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Research

Contributions of dorsal striatal subregions to spatial alternation behavior

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Considerable evidence has shown a clear dissociation between the dorsomedial (DMS) and the dorsolateral (DLS) striatum in instrumental conditioning. In particular, DMS activity is necessary to form action-outcome associations, whereas the DLS is required for developing habitual behavior. However, few studies have investigated whether a similar dissociation exists in more complex goal-directed learning processes. The present study examined the role of the two structures in such complex learning by analyzing the effects of excitotoxic DMS and DLS lesions during the acquisition and extinction of spatial alternation behavior, in a continuous alternation T-maze task. We demonstrate that DMS and DLS lesions have opposite effects, the former impairing and the latter improving animal performance during learning and extinction. DMS lesions may impair the acquisition of spatial alternation behavior by disrupting the signal necessary to link a goal with a specific spatial sequence. In contrast, DLS lesions may accelerate goal-driven strategies by minimizing the influence of external stimuli on the response, thus increasing the impact of action-reward contingencies. Taken together, these results suggest that DMS- and DLS-mediated learning strategies develop in parallel and compete for the control of the behavioral response early in learning.

The dorsal striatum is assumed to mediate procedural learning, which is based on the acquisition of context-appropriate responses leading to habitual behavior (Packard and Knowlton 2002; White and McDonald 2002). Indeed, a large number of studies have shown that dorsal striatal activity is specifically required to solve complex maze tasks based on the acquisition and performance of rigid motor actions (Cook and Kesner 1988; Jog et al. 1999; Packard 1999; White and McDonald 2002; Barnes et al. 2009).

In contrast to the dorsal striatum, the dorsal hippocampus is central for rapid and flexible acquisition of knowledge about the external environment, generating a so-called “cognitive map” (O’Keefe and Nadel 1978). These studies suggest the existence of distinct and anatomically defined memory systems supporting navigational memory, which are based on different representations: the striatum-dependent habitual memory system, and the hippocampus-dependent declarative memory system. Currently, results are inconclusive in determining whether and how these two systems interact in controlling the behavioral response. Some studies suggest a competitive interaction (McDonald and White 1995; Poldrack and Packard 2003; Lee et al. 2008), whereas others point toward cooperative interaction (Compton 2001; Voermans et al. 2004). Moreover, early studies have shown that striatal lesions impair animal performance in spatial learning tasks that generally require the integrity of the hippocampus (Devan and White 1999; Devan et al. 1999; van Golf Racht-Delatour and El Massioui 1999). This evidence is consistent with recording studies showing that hippocampal and striatal neuronal activity are similar during the performance of goal-directed spatial tasks (Wiener 1993; Yeshenko et al. 2004). The striatum, therefore, likely contributes in a complex manner to different types of memory functions. This may be a direct consequence of the heterogeneous anatomical organization of the striatal complex along the mediolateral axis.

The dorsal striatum is generally subdivided into medial and lateral compartments, homologous to the primate caudate

nucleus and the putamen, respectively. The dorsomedial striatum (DMS) receives cortical inputs primarily from the medial prefrontal and orbitofrontal cortices, whereas the primary sensory and motor cortices selectively contact neurons located in the dorsolateral striatum (DLS) (McGeorge and Faull 1989; Voorn et al. 2004). Several studies have demonstrated distinct roles for the two striatal regions in instrumental learning and in navigation tasks. Devan et al. (1999) demonstrated that DMS, but not DLS, lesions impair performance of both the place and the cued versions of the water maze task, and also bias the rat’s response toward the inflexible cued strategy in a competition test. These data are consistent with a specific role of the DMS in forming action-outcome associations that mediate flexible and deliberated behaviors (Corbit and Janak 2010). Indeed, in a lever-press task, rats’ responses become insensitive to both outcome devaluation and contingency degradation following DMS lesions (Yin et al. 2005). In contrast, the DLS is involved in the integration of sensory and motor representations in the classical stimulus-response associations mediating inflexible and automatic habitual behaviors. Thus, it has been shown that the instrumental response in DLS lesioned animals is still sensitive to outcome devaluation following overtraining, whereas control rats develop habitual behavior (Yin et al. 2004). In combination, these results suggest the existence of two independent decision-making processes; one inflexible and dependent upon DLS activity, the other based on explicit action-outcome associations and mediated by the DMS (Balleine and O’Doherty 2010).

The aim of this study is to further investigate this issue by analyzing the effects induced by selective excitotoxic lesions of the DMS and the DLS in a continuous spatial alternation task. This task was originally employed to investigate context-dependent activity of the dorsal hippocampal neurons. In earlier studies, Wood et al. (2000) have shown that place cells differentially activate when an animal is in the central stem of the maze according to the proceeding choice—i.e., a turn to the left or right. However, hippocampal lesions that include both dorsal and ventral parts do not impair performance, unless memory demands are increased by inserting a delay (of 10 sec) before the animal’s

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choice (Ainge et al. 2007). This suggests that context-dependent place cell activity is not required to perform a continuous alternation. Other brain areas may therefore be responsible for such processes. The present study demonstrates that both the DMS and the DLS are involved in the acquisition of the continuous-T-maze task, and that they function in an opposing manner. The contrasting effects obtained following lesions of either one or the other structure support the hypothesis of competitive interaction between the two striatal areas over control of the animal's performance.

