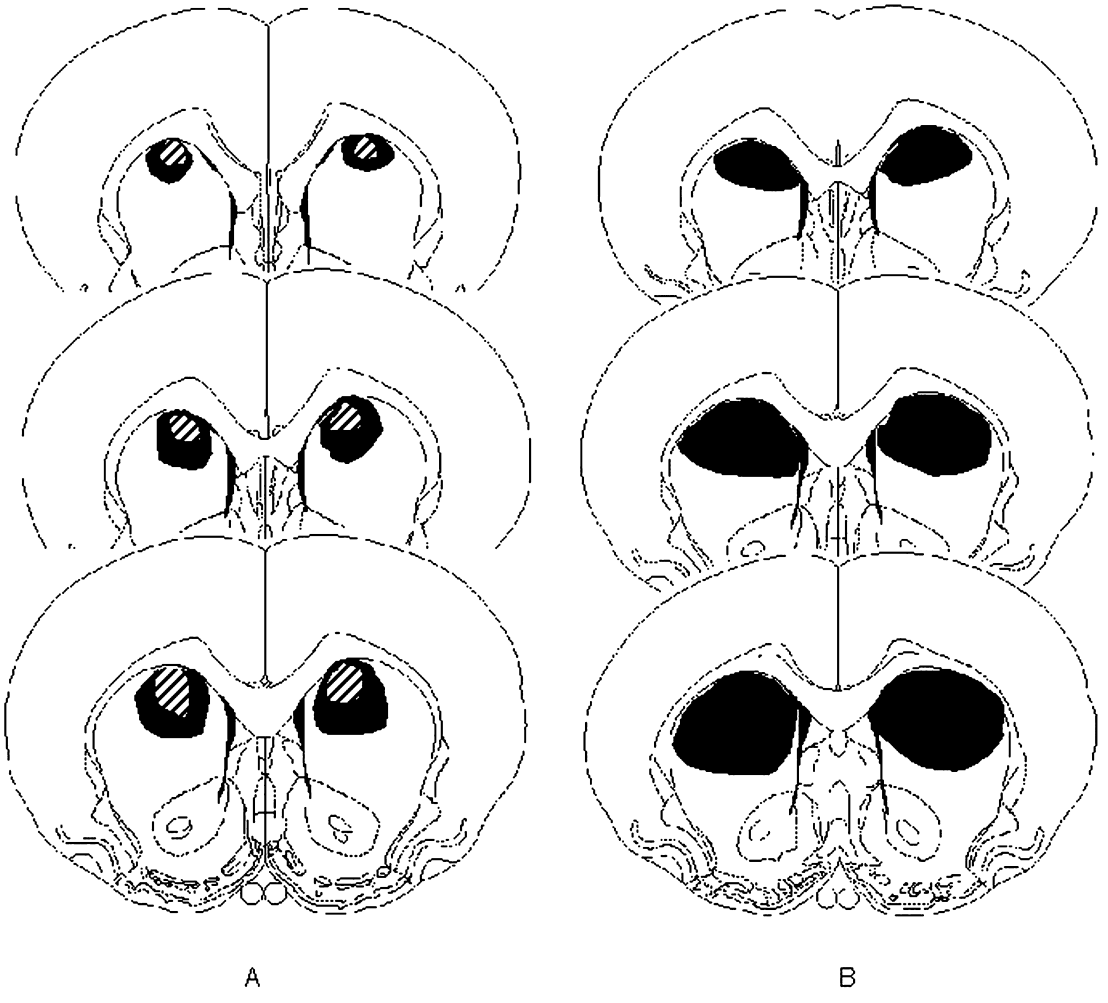

Fig. 1. Schematic representation of coronal sections from rat brain (adapted from [27]) indicating the location of the smallest (diagonal lines) and biggest sizes (black+diagonal lines) of dorsal striatal lesions. (A) Electrolytic lesions; (B) neurotoxic lesion.

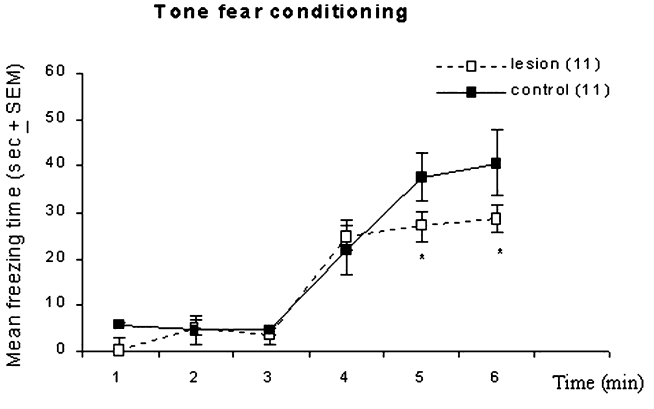

Fig. 2. Effects of electrolytic dorso-striatal lesion on freezing response of rats in tone fear conditioning test measured during 3 min before and 3 min after tone. The animals were tested 14 days after surgery. The number of animals per group is shown in parentheses after the group names; *, $P<0.05$ compared to control.

