Effects of Bilateral Electrolytic Lesions of the Dorsomedial Striatum on Motor Behavior and Spatial Learning in Rats

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ABSTRACT

Introduction: The dorsal striatum plays an important role in the control of motor activity and learning processes within the basal ganglia circuitry. Furthermore, recent works have suggested functional differentiation between subregions of the dorsal striatum

Methods: The present study examined the effects of bilateral electrolytic lesions of the dorsomedial striatum on motor behavior and learning ability in rats using a series of behavioral tests. 20 male wistar rats were used in the experiment and behavioral assessment were conducted using open field test, rotarod test and 8-arm radial maze.

Results: In the open field test, rats with bilateral electrolytic lesions of the dorsomedial striatum showed a normal motor function in the horizontal locomotor activity, while in rearing activity they displayed a statistically significant motor impairment when compared to sham operated group. In the rotarod test, a deficit in motor coordination and acquisition of skilled behavior was observed in rats with bilateral electrolytic lesions of the dorsomedial striatum compared to sham. However, radial maze performance revealed similar capacity in the acquisition of learning task between experimental groups.

Discussion: Our results support the premise of the existence of functional dissociation between the dorsomedial and the dorsolateral regions of the dorsal striatum. In addition, our data suggest that the associative dorsomedial striatum may be as critical in striatum-based motor control.

1. Introduction

The basal ganglia are large subcortical nuclei, including the dorsal striatum, that are strongly interconnected with the neocortex. An increasing number of evidence indicates that the basal ganglia play a central role in motor control and learning processes that lead to habit formation or the acquisition of skilled behavior (Djurfeldt, Ekeberg, & Graybiel, 2001; Graybiel, 1995, 1998; Knowlton, Mangels, & Squire, 1996; McDonald & White, 1994; Ogura, et al., 2005; White & McDonald, 2002). As the importance of the dorsal striatum in the control of motor activity and learning processes

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such as acquisition of habits and skills has been recognized from the literature (Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999; Smith, Amalric, Koob, & Zigmond, 2002; Van Golf Racht-Delatour & El Massioui, 1999), there is growing evidence from anatomical and behavioral studies in animals and humans demonstrating that the dorsal striatum is functionally differentiated (Corbit & Janak, 2007; Devan, McDonald, & White, 1999; Moussa, Poucet, Amalric, & Sargolini, 2011; O'Doherty, et al., 2004; Yin, Knowlton, & Balleine, 2004; Yin, Ostlund, Knowlton, & Balleine, 2005). The dorsolateral striatum (DLS) may support instrumental stimulus–response (S–R) habit formation via input from sensorimotor neocortex, while the dorsomedial striatum (DMS) appears to contribute to behavioral flexibility – the cognitive control of behavior – via prefrontal and limbic circuits engaged in relational and spatial information processing (B. D. Devan, Hong, & McDonald, 2011; Grahn, Parkinson, & Owen, 2008). In rodents, the DMS is part of the associative striatum connected to the prefrontal cortex and limbic territories whereas the sensorimotor striatum includes the DLS, which is connected to the somatosensory and motor cortical areas (Alexander & Crutcher, 1990).

Although considerable amount of studies have demonstrated the functional dissociation between the DMS and the DLS in learning processes, only few of them have investigated the effects of dorsomedial striatum lesions on motor coordination concomitantly to the spatial learning (Ashby, Turner, & Horvitz, 2010; Braun & Hauber, 2011; Corbit & Janak, 2007, 2010; Moussa, et al., 2011; Yin & Knowlton, 2004, 2006; Yin, et al., 2004). The present study aimed at investigating the effects of bilateral electrolytic lesions of the DMS on the striatum-based function underlying motor control and acquisition of learning tasks, using various behavioral tests such as an open field test for spontaneous locomotor activity, a rotarod test for motor coordination and acquisition of skilled behavior or a baited 8-arm radial maze for learning and spatial memory.

2. Methods

2.1. Animals

Experiments were carried out on adult male Wistar rats weighing in average 250 g. Animals were bred and reared in the colony room of Mohammed-V University (Rabat, Morocco). They were placed pair per cage in an animal room with natural light and temperature conditions, the temperature varying between 18 and 25°C and the humidity around 45%. All animals had free access to food and water. Rats were randomly assigned to one of the two groups: one group received bilateral lesion of the striatum (n = 10) and the other one served as control group (n = 10). Experiments were conducted in accordance with international guidelines on the ethical use of animals and all efforts were made to minimize animal suffering.

