

Differential Roles of the Dorsolateral and Midlateral Striatum in Punished Cocaine Seeking

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Continued instrumental drug seeking despite contingent punishment is a core phenotype of drug addiction. Although the neuroanatomical basis of punished drug seeking is unclear, we hypothesize that the sensorimotor striatum, a structure that mediates habitual drug seeking, also mediates punished cocaine seeking. Forelimb sensorimotor projections into the striatum of the rat extend from the dorsolateral to midlateral striatum. Here, we selectively inactivated the dorsolateral and midlateral striatum in rats responding for cocaine in a seeking–taking task. We inactivated both regions after the acquisition of cocaine seeking, after extended cocaine self-administration and finally after the introduction of intermittent, seeking-contingent foot shock. The results show that inactivation of the dorsolateral striatum selectively disrupted punished drug seeking but did not affect unpunished drug seeking, even after extended training. Inactivation of the midlateral striatum, on the other hand, disrupted drug seeking at all stages of training. The effect of inactivating the dorsolateral striatum under punishment conditions was present before delivery of the first shock in the session, and responding reverted to baseline the next day. Thus, inactivation of the dorsolateral striatum seems to enhance the influence of recalled threat of negative consequences of cocaine seeking. The proportional reduction in responding after inactivation of the dorsolateral striatum did not vary with the individual level of compulsivity. Together, these results suggest a novel differentiation of function in the sensorimotor striatum, where the dorsolateral striatum selectively mediates the rigidity of responding after overtraining, while the midlateral striatum mediates responding itself at all stages of training.

Introduction

Habitual instrumental responding for rewards is characterized by insensitivity to reward devaluation when tested under extinction conditions, but normal sensitivity to devaluation when the devalued outcome is actually delivered after the response (Adams, 1982; Miles et al., 2003). On the other hand, compulsive responding is characterized by insensitivity to reward devaluation even when negative outcomes are actually delivered after the instrumental response (Deroche-Gamonet et al., 2004; Pelloux et al., 2007). Chronic cocaine self-administration in rats leads to habitual responding at the group level (Zapata et al., 2010), and compulsive cocaine seeking in a subgroup of animals (Pelloux et al., 2007).

Habitual responding for food (Yin et al., 2004, 2006) and cocaine (Zapata et al., 2010) is mediated by the dorsolateral striatum (DLS). There are several indications that the DLS may also regulate compulsive cocaine seeking (Everitt and Robbins, 2005). Studies using PET imaging of [^{11}C]raclopride binding in human

cocaine addicts have shown a cocaine cue-elicited dopamine response in the putamen that correlated significantly with addiction severity (Volkow et al., 2006). Second, it has been shown that dorsal striatal overexpression of BDNF in rats leads to an extreme form of escalation of cocaine taking that strongly suggests a loss of sensitivity to overdosing (Im et al., 2010).

Rats press levers with their forepaws, and rodent cortical forelimb motor areas project to the lateral striatum in an elongated zone (see Fig. 1B) from the dorsolateral to midlateral striatum (Ebrahimi et al., 1992). Electrophysiological correlates of forepaw lever pressing have been observed in this entire striatal region (West et al., 1990; Carelli et al., 1997). Unfortunately, investigation of the function of this region in compulsive responding after overtraining is complicated by the fact that it has also been associated with forelimb lever pressing per se (Whishaw et al., 1986; Fricker et al., 1996; Yin et al., 2006).

However, careful reading of the literature suggests a potential regional differentiation within the forelimb area of the striatum. Inactivation of the dorsal part of the forelimb projection field (DLS) has no effect on baseline responding for food (Corbit and Janak, 2007) or cocaine (Kantak et al., 2009; Zapata et al., 2010), whereas inactivation or lesion studies that have targeted the more ventral part of the forelimb projection field (midlateral striatum, MLS) do show a decrement in baseline responding for food (Fricker et al., 1996) or cocaine (Fuchs et al., 2006).

These findings, together with those from our pilot experiments, led us to investigate the differential contribution of these two regions to cocaine seeking in the context of an extended

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self-administration study with contingent punishment. We hypothesized that the MLS would mediate drug seeking at all stages of training (early in training, after overtraining, and after introduction of contingent punishment), while the DLS would mediate drug seeking in animals under the threat of punishment, perhaps selectively in animals that become insensitive to punishment after extended cocaine self-administration (Pelloux et al., 2007).

Materials and Methods

Subjects

Male outbred Lister hooded rats (Charles River), weighing 275–325 g at the start of the experiments, were housed in pairs in polycarbonate cages (length, 40 cm; width, 25 cm; height, 18 cm) and maintained under a reversed 12 h light/dark cycle (lights on at 7:00 P.M.) at a constant temperature ($21 \pm 1^\circ\text{C}$) with *ad libitum* access to water. Each subject was given 18 g of laboratory chow (SDS Ltd) per day, which was sufficient to maintain body weight at no less than 85% of free feeding weight. The experimental procedures were conducted in accordance with the United Kingdom's 1986 Animals (scientific procedures) Act (project license PPL 80/2234).