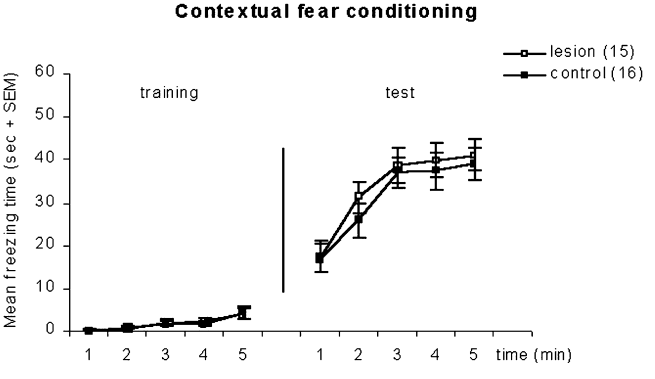

Fig. 3. Effects of electrolytic dorso-striatal lesion on freezing response of rats in contextual fear conditioning measured for 5 min during training and test sessions. The animals were tested 14 days after surgery. The number of animals per group is shown in parentheses after the group names.

0.87] interactions. Session effect was significant [$F_{(1,29)}$= 186.72; $P<0.0001$]. The animals showed more freezing behavior at test session as compared to training session

(Duncan test, $P<0.05$). There was also a significant Minute effect [$F_{(4,116)}=40.30$; $P<0.0001$].

3.2.2. Experiment 2

Since the lesioned animals differed from controls in the last 2 min only, the time of observation was extended from 6 to 8 min in order to check that results were consistent and replicable.

3.2.2.1. Tone fear conditioning 2. As can be seen in Fig. 4, the lesion affected conditioning to a tone. There was a significant Minute effect [$F_{(7,182)}=90.7$; $P<0.0001$] and both groups displayed more freezing behavior after tone presentation (Duncan, $P<0.05$). The Minute×Group interaction was significant [$F_{(7,182)}=3.1$; $P=0.004$] and the posthoc analyses (Duncan, $P<0.05$) showed that lesioned animals displayed less freezing than control animals at all times after tone presentation. The main effect of Group was also significant [$F_{(1,26)}=5.3$; $P<0.03$].

3.2.3. Experiment 3

The purpose of the experiment was to find whether electrolytic lesion effects on tone fear conditioning would still occur if the postsurgical recovery period was extended from 14 days to 2 months before beginning behavioral procedures. This experiment was conducted because there is a report in the literature showing that the postsurgical recovery period can influence the lesion effect [9].

3.2.3.1. Tone fear conditioning 3. When the postsurgery recovery period was extended to 2 months the lesioned animals showed no impairment in tone fear conditioning (Fig. 5). The results shown are from two experiments. As there were no differences between the experiments nor between the groups, the data from both experiments were collapsed. Two-way ANOVA of the collapsed data showed that there was a significant Minute effect [$F_{(5,260)}=227.70$; $P<0.0001$], with animals displaying more freezing after tone presentation (Duncan, $P<0.05$). The main Group effect [$F_{(1,52)}=0.16$; $P=0.68$] and the interaction [$F_{(5,260)}=0.55$; $P=0.73$] were not statistically significant.

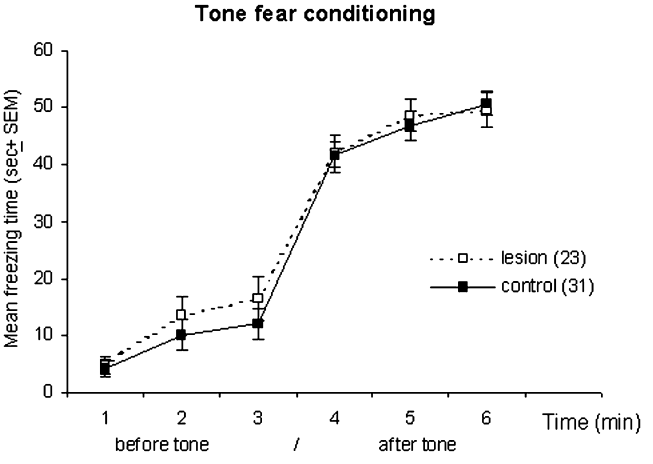

Fig. 5. Effects of electrolytic dorso-striatal lesion on freezing response of rats in tone fear conditioning test measured during 3 min before and 3 min after tone. The animals were tested 60 days after surgery. The number of animals per group is shown in parentheses after the group names.