2.2. Stereotaxic Surgery

Rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and placed in a stereotaxic frame. The scalp was incised and small holes were drilled through the skull at sites corresponding to the striatal lesion coordinates. The following coordinates were used: 1.2 mm anterior to bregma, 2.0 mm lateral to the midline, and 5.5 mm ventral from the surface of the skull (Paxinos & Watson, 2007). Bilateral striatal lesions were made by passing 2 mA of direct anodal current for 20 seconds through an insulated nichrome electrode exposed 0.8 mm at the tip and connected to the current generator. Sham animals received surgical treatment identical to the lesioned animals except that the electrode was lowered into the brain and brought back without current having been passed.

2.3. Open Field Test

The open field, a rectangular black wooden box (75 cm length × 45 cm width × 35 cm height) with a grid of 15 × 15 cm squares drawn on the floor with white paint is described elsewhere (Alamy, Errami, Taghzouti, Saddiki-Traki, & Bengelloun, 2005; Bengelloun, Nelson, Zent, & Beatty, 1976). The testing took place in an isolated room between 08:30 and 03:00 am, with the lights dimmed. Each rat was tested during a 5-minutes session on 3 consecutive days. At the beginning of each trial the rat was placed in a corner square facing the wall. The rats' locomotor activity was recorded as the total number of squares crossed during a five minutes period. A square crossing was defined as the passage of all four of the subject's paws over one of the lines of a square. Number of rearings (defined as raising both forepaws off the ground and extension of body) was also counted. Moving time was counted using a stopwatch. The test box was cleaned between the testing of each individual rat.

2.4. Eight-Arm Radial Maze

The 8-arm radial maze apparatus, constructed from wood, consisted of an octagonal central platform (35.5 cm diameter), with eight unenclosed arms of 45 cm length and 15 cm width radiating outward from the open

center area and numbered in a clockwise fashion from 1 to 8. The maze was positioned on a stool 75 cm above the floor, and a small plastic feeding bowl was embedded at the end of each arm. All animals were submitted to daily food restriction so that their body weight was reduced to maintain 75% of their normal weight. This reduction was meant to motivate maze learning behavior.

To accustom animals to the radial maze, they were allowed a 15-minute daily habituation session for 3 consecutive days. All arms were maintained baited during all the trial time. Trials were run once per day. Each trial started when a rat was placed onto the centre of the platform facing the arm 1 and was allowed to make an arm choice to find and eat food pellets until all eight pellets had been eaten or 10 min had elapsed. Each rat was placed in the radial maze in a random order changed every day. Radial maze was cleaned between each animal with water and absorbing paper to minimize olfactory intra-maze cues.

During daily sessions, data considered were (i) arm entries, (ii) pellets eaten and (iii) total time elapsed. With those data, the number of errors and the total time spent in the maze were counted. Any arm is considered visited when the animal entered it with all its four paws. Every entry in an already visited arm was considered as an error. Entering an arm without consuming the food pellet was also considered an error. Acquisition was considered complete when no more than one error was committed on two consecutive days.

2.5. Rotarod Test

To assess motor coordination and the acquisition of skilled behavior in rats with bilateral partial lesions of the dorsal striatum, we performed a rotarod test. The rotarod unit consisted of a rotating spindle (2.5 cm diameter and 53 cm length) and a power source for turning the spindle (Buitrago, Schulz, Dichgans, & Luft, 2004; Monville, Torres, & Dunnett, 2006; Paylor, Spencer, Yuva-Paylor, & Pieke-Dahl, 2006). The rod was elevated 60 cm above the floor. Rats were placed individually on the revolving rod and tested through two different sessions on two consecutive days (one session a day), whereby each session included three separate test trials. Testing sessions consisted of evaluating the animals' motor coordination using two acceleration rates, 10 and 25 revolutions per minute (rpm). Rats were trained at 10 rpm on day 1 and at 25 rpm on day 2. Each animal received three consecutive trials per day. Before the test, rats were not allowed to accommodate on the device. The time spent as well as the strategy used (walking or grasping) by the animal to maintain its balance on top of the rod was recorded. The time in seconds at which each animal fell from the rod was recorded using a stopwatch.