Results

Figure 1A provides a schematic representation of dorsolateral and dorsomedial striatal NMDA lesions. The minimum and maximum lesion extents are represented in light and dark gray, respectively. Inspection of the stained tissue showed clear neuronal loss in the target striatal areas, and did not reveal extensive damage outside the striatum. Tissue shrinkage resulted in a visible widening of the lateral ventricles in all cases. For each DMS and DLS rat we calculated the percentage of tissue damaged, using a baseline calculated from the averaged volumes of the DMS and DLS in three Sham rats. The averaged percentage of damaged striatal tissue in the DMS and DLS groups were 31.97 ± 2.07 and 29.94 ± 1.55 , respectively. An analysis of variance (ANOVA) showed no significant difference between the two groups ($F_{(1,14)} = 0.07$, $P = 0.78$). Figure 1B shows examples of NeuN-stained sections from a DMS (a), a DLS (b), and two Sham (c,d) rats.

Figure 1C shows a picture of the continuous spatial alternation task. Animals were required to run up the central stem of the maze and alternatively enter the left or right arm to obtain the reward. A correct response was scored each time the rats executed sequences corresponding to LSCR or RSCL (Fig. 1D). The evolution of performance during learning was analyzed by computing the average percentage of total errors in each training session for the three experimental groups. Further, we dissociated three different types of errors: procedural errors, working memory errors, and perseverative errors. A *procedural error* was scored each time the rat traversed one of the runways of the maze in the direction opposite to that defining a correct sequence (SR, SL, RCL, LCR, or CS). A single procedural error included all the incorrect sequences that the rat performed until it modified its trajectory and resumed the correct direction. A *working memory error* was defined as the rat reentering the previously chosen arm (RSCR or LSCL) a single time. If the rat repeated its choice (reentering a previously chosen arm more than once) a *perseverative error* was scored.

DMS lesions impair the acquisition of a continuous spatial alternation task

DMS lesions impaired animal performance across all training sessions. Figure 2 shows the percentage of total errors (A) and the percentage of error types (B) for Sham, DLS and DMS rats,

during the 20 training sessions. The percentage of total errors significantly increased in DMS animals. ANOVA showed significant group and session effects ($F_{(2,21)} = 4.53$, $P = 0.0231$ and $F_{(19,399)} = 54.84$, $P = 0.0001$, respectively), but no interaction between the two factors ($F_{(38,399)} = 0.93$, $P = 0.595$). Post-hoc analysis revealed the DMS group to be significantly different from both Sham and DLS rats ($P < 0.05$). DMS lesions increased the percentage of all error types during training (Fig. 2B). For the procedural and perseverative errors, ANOVA showed significant effects of group and session, but no significant interaction (procedural errors: group effect $F_{(2,21)} = 3.57$, $P = 0.046$, session effect $F_{(19,399)} = 40.07$, $P = 0.0001$; perseverative error: group effect $F_{(2,21)} = 11.36$, $P = 0.0004$, session effect $F_{(19,399)} = 7.42$, $P = 0.0001$). Post-hoc analysis revealed that the DMS group was significantly different from the Sham and DLS rats ($P < 0.05$), for both error types. For the working memory errors, ANOVA showed significant group ($F_{(2,21)} = 6.13$, $P = 0.008$) and session ($F_{(19,399)} = 36.32$, $P = 0.0001$) effects, and significant group \times session interaction ($F_{(19,399)} = 2.05$, $P = 0.0004$). Post-hoc analysis revealed that DMS animals differed significantly from both Sham and DLS groups during the initial training sessions ($P < 0.05$: from S2 to S7 for DMS vs. Sham; from S3 to S7 for DMS vs. DLS).

The deficit observed in the DMS group during training could not be ascribed to a difference in velocity. The average speeds were 34.19 ± 2.19 , 36.09 ± 1.68 , 29.54 ± 3.81 cm/sec, respectively for Sham, DLS, and DMS animals. An ANOVA of average speed showed no significant effect ($F_{(2,21)} = 1.32$, $P = 0.31$).