3.2.4. Experiment 4

The purpose of the present experiment was to observe the effect of neurotoxical lesion of the dorsal striatum on the acquisition of tone fear conditioning.

3.2.4.1. Tone fear conditioning 4. As in Experiments 1 and 2, lesioned animals showed an impairment in the acquisition of tone fear conditioning (Fig. 6). There was a significant Minute effect [$F_{(5,110)}=76.94$; $P<0.0001$]; and a significant interaction between Minute and Group effects [$F_{(5,110)}=2.9$; $P<0.02$]. Posthoc test (Duncan $P<0.05$) for

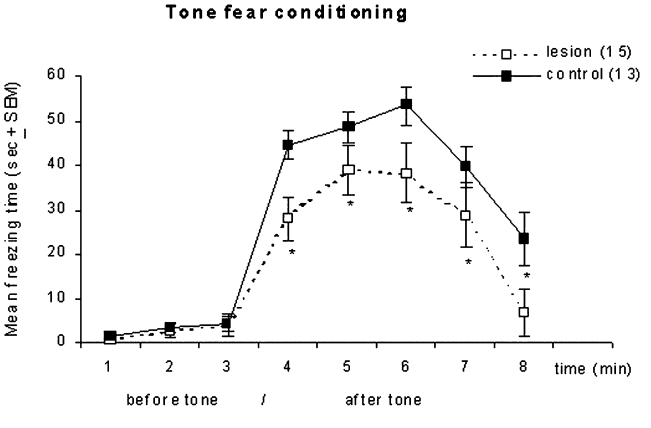

Fig. 4. Effects of electrolytic dorso-striatal lesion on freezing response of rats in tone fear conditioning test measured during 3 min before and 5 min after tone. The animals were tested 14 days after surgery. The number of animals per group is shown in parentheses after the group names; *, $P<0.05$ compared to control.

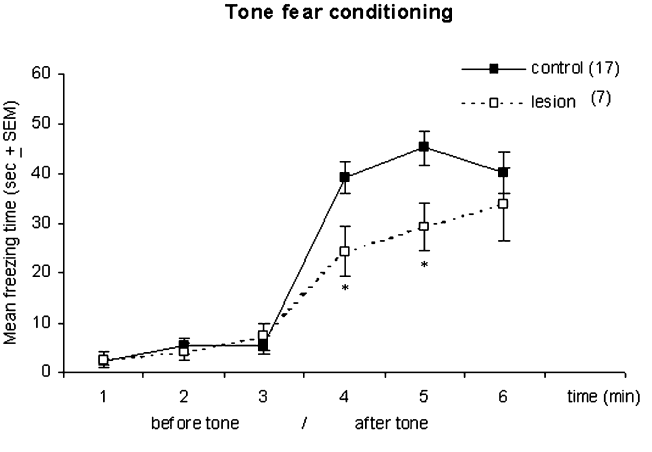

Fig. 6. Effects of neurotoxic dorso-striatal lesion on freezing response of rats in tone fear conditioning test measured during 3 min before and 3 min after tone. The animals were tested 14 days after surgery. The number of animals per group is shown in parentheses after the group names; *, $P<0.05$ compared to control.

the Minute effect showed that the animals increased freezing after tone presentation, and Posthoc test (Duncan $P<0.05$) for the interaction showed that lesioned animals displayed less freezing than the control animals during minutes 4 and 5 of the test. Main Group effect was not significant [$F_{(1,22)}=2.21$; $P=0.15$].

4. Discussion

The main finding of the present study is that, although dorsal striatal lesion did not completely abolish tone fear conditioning, it produced a slight but selective impairment in this task. This result was obtained with electrolytic lesion in both Experiments 1 and 2 (the observation period was extended from 6 to 8 min in the latter). Neurotoxic dorsal striatal lesion also induced the same pattern of impairment as compared to electrolytic lesion. But the neurotoxic lesions were larger than the electrolytic ones, rendering a direct comparison between them somewhat tenuous. The same electrolytic lesion that affected tone fear conditioning, however, did not affect contextual fear conditioning. Therefore, we observed dissociation between lesion effects for two classical fear conditioning tasks. A cautionary note is advisable, however, against a full generalization of such a conclusion to the whole dorsal striatum, since this structure is large and heterogeneous.