2.6. Histological verification

After the completion of behavioral testing, the lesioned rats were deeply anaesthetized with an i.p. injection of 6% chloral hydrate and perfused intracardially via the ascending aorta with 0.9% saline followed by 4% paraformaldehyde. The brains were removed from the skull and stored in 4% paraformaldehyde for 1 week. Frozen coronal sections were cryostat cut at 40 µm and every fifth section was mounted on glass microscope slides. The mounted sections were stained with toluidine blue and examined under light microscopy. The lesion sites were determined using the atlas of Paxinos and Watson (1998).

2.7. Statistical Analysis

Data were expressed as mean ± SEM and the results were subjected to a one-way ANOVA analysis using the SPSS 11.5 software (SPSS statistical software package, Chicago, IL). The P-value < 0.05 was considered to be statistically significant.

3. Results

3.1. Open Field Test

The open field test assessed locomotor and exploratory activity in animals (n = 10 each group) after electrolytic lesions of the striatum. Results for the spontaneous locomotor activity measured as travelled squares per 5 min (squares/5 min) are shown in Fig. 1A for the three-day sessions. Statistical analyses of spontaneous locomotor activity (crossing) revealed that there were no significant differences in the lesioned rats' activity compared to sham operated group.

The vertical exploratory activity (rearing) of rats was measured by counting the number of rearing events (events/5 min). As shown in the Fig. 1B, the lesioned rats showed less rearing activity compared to sham operated group. One-way ANOVA performed revealed significant differences between the activity of electrolytic lesioned rats and that of sham operated rats on day 1 and day 2 ($(F(1,18) = 21.819, p<0.001)$ and $(F(2,18) = 34.27, p<0.001)$, respectively). There were no significant differences on day 3 between the two groups of rats, due probably to the habituation effect.

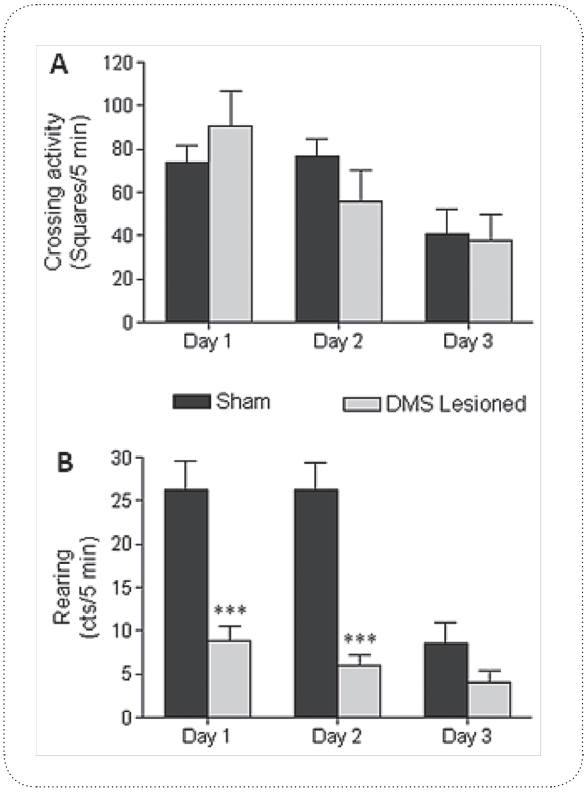

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Figure 1. Open field performance of sham operated and bilaterally DMS lesioned rats. The histograms represent the mean number of squares entered with four paws per 5 min (A) and the mean number of rearing events (B) during 3 consecutive daily sessions. ***p<0.001 as compared to sham operated group.