In order to obtain an overall measure of performance, we measured the number of training sessions necessary to achieve a learning criterion of $<30\%$ of errors during three consecutive

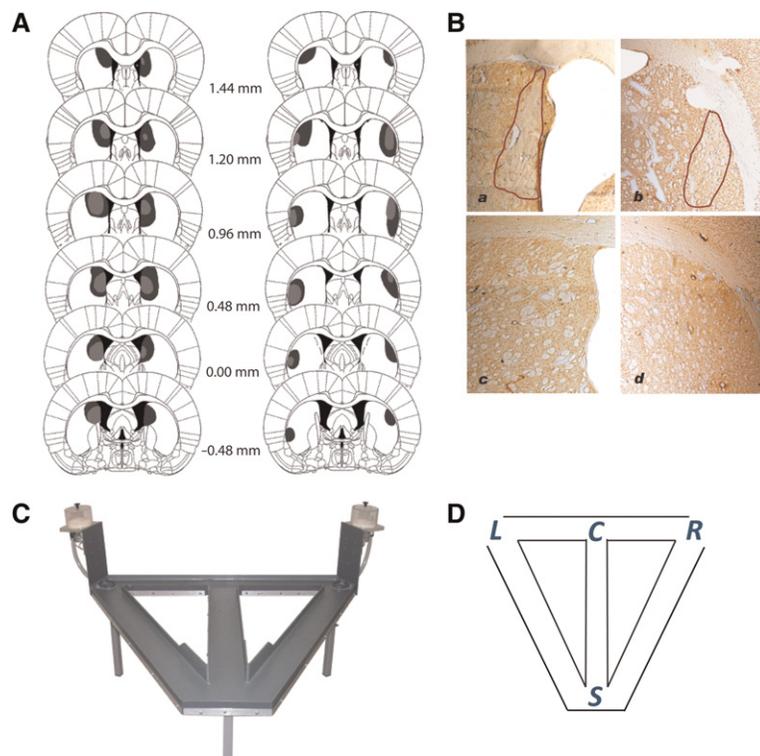


Figure 1. (A) Schematic representation of excitotoxic lesions of the DMS (left panel) and the DLS (right panel). Shaded areas represent the maximum (dark gray) and the minimum (light gray) extent of the lesions. (B) Microscope photographs of representative lesions of the DMS (a) and the DLS (b). The insets c and d show photos from sham lesions at both DMS and DLS coordinates, respectively. (C) Picture of the continuous alternation T-maze task. (D) Schematic representation of the T-maze task (S, start; C, center; L, left goal arm; R, right goal arm).

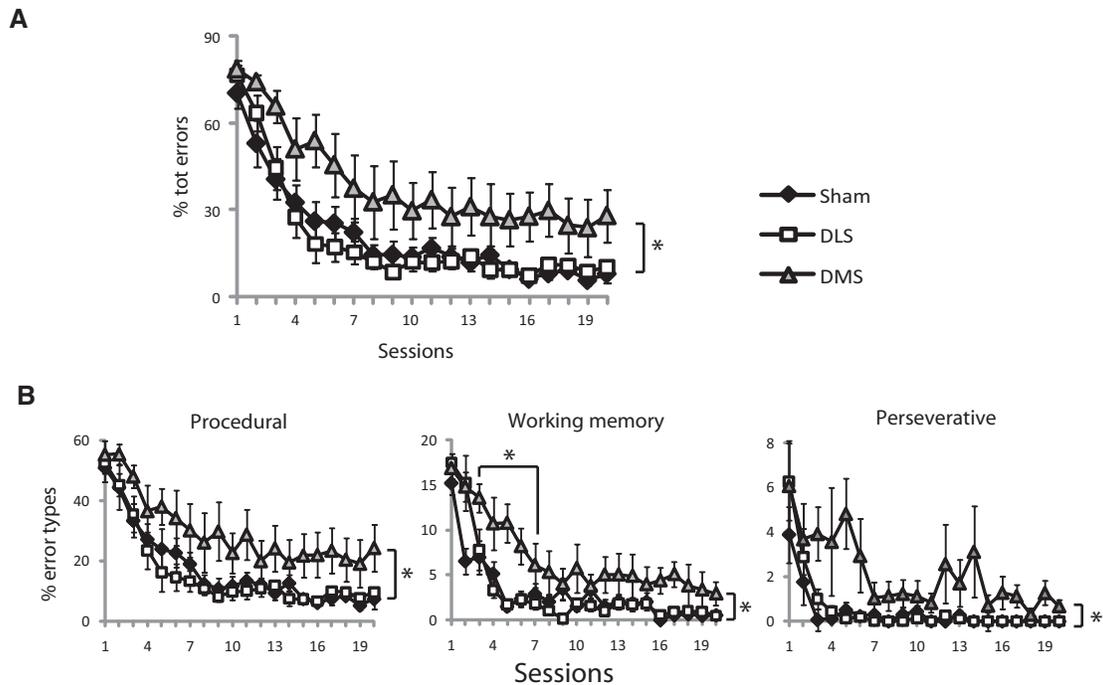


Figure 2. (A) Average percentage of errors for Sham, DLS, and DMS animals, during the 20 daily training sessions. (B) Averaged percentage of error types (*left*: procedural errors; *center*: working memory errors; *right*: perseverative errors) for Sham, DLS, and DMS groups during the 20 daily training sessions. A procedural error was defined as the animal traversing one of the runways of the maze in the opposite direction of that defining a correct sequence. A working memory error was defined as the rat reentering only once the arm previously chosen. If the rat continued to choose the same arm, a perseverative error was scored. * $P < 0.05$ DMS vs. Sham and DLS.

sessions for each rat. Figure 3A shows the average scores for Sham, DMS, and DLS groups. ANOVA showed a significant group effect ($F_{(2,21)} = 4.86$, $P = 0.018$). Post-hoc analysis revealed significant differences between DMS and both Sham and DLS groups ($P < 0.05$). We then correlated the performance scores of each DMS rat with the extent of the lesions, calculated as a percentage of damaged DMS (Fig. 3B; dots refer to individual animals). Linear regression and Pearson's product-moment correlation coefficient measures showed significant correlation between the size of DMS lesions and the index of performance ($P < 0.05$), indicating that the learning deficit in the DMS group was proportional to the extent of the lesion.