Since impairment was restricted to tone conditioning, without affecting contextual conditioning, it is not possible to attribute the observed impairment to motor alterations that could possibly interfere with the animal's ability to exhibit freezing behavior or to motivational alterations (e.g. insensitivity to shock, reduced anxiety). It is also unlikely that the impairment of tone fear conditioning is due to lesions of fibers of passage since neurotoxic lesion affected performance as well.

It must be emphasized that the effect was observed when freezing was used to measure acquisition of conditioning. Reyes-Vazquez et al. [34] observed that an almost total striatum electrolytic lesion (including part of the nucleus accumbens) did not interfere with an autonomic conditioned response such as heart rate. Moreover, a dissociation between somatomotor and autonomic responses was reported in tone classical conditioning in rabbits using shock as US [29]. These authors observed that caudate lesion impaired acquisition of Pavlovian conditioned eyelid reflex in the rabbit, whereas conditioned heart rate was unaffected. They also observed that other motor responses were preserved, suggesting that the lesion interferes selectively with somato-motor learning, whereas the more generalized motor activity remains intact. These data may indicate that the lesion does not impair the animal's ability to learn the relationship between CS and US but only the somatomotor response in response to CS [29]. However, it can be argued that heart rate is not a good measure of autonomic conditioning in striatal-lesioned animals since it may also respond to nonassociative features of classical fear conditioning [12]. Whether dorsal striatal lesion impairs tone–shock (CS–US) association or the motor response in response to the tone used as CS is an open question that deserves more investigation.

Contextual fear conditioning is affected by hippocampal lesion, possibly due to the role of this structure in storing spatial information [13,30]. Many studies have shown that lesions or pharmacological manipulations of the hippocampus impair spatial processing-based tasks (for a review see [20]) although some controversial about the involvement of the hippocampus in mediating spatial memory exists (for a review see on this topic [11]). In contrast, nonspatial tasks are not affected [8,19,20,22,25,26,38]. Several of these nonspatial tasks are impaired by lesions in the dorsal striatum [6,17,23,24], supporting early findings that have suggested a role for the caudate-putamen in mediating learning and memory [32,33], and in accordance with the notion that there are multiple parallel memory systems in the brain [37]. The acquisition of certain hippocampal-independent tasks such as left/right discrimination, however, does not seem to be affected by striatal lesion [21,31], suggesting that not all hippocampal-independent tasks are dependent on dorsal striatum functioning. The results of the present study extend to anterodorsal striatum the involvement in fear conditioning.

Another factor that may be responsible for the apparent disagreement in the literature is the site of the lesion. Regarding its connections, the striatum is a large and heterogeneous region. Its cortical afferents are topographically organized as different cortical areas project to different striatal areas [18], so different striatal regions are likely to be related to different functions. Therefore, lesions in two distinct parts of the striatum differentially affect performance of rats on tests of olfactory and visual conditioned emotional responses [39].

In the present study, the lesion affected the anterior dorsal striatum and partially both medial and lateral areas but predominantly the medial part, that is, our lesion probably reached regions which receive visual and to a lesser extent auditory projections [18]. However, the attempt to explain the effect of dorsal striatum lesion through its cortical connections is not entirely satisfactory since direct lesions of the auditory cortex do not prevent tone conditioning [14]. The critical structures necessary for tone fear conditioning appear to be the amygdala and the medial geniculate body [35].

Nonetheless, the present results suggest that the lesioned area of the striatum is somehow involved in mediating tone fear conditioning, but not contextual conditioning. But, in spite of being replicable, the effect of the lesion is transient. When the recovery period is extended to 2 months, impairment is no longer observed. So our data showed that animals may not need the lesioned area for execution of the tone classical conditioning task. Therefore, despite some involvement in this task, the dorsal

striatum does not seem to be as critical as the medial geniculate body and the amygdala. An alternative interpretation is that the regions around the lesion underwent a functional reorganization during the extended recovery period in an attempt to supply the lesioned area, which may explain the lack of impairment after this period. This is not unlikely if one remembers that there are no borderlines limiting anatomic subregions within the striatum, which means that a similar kind of neural tissue surrounds the affected area. Functional recovery after striatal lesion was also observed by others [9] in an inhibitory avoidance task in mice. Glick et al. [9] tested the animals 2 and 28 days after striatal electrolytic lesion and impairment of performance was observed only after the shorter recovery period. In most studies, however, behavioral procedures subsequent to striatal lesion begin 2 weeks after surgery (as in Experiments 1, 2 and 4). It is therefore possible that recovery may not be specific for the tone fear conditioning task and may rather be a general phenomenon that occurs in other tasks, but has not yet been observed because the testing period was too short.

In summary, the results point to transient involvement of the lesioned area of dorsal striatum in mediating tone fear conditioning, but not contextual classical fear conditioning.

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