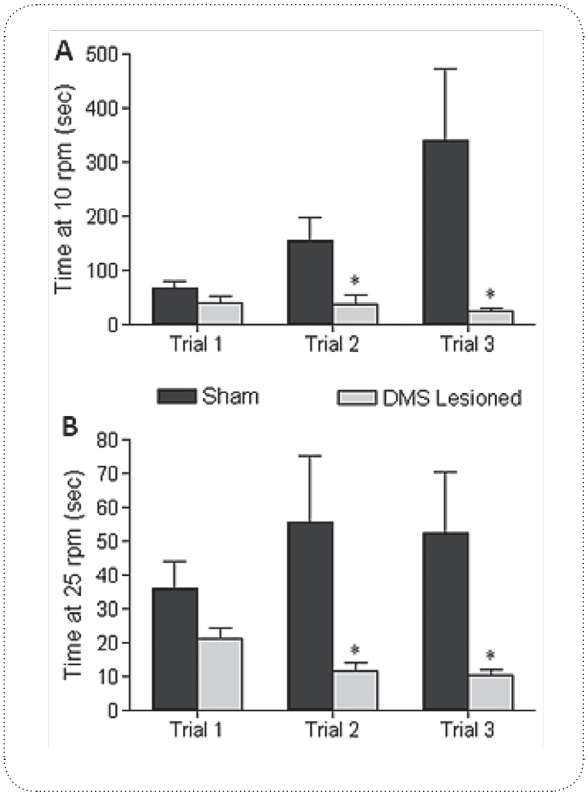

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Figure 2. Rotarod performance. The histograms represent the time spent by sham operated rats and rats with bilateral electrolytic lesions of the DMS walking on the rotating rod at 10 rpm (A) and 25 rpm (B). *p<0.05 as compared to sham operated group.

3.2. Rotarod Test

Motor coordination and balance performance as well as acquisition of skilled behavior were measured using a rotarod test. Rats were placed on the revolving rotarod and the latency to fall was recorded. Three trials per session a day were given to each rat at respective constant speeds of 10 rpm on day 1 and 25 rpm on day 2 and the time value in seconds was recorded for each trial per rat. Statistical analyses of the results of the experiments (using a one-way ANOVA), as shown in Fig. 2, reveal significant differences between the two experimental groups of rats in term of time spent on the rotating rod ($p<0.05$) during trials 2 and 3 at both 10 rpm and 25 rpm sessions. The motor impairment manifested from the first session of the rotarod test; this suggests that the baseline of motor coordination was impaired in the bilateral lesioned rats. In fact, we observed a trend in the first session and a statistically significant difference by one-way ANOVA in the second and third sessions in both 10 rpm- and 25 rpm-sessions. The results indicate that DMS lesioned rats stayed less time on the rotarod when compared to sham operated rats. Furthermore, it can be seen that sham operated rats improved their rotarod performance by increasing the time spent on the rotating rod across sessions when compared to the DMS lesioned animals.

3.3. Radial Maze Performance

In this experiment, number of errors committed and time spent by the rats on the maze were considered. As shown in Fig. 3, no significant differences were found between the two groups of animals in terms of number of errors either on the first day ($F(2,26) = 0,334$; $p>0.05$) or during the entire acquisition phase. Three days were sufficient for all rats to attain the criterion, suggesting that electrolytic lesions to the striatum did not affect rats' capability of learning. Session duration also did not appear to be affected by the striatal lesions.

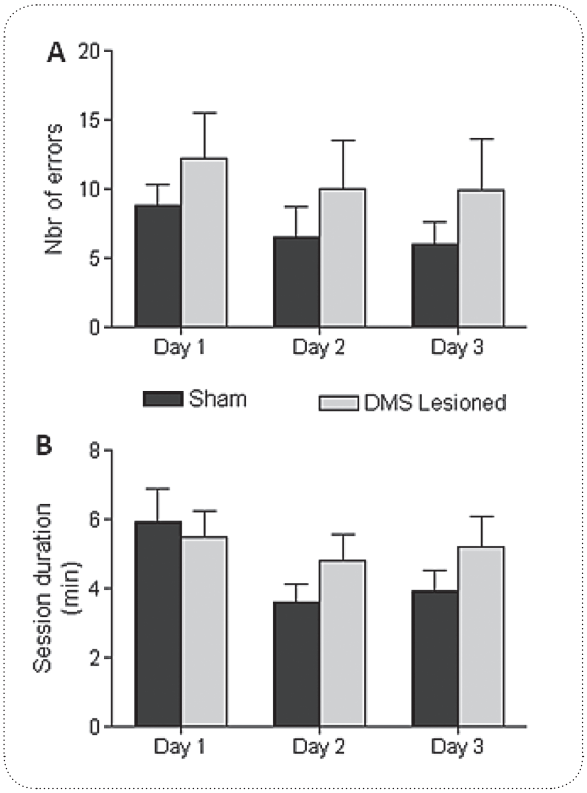

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Figure 3. Radial maze performance of sham operated and bilaterally DMS lesioned rats. The histograms represent the mean number of errors (A) and the mean time of session duration (B).