DLS lesions accelerate learning rate and extinction

To further characterize how performance changes across sessions, we analyzed the percentage of errors during the first quarter of each training session. The results of which are shown in Figure 4A. Similar to the learning curves based on the entire duration of the learning sessions, DMS rats had an increased percentage of errors compared to the two other groups. ANOVA showed significant group and session effects ($F_{(2,21)} = 7.37$, $P = 0.0037$ and $F_{(19,399)} = 43.85$, $P = 0.0001$, respectively), but no interaction between the two factors ($F_{(19,399)} = 1.39$, $P = 0.068$). Post-hoc analysis revealed the DMS group to be significantly different from both the Sham and DLS rats ($P < 0.05$). A curve fitting analysis was performed in order to analyze the evolution of animal performance across sessions. To characterize the rate of improvement across training sessions, the exponential law, previously used to analyze subject performance in simple reaction time tasks (Heathcote et al. 2000), was selected. For each rat the theoretical exponential curve that best fitted the real learning curve was

computed. We then extracted for each animal the learning rate coefficient (\ln), i.e., the slope of the theoretical curve. Representative examples of theoretical curves for a Sham, a DLS, and a DMS rat are shown in Figure 4C. The average coefficients of the three

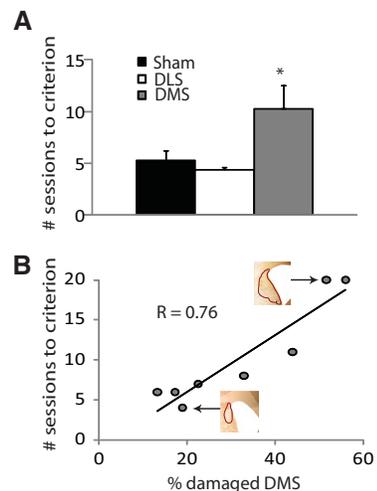


Figure 3. (A) Average number of sessions necessary to reach the learning criterion ($< 30\%$ of error trials during three consecutive sessions) for Sham, DLS, and DMS groups. * $P < 0.05$ DMS vs. Sham and DLS. (B) Scatter plot showing the relation between the lesion size (i.e., the percentage of damaged DMS) and the number of sessions to the learning criterion, for the DMS group. Dots refer to individual DMS lesioned rats. Linear regression line and the Pearson's product-moment correlation value are indicated.

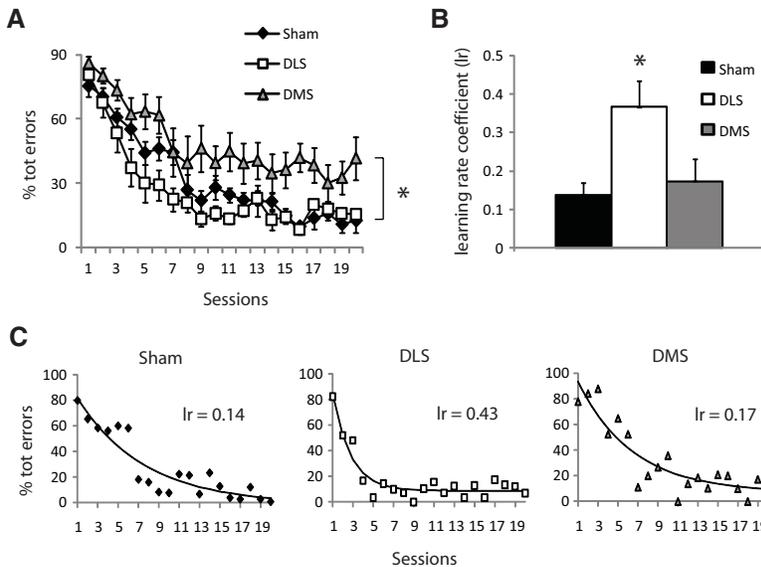


Figure 4. (A) Average percentage of errors during the first quarter of each session, during the 20 learning sessions, for Sham, DLS, and DMS groups. * $P < 0.05$ DMS vs. Sham and DLS. (B) Average learning rate coefficients obtained from the exponential curve fitting analysis of the performance during the first quarter of the learning sessions for each rat of the three groups. * $P < 0.05$ DMS vs. Sham and DLS. (C) Examples of three theoretical curves obtained by fitting the exponential function to the performance of individual rats from Sham (left), DLS (center), and DMS (right) groups. Dots refer to the percentage of errors during the first quarter of each learning session for a single animal. The learning rate scores are indicated.

experimental groups are shown in Figure 4B. Sham and DMS animals had similar lr values, whereas DLS animals showed significantly higher values. ANOVA revealed a significant group effect ($F_{(2,21)} = 4.36$, $P = 0.026$) and post-hoc comparisons showed a significant difference between DLS and both Sham and DMS groups ($P < 0.05$). A similar trend (Sham: $lr = 0.27 \pm 0.06$; DLS: $lr = 0.37 \pm 0.05$; DMS: $lr = 0.19 \pm 0.06$) was observed when the same curve fitting analysis was performed on learning curves based on the entire session, although no significant differences between groups were found (ANOVA: $F_{(2,21)} = 2.34$, $P = 0.12$).

At the end of the training, a subset of animals (Sham: $N = 4$; DLS: $N = 5$; DMS: $N = 5$) was submitted to a single 10-min extinction session, where no reinforcement was delivered. The results of which are shown in Table 1. In order to obtain a measure of performance less influenced by the motor activity of individual rats, we analyzed the number of correct trials rather than the number, or percentage, of errors. Using this measure of performance, we confirmed our previous results by demonstrating that DMS animals were significantly impaired during the last training session (S20), in comparison to Sham and DLS rats (Sham and DLS: 100 ± 0 ; DMS: 72.60 ± 15.37 ; Kruskal–Wallis analysis: $H_{(2,14)} = 6.27$, $P = 0.043$). Despite this difference, all three groups showed extinction by decreasing the number of correct trials during the extinction session relative to the final training session. However, extinction was greater in DLS rats. DLS animals performed a lower number of correct trials during the extinction session, compared to Sham and DMS rats (Kruskal–Wallis analysis: group effect $H_{(2,14)} = 7.05$, $P = 0.029$; Mann–Whitney U -test: $P < 0.05$ DLS vs. Sham and DLS vs. DMS). In order to analyze the evolution of animal performance during the extinction session, the number of correct trials during the first and second half of the session was counted and an extinction index calculated as the difference between the second and first halves, divided by the total number of correct trials. While no major differences among groups were observed during the first 5 min of extinction (Kruskal–Wallis

analysis: $H_{(2,14)} = 2.97$, $P = 0.226$), DLS rats performed less correct trials during the second half of the extinction session (Kruskal–Wallis analysis: group effect $H_{(2,14)} = 8.06$, $P = 0.017$; Mann–Whitney U -test: $P < 0.05$ DLS vs. Sham and DLS vs. DMS). The extinction index was significantly lower in DLS rats compared to Sham and DMS animals (Kruskal–Wallis analysis: group effect $H_{(2,14)} = 6.96$, $P = 0.03$; Mann–Whitney U -test: $P < 0.05$ DLS vs. Sham and DLS vs. DMS), thus indicating an accelerated extinction in the DLS group.

Discussion

This study demonstrates that dorsomedial and dorsolateral striatal lesions affect the acquisition of a continuous spatial alternation task in opposite ways. DMS lesions decreased animal performance during training, whereas DLS lesions accelerated learning during the initial trials of each training session and during extinction.

The dorsomedial and dorsolateral striatum are part of parallel cortico-striatal loops: the sensorimotor loop, connecting somatosensory and motor cortical areas with the DLS, and the associative loop, interconnecting the prefrontal cortex with regions of the DMS (Alexander and Crutcher 1990). Accordingly, several studies have demonstrated an involvement of the two areas in distinct learning processes. DMS activity is necessary to form action–outcome associations during instrumental learning and to correctly perform spatial navigation tasks (Devan et al. 1999; Yin et al. 2005). Our results confirm and expand these findings by demonstrating that DMS integrity is necessary for the acquisition of spatial alternation behavior. Indeed, DMS lesions increase the percentage of, mainly procedural, errors during training. Accordingly, DMS animals are less efficient in acquiring and performing specific spatial trajectories. However, although procedural performance was consistently impaired throughout all training sessions, working memory performance was impaired only during the first training sessions. This suggests that during the initial acquisition of the task, DMS lesions may impair the flexibility of the behavioral response, as previously suggested in instrumental tasks (Ragozzino 2007; Clarke et al. 2008). In that

Table 1. Performance of Sham, DLS, and DMS animals during the extinction session

	Extinction ^a	Extinction (first half)	Extinction (second half) ^a	Index ^a
Sham	23.75 ± 2.10	17.25 ± 1.89	6.75 ± 1.65	0.45 ± 0.09
DLS	16.60 ± 1.95 ^b	14.02 ± 1.63	2.40 ± 0.67 ^b	0.71 ± 0.07 ^b
DMS	28.80 ± 5.02	19.60 ± 2.66	9.20 ± 2.46	0.39 ± 0.06

Percentage of correct trials (\pm SEM) during the entire 10-min session (Extinction) and for the first and second halves of the session.

The Index represents the difference between the number of correct trials during the second and the first half of the extinction session, divided by the total number of correct trials.

^a $P < 0.05$ Kruskal–Wallis.