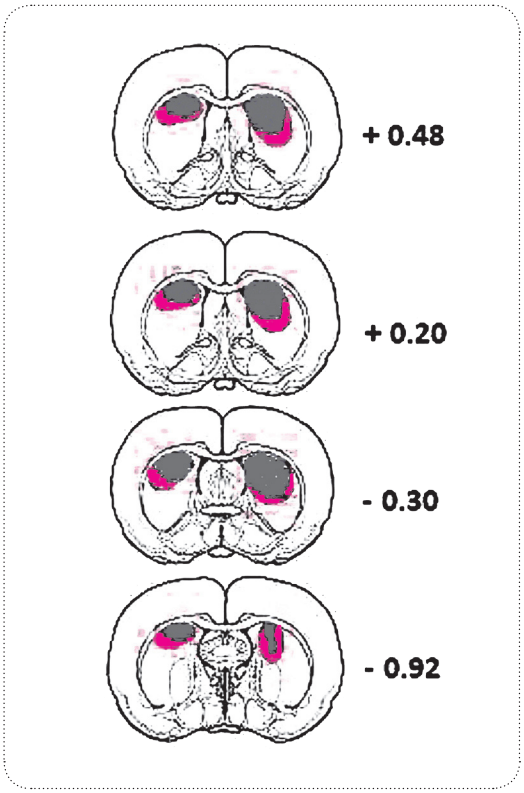

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Figure 4. Minimum (blue hatching) and maximum (red hatching) extent of damage at the striatal electrolytic lesion sites summarized on four representative coronal sections (Adapted from Paxinos and Watson, 1998). The extent of both lesion types ranged from +1.2 to −1.8 antero-posterior from Bregma. Inspection of the stained tissue did not reveal extensive damage outside of the striatum.

3.4. The histological verification revealed that the electrolytic lesions affected the posterior subregion of the dorsal striatum and the medial part of this area (Fig.4).

4. Discussion

In this study, we assessed motor coordination and learning ability in rats after bilateral electrolytic lesions of the dorsal striatum. Our results indicate that striatal lesions dramatically impaired motor coordination in rats but did not affect rats' cognitive function as well as radial-maze performance. In fact, our results show that rats with lesions to the dorsomedial striatum were able to learn tasks in the maze as rapidly as sham operated rats, indicating that damage to this specific area of the dorsal striatum did not affect the animals' ability to learn.

The open field test assesses locomotor activity and gives an idea of anxiety-like behavior of a particular animal. In the present study, the spontaneous locomotor activity measured as crossed squares per 5 min, showed no significant differences in terms of mobility between the two groups of rats, suggesting that bilateral electrolytic lesions of the dorsmedial striatum did not disrupt general motor functions in these rats.

Accordingly, Ogura and his colleagues (Ogura, et al., 2005) reported that rats with 6-hydroxydopamine-induced incomplete destruction (50-77%) of nigral dopamine cells after intra-striatal injections of 6-hydroxydopamine (6-OHDA) displayed normal spontaneous locomotor activity, in contrast to the rats with complete lesion of nigral dopamine cells which suffered a significant impairment in the initiation of movement. Therefore, given that both electrolytic and neurotoxin lesions of the striatum cause degeneration of dopaminergic terminals in the striatum (Devan, et al., 1999) which results in functional impairment, and based on our present finding we can conclude that electrolytic lesions of the dorsomedial striatum did not affect the dopamine-medi-

ated control of motor activity underlying striatum-based motor function.

In the vertical activity, however, the striatal lesioned rats showed a decreased amount of rearing events in the open field test when compared to control animals. Rearing activity in rodents is generally considered an essential component of exploratory behavior, and therefore a reduced number of rearing events would indicate an increase of anxiety and a deficit in exploratory behavior in rats. Even though, the decrease of vertical activity in our study could also be related to a decrease in the balance and/or motor coordination abilities of the lesioned animals and not directly related to the anxiety and exploratory behavior of rats. Indeed, Chauhan and co-workers have stated that the two legged stance used for rearing is less stable than the four legged stance used for horizontal movement (Chauhan, Moretti, Iaconcig, Baralle, & Muro, 2005), supporting the fact that horizontal exploratory behavior was normal in our rats.

In addition, in a previous study, Ogura and co-workers have found that rats with bilateral partial lesions of the nigrostriatal dopamine (DA) system showed intact general motor functions with a normal spontaneous locomotor activity in an open field test, whilst they displayed a drastic impairment during acquisition of skilled behavior on the rotarod task (Ogura, et al., 2005). Similar observations were reported by Barnéoud and co-workers in rats bearing a partial lesion of nigrostriatal DA cells. The animals were able to perform normal stepping adjustments when evaluated in a staircase test, but exhibited impairments in skilled paw use task, indicating a coordination deficit of the paw rather than a deficit of movement initiation (Barnéoud, Descombris, Aubin, & Abrous, 2000). They evaluated such paw-reaching impairment as a deficit of complex sensorimotor behavior.