^b $P < 0.05$ U Mann–Whitney DLS vs. Sham and DLS vs. DMS.

regard it is worth noting that prior to surgery, animals received six to nine pretraining sessions, during which they were trained to run unidirectional laps on either the left or right side of the maze. Therefore, in order to learn the spatial alternation, the animals needed to switch the rule and overcome a habit-based behavioral strategy. However, if the deficit observed in the DMS rats resulted from the inability to switch the learning rule, we would expect a higher number of working memory and perseverative errors. The fact that DMS rats mainly perform procedural errors indicates that the nature of the deficit is more complex and does not exclusively involve a lack of behavioral flexibility.

The decreased performance of DMS animals was neither the result of motor deficits or impaired reward representation. DMS rats rapidly extinguished their behavioral responses during the extinction test, similar to control animals. It is more likely that the lesion disrupted the ability to acquire and execute a goal-directed spatial strategy. Other studies have demonstrated disruption of instrumental goal-directed responses following DMS inactivation (Yin et al. 2005). Further, rapid changes in firing patterns of DMS neurons have been shown during the initial acquisition of cue-response associations (Pasupathy and Miller 2005) and after a switch in stimulus-reward contingencies (Kimchi and Laubach 2009). DMS activity may therefore support the acquisition of spatial alternation behavior by generating the signal necessary to link goals with specific spatial sequences. Previous studies demonstrated that the posterior DMS is specifically involved in spatial learning, whereas the integrity of the anterior DMS is not required for such processes (Yin and Knowlton 2004). In our study, the deficit appears more related to the extent of the DMS lesion, rather than its location along the anterior–posterior axis. It is interesting to note that both the anterior and the posterior DMS receive prefrontal cortical inputs (McGeorge and Faull 1989), and lesions of the prefrontal cortex produce deficits in instrumental conditioning similar to those of DMS lesions (Killcross and Coutureau 2003; Tran-Tu-Yen et al. 2009). The interaction between the prefrontal cortex and the dorsomedial striatum may therefore be necessary for the acquisition of goal-directed responding in both instrumental learning and spatial navigation.

The dorsolateral striatum, on the other hand, is involved in habit formation (Hernandez et al. 2006) and in developing rigid motor sequences in complex mazes (Yin and Knowlton 2004). In the present study, we observed that the acquisition of a goal-directed spatial strategy is accelerated by DLS lesions. Using a curve fitting analysis, we showed that learning rates were increased following DLS lesions, particularly during the initial trials of training sessions. Similar conclusions can be drawn on the basis of results obtained during the extinction test, which demonstrate that DLS animals stopped alternating between the two arms more rapidly than Sham and DMS rats. This suggests that DLS lesions accelerate the learning of reward-response contingencies. Previous studies have shown that lesions of the DLS bring normally habitual actions under the control of the goal-directed system (Yin et al. 2004), but, to our knowledge, this is the first study showing an acceleration of goal-directed learning following DLS inactivation. We suggest the hypothesis that disruption of the habit-formation system (based on the association between stimuli and actions) may facilitate goal-directed strategies by minimizing the influence of external stimuli on the response, thus increasing the impact of action-reward contingencies. An alternative explanation would be that DLS lesions disrupt the habit-based behavioral strategy that was acquired during the pretraining phase, thus accelerating learning of the spatial alternation rule. Whereas this hypothesis is consistent with the role of the DLS in mediating the acquisition and the performance of rigid motor actions, it is not fully supported by the rapid extinction induced by DLS

lesions. In the rapid extinction case, animals would have to overcome a behavioral strategy that is not habitual and therefore not DLS-dependent. This suggests a possible effect of DLS lesions in accelerating goal-driven strategies. It would be of interest to investigate whether a similar acceleration of spatial alternation learning occurs without the unidirectional pretraining.

Available evidence suggests that learning new skills by trial and error is often accompanied by an evolution of behavior with a shift from flexible and goal-directed toward becoming habitual. As this transition occurs, neural control by dorsal striatal circuits shifts from DMS-mediated formation of action-outcome contingencies to DLS-dependent development of inflexible stimulus-response associations (Miyachi et al. 2002; Costa et al. 2004; Yin et al. 2009). Indeed, rats overtrained in a cross maze shift from a place strategy, mediated by hippocampal and DMS activity, to a DLS-dependent response strategy (Packard 1999; Yin and Knowlton 2004). However, lesions of either the DMS or the DLS may result in the rapid development of the alternative learning process. For example, Devan and White (1999) demonstrated that DMS and DLS lesions produced a preference for the cue and the place response respectively, on a place-cue competition test in the water maze. This suggests that the two systems work in parallel rather than in a serial manner. Accordingly, it has been recently shown that different neuronal activity patterns emerged simultaneously in the DMS and DLS during learning in a conditional T-maze (Thorn et al. 2010). Whereas task-related activity in the DLS increases as animal responses become habitual, experience-dependent firing patterns in the DMS weakened during the same period (Thorn et al. 2010). The authors suggest that the two structures work in parallel during the course of learning, and that the DMS may assume a permissive role on DLS-mediated processing. In our study, DLS activity plays an opposite role on DMS-mediated processes, as its inactivation facilitates the acquisition of goal-directed strategy. Whether this facilitation effect is, at least in part, the consequence of an increased behavioral flexibility (i.e., the ability to switch between task rules) remains to be investigated. Nevertheless, these results suggest that DMS- and DLS-mediated learning strategies compete for control of the behavioral response early in learning. The mechanism of selection that allows for the expression of either of the two strategies is not clear. Several authors have suggested that frontal cortical areas play an executive role in switching between behavioral strategies (Shima and Tanij 1998; Brass et al. 2005). Alternatively, this action may be exerted through competition on downstream targets, as recently suggested by Stalnaker et al. (2010). The investigators showed that neuronal activity in the DLS and DMS represents both action-outcome and stimulus-response associations, suggesting that interaction with output structures is a determinant for the expression of either learning strategy.

In conclusion, our study demonstrates the existence of competitive interactions between DMS- and DLS-mediated decision-making processes, whose control over behavior establishes early in learning and extends beyond instrumental conditioning.

Materials and Methods

Subjects

Twenty-four male Long-Evans rats (350–400 g) purchased from a commercial supplier (Janvier, Le Genest-St-Isles, France) were housed in pairs in standard breeding cages (40 cm long × 26 cm wide × 16 cm high) with food and water ad libitum, kept in a temperature controlled room (20°C ± 2°C) on a 12-h light/dark cycle. One week after arrival, animals were handled daily by the experimenter for seven consecutive days. They were then submitted to a progressive food deprivation schedule and maintained at

80%–85% of their initial body weight throughout the entire behavioral procedure. Rats were assigned to Sham ($N = 8$), DLS ($N = 8$), or DMS ($N = 8$) groups on the basis of their presurgery performance.

All procedures were conducted in accordance with the European Community Council Directive of November 24, 1986 (86/609/EEC), and with the French Agriculture and Forestry Ministry (decree 87–849).

Surgery

Rats were deeply anesthetized by i.m. injections of xylazine (15 mg/kg) and ketamine (100 mg/kg) and placed in a stereotaxic apparatus (Kopf Instruments). Small holes were drilled into the skull bilaterally, and 23-gauge injection cannulas were lowered at the following coordinates (Paxinos and Watson 1997): DLS: first injection site, AP = 1.4 mm, ML = ± 3.7 mm, DL = -5 mm; second injection site, AP = -0.1 mm, ML = ± 4.5 mm, DV = -5 ; DMS: first injection site, AP = 1.4 mm, ML = ± 1.8 mm, DL = -5 mm; second injection site, AP = -0.1 mm, ML = ± 2.2 mm, DV = -4.8 . For the lesion groups, 0.4 μ L of NMDA (Sigma Aldrich) 0.12M (20 mg/mL NaCl 0.9%) were infused on each site over 5 min. The sham group received an equal volume of vehicle solution either at DMS ($N = 4$) or DLS ($N = 4$) coordinates. Five minutes after the infusion, the injection cannulas were removed.

Apparatus

The modified T-maze apparatus (Fig. 1C) was similar to that described by Wood et al. (2000). It consisted of four wooden runways 10 cm wide and painted gray (equipped with 2-cm-tall walls on each side), a 100-cm-long central stem, a crosspiece 100 cm long forming the two choice arms and two additional runways each connecting the distal end of one choice arm to the base of the central stem. At the cross point between the central stem and the two diagonal runways the walls were raised to 5 cm to prevent animals from making shortcuts. Reward wells were located at the distal end of each choice arm. Food rewards (45-mg sugar pellets) were delivered through two food pellet dispensers (MedAssociates) mounted above the wells and activated by remote hand-operated switches. The maze was elevated 40 cm from the ground on a metal frame, located in a room containing several visual cues attached to the walls. The apparatus was illuminated by four symmetrical light spots (40 W) fixed to the ceiling. A radio centered above the maze was used to mask uncontrolled directional sounds. The experimenter was in the adjacent room.

Behavioral procedure

Before surgery, rats were familiarized with the maze for a 20-min session, during which they were allowed to freely explore the apparatus and to collect randomly dispersed sugar pellets. The pretraining started the following day and required rats to run unidirectional laps either on the left or the right side of the continuous T-maze. Access to the opposite side of the maze was prevented by two gray plexiglas barriers placed at the start of the opposite arm and the end of the opposite return arm (Lee et al. 2006). Each pretraining session required the rat to run exclusively on one side of the maze (i.e., LSCLSC, Fig. 1D), and was followed 24 h later by a session in which they ran exclusively on the other side (i.e., RSCRSCL). A single 45-mg sugar pellet was given each time the animal performed a correct trial (LSC or RSC). No food was delivered when the rats performed an incorrect trial (LCS or RCS). Animals were submitted to daily 20-min sessions until they reached the criterion of 70% correct trials over three consecutive sessions. This pretraining period lasted six to nine sessions at most (three to five sessions on each side of the maze). Rats were then assigned to one of the three experimental groups and underwent surgery. Following a recovery period of 1 wk, rats reran in unidirectional laps for two to three 20-min sessions daily, but no criterion was fixed. Animals were then submitted to the training phase, during which access to both choice arms was open and rats were required to run up the central stem (SC) and alternatively

enter the left (L) or right (R) choice arm in order to obtain the reward (Fig. 1D). An arm entry was registered when the rat placed four paws into the runway. If the animal reached the end of the choice arm but failed to perform a correct alternation sequence no sugar pellet was delivered. Rats were trained for 20 consecutive daily sessions. Each session lasted for a maximum of 20 min and was stopped once the animals made 100 correct trials (average session duration: 10 min).