Therefore, to investigate the deficit in motor coordination and balance in our rats, we used a rotarod test which requires enhanced motor coordination skills. In this test, the acquisition of skilled behavior consisting of a new combination of posture and forward locomotive steps (Ogura, et al., 2005) is needed for the rats to be able to last on the rotating rod. In the present study, rats with bilateral electrolytic lesions of the striatum displayed a drastic impairment in the acquisition of skilled behavior on the rotarod task despite the fact that they showed intact general motor function through a relatively normal locomotor activity in the open field.

While sham operated rats continued to improve their rotarod performance, displaying continuous increase of time spent walking on the rotating rod, the DMS lesioned rats exhibited a significant decrease in their rotarod performance. This finding suggests that the lesioned rats were impaired in motor coordination according to the results of rearing activity in the open field test.

We compared radial maze performance between DMS lesioned and sham operated rats. All the arms of the maze were baited during experiment and the animals had to acquire a win-shift strategy over trials and days to be able to visit baited arms only once within a daily training session. Analysis of data from the 8-arm radial maze task showed that both DMS lesioned rats and sham operated rats were similar in rate of acquisition of the task, since no differences were found on any of the behavioral measures. These results show that rats with lesions to the dorsal striatum were able to learn tasks in the maze as efficiently as sham control rats, indicating that damage to the dorsal striatum had no effect on the animals' ability to learn.

Our results line up with several previous rodent studies demonstrating the role of the dorsal striatum in different learning processes. More specifically, the dorsolateral striatum has been reported to be strongly implicated in habit learning and the formation of stimulus-response (S-R) habit (Corbit & Janak, 2010; McDonald & White, 1994; Moussa, et al., 2011; Van Golf Racht-Delatour & El Massioui, 1999; Yin, et al., 2004), whereas the dorsomedial striatum is known to be necessary for learning and expression of goal-directed actions (Grahn, et al., 2008; Yin & Knowlton, 2006; Yin, et al., 2004). On the basis of this hypothesis, Yin and co-workers had trained rats with both dorsolateral and dorsomedial striatum lesions to press a lever for sucrose under interval schedules. They found that rats with lesions of dorsolateral striatum, but not the dorsomedial lesioned group, reduced responding after outcome devaluation, providing direct evidence that intact dorsolateral striatum is necessary for habit formation (Corbit & Janak, 2007, 2010; Faure, Haberland, Condé, & Massioui, 2005; Van Golf Racht-Delatour & El Massioui, 1999; Yin, et al., 2004), as is the case in our radial maze results.

According to our results, DMS lesions probably reached regions which receive primarily inputs from the medial prefrontal and orbitofrontal cortices (McGeorge & Faull, 1989; Moussa, et al., 2011), and additionally significant projections from the perirhinal and agranular insular regions as well as from the entorhinal cortex and basolateral amygdala (BLA) (Corbit & Janak,

2010; McGeorge & Faull, 1989; Moussa, et al., 2011; Yin & Knowlton, 2004). Interestingly, Corbit and Janak (2010) reported that the more posterior regions of the dorsomedial striatum receive dense BLA projections. Furthermore, it has been reported that rats with BLA lesions were not impaired in the acquisition of simple or instrumental tasks, indicating that basic reward mechanisms were intact in these animals (Blundell, Hall, & Killcross, 2001; Corbit & Balleine, 2005; Corbit & Janak, 2010). These findings are consistent with our results, in the fact that the DMS lesioned rats were not impaired in the acquisition of learning tasks in the radial maze.

In conclusion, data from this study support the premise of the existence of functional dissociation between the dorsomedial and the dorsolateral regions of the dorsal striatum. In addition, our data suggest that the associative dorsomedial striatum may be as critical in striatum-based motor control. Behavioral assessment reveals that bilateral lesions of dorsomedial striatum seriously impaired rats' motor coordination whilst general motor functions remained relatively intact. Lesions did not disrupt rats' learning ability. Finally, these results highlight a possible critical role of the dorsomedial striatum in striatum-based motor function.

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