At the end of training, a subset of animals (Sham: $N = 4$, DLS: $N = 5$, DMS: $N = 5$) were submitted to a single 10-min extinction test, in which no food reward was delivered.

Behavioral measurements and statistical analysis

During each training session, the number of correct trials and the number of errors were counted, and the animal's performance expressed as a percentage of total errors. A correct trial consisted of either RSCL or LSCR sequences (Fig. 1D). Three different types of errors were distinguished. A procedural error was defined as the rat traversing one of the four runways of the maze in the opposite direction to that defining a correct sequence (SR, SL, RCL, LCR, CS). A single procedural error included all the incorrect sequences performed by the rat until the trajectory was modified and the correct direction resumed. A single re-entry to the arm, which was previously chosen (RSCR or LSCL), was considered a working memory error. If the rat continued to incorrectly choose the same arm, a perseverative error was scored.

The percentage of total errors across sessions (either for the entire duration or for the first quarter of the training sessions) were analyzed using repeated measures analysis of variance (ANOVA), with sessions ($N = 20$) as within subject factor and lesion groups ($N = 3$: Sham, DLS, and DMS) as between subject factor. A Newman–Keuls post-hoc analysis was employed when allowed (lesion group effect or lesion group \times sessions effect). Curve fitting analysis (Python 2.6.5.1) was performed in order to further the analysis of possible differences between the learning curves of the three experimental groups. An exponential curve was used to characterize the evolution of performance in individual rats (i.e., the decrease of the percentage of errors over sessions). The exponential function used to relate the percentage of errors to learning sessions N was

$$as + st(1 - lr)^N,$$

where as represents the theoretical asymptote, st the starting value (relative to the asymptote), and lr the learning rate. Initial values for the search procedure were set at 0 for st and 100 for as . The analysis was performed for individual rats in the Sham, DLS, and DMS groups, and learning rate coefficients (lr) were computed for the learning curves based on the entire duration or the first quarter of each training session. We then analyzed the differences in average lr between experimental groups using a one-way ANOVA design, with lesion group as the main factor.

In addition to the percentage of errors, we calculated the number of training sessions necessary to achieve the learning criterion of <30% of errors during three consecutive sessions. Possible differences between Sham, DMS, and DLS animals were analyzed using a one-way ANOVA design, with the lesion group as the main effect. The relation between the extent of the dorso-medial striatal lesions (percentage of damaged striatal tissue over controls) and learning deficits was estimated for the DMS group by both linear regression and via computation of the Pearson product-moment correlation coefficient between lesion size and the number of sessions to reach criterion.

Finally, during extinction, animal performance was quantified in a similar manner to that used for the training phase. The number of correct trials for the entire duration of the session, and for the first and the second halves, were compared in the three lesion groups using a Kruskal–Wallis test. A Mann–Whitney U -test was employed to perform group-by-group comparisons (Sham vs. DMS, Sham vs. DLS, DMS vs. DLS). An index of extinction was calculated based on the difference between the number of correct trials during the second and the first half of the

extinction session, divided by the total number of correct trials. Possible differences among groups were analyzed using a Kruskal–Wallis test and group-by-group comparisons were performed using Mann–Whitney *U*-tests.

Histological assessment of lesion sizes

At the end of the experiment, all rats were sacrificed using a lethal sodium pentobarbital overdose and perfused transcardially with 0.9% NaCl followed by 4% paraformaldehyde solution. Brains were stored in three different sucrose solutions (10%, 20%, 30%) over three consecutive days, and rapidly frozen before 30- μ m coronal sections were cut throughout the anterior and posterior striatum on a cryostat. Every second section was mounted and stained with Cresyl Violet. In order to visualize neural loss more clearly, the remaining sections were stained with a marker for neural nuclei, NeuN, and mounted on glass. Sections were studied using a Zeiss microscope with a mounted camera. All pictures were processed with AxioVisionLE (Carl Zeiss Vision, GmbH). Lesion extent was calculated by manually delimiting the area of cell loss on each section. The volume of the damaged area was then estimated by multiplying the measured surfaces by the intersections distance. The total volume of dorsomedial and dorsolateral striatum was calculated in three sham-operated rats. The average DMS and DLS size was computed and used as a baseline to calculate the percentage of damaged striatal tissue for each rat in the DMS and DLS groups.

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