Apparatus

Instrumental training and testing took place in 12 operant conditioning chambers ($29.5 \times 32.5 \times 23.5$ cm; Med Associates) equipped with two 4-cm-wide retractable levers that were mounted in the intelligence panel 12 cm apart and 8 cm from the grid floor. Above each lever was a cue light (2.5 W, 24 V), and a white house light (2.5 W, 24 V) was located on the opposite wall. The floor of the chamber was covered with a metal grid with bars separated by 1 cm and connected to a shock generator and scrambler (Campden Instruments), which delivered 0.50 mA foot shocks. SILASTIC tubing shielded with a metal spring extended from each animal's intravenous catheter to a liquid swivel (Stoelting) mounted on an arm fixed outside the operant conditioning chamber. Tygon tubing extended from the swivel to a Razel infusion pump (Semat Technical) located adjacent to the housing. The testing chamber was placed within a sound- and light-attenuating housing equipped with a ventilation fan that also screened external noise. The operant conditioning chambers were controlled by software written in C++ using the Whisker control system (Cardinal, 2001).

Surgery

Subjects were anesthetized with ketamine (Ketalar, 90 mg/kg, i.p.) and xylazine (Rompun, 6.7 mg/kg, i.p.) and implanted with an intravenous catheter and intracranial cannulae. For intravenous surgery, rats were implanted with a single catheter in the right jugular vein. Catheters were made from 22 gauge steel cannulae with elongated ends. SILASTIC tubing (0.012 inner diameter) was secured to one end of the cannula, and the top was fixed to nylon mesh. The mesh end of the catheter was sutured subcutaneously between the scapulae. To prevent infection, rats were treated from the day before to 7 d after the surgery with 10 mg/kg Baytril (Bayer) subcutaneously. For intracranial cannulae implantation, rats were placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3.3 mm below the interaural line (Paxinos and Watson, 1998). Bilateral stainless steel guide cannulae (26 gauge; Plastics One), targeting the lateral striatum ($+1.0$ mm anterior from bregma, ± 3.0 mm lateral from the midline, 3.0 mm ventral from the skull surface) were implanted stereotactically and secured to the skull using dental cement anchored to stainless steel screws tapped into the skull. Obturators (Plastics One) were placed into the cannulae to prevent occlusion. The rats were allowed to recover for at least 7 d after surgery before behavioral testing.

Drug infusions

Before the start of experimental infusions, the rats were habituated to the infusion procedure with a surrogate infusion, which consisted of the removal and replacement of the obturator during gentle restraint within a time course identical to that of drug infusion. During infusions, the rats were gently restrained while the obturators were removed and 33-gauge

bilateral injectors (Plastics One) that protruded either 1.5 mm (dorsolateral striatum) or 2.5 mm (midlateral striatum) beyond the guide cannulae were inserted, and 0.5 μl of solution was then infused over a 1 min period into each injection site. The injector was left in place for 1 min to allow the drug to diffuse in the local vicinity of the injector tip. The injector was then carefully removed and the obturator was replaced. All infusions were given in the behavioral testing room. The animals were infused with either PBS or a mixture of the GABA-B and GABA-A receptor agonists baclofen (bac) and muscimol (mus) at the doses of 0.3 nmol and 0.03 nmol per side, respectively, in PBS to inactivate neurons in the region of the infusion (McFarland and Kalivas, 2001).

Procedure

Task acquisition. The procedures are illustrated in Figure 1A. Each session began with the insertion of the taking lever, and the assignment of the left or right lever as the taking lever was counterbalanced across rats. Responding on the taking lever was reinforced under a fixed ratio (FR) 1 schedule and each lever press produced a 0.25 mg/kg infusion of cocaine at the rate of 0.1 ml/5 s, accompanied by the withdrawal of the taking lever for 20 s, the extinction of the house light, and the illumination of the stimulus light above the lever for 5 s. The sessions terminated after 2 h, or before if 30 infusions had been earned. After 5 sessions with just the taking lever, the seeking lever was introduced. The seeking and taking levers were never present simultaneously, because meeting the response requirement on the seeking lever led to retraction of the seeking lever and introduction of the taking lever. The schedule on the seeking lever was gradually increased from Random Interval 2 s (RI 2), to RI 15 s, RI 30 s, RI 60 s, and RI 120 s over 5 d, while the schedule on the taking lever remained at FR 1. Completion of the seeking and taking components together constituted one seeking-taking cycle. Thereafter, the postinfusions timeout was increased from 20 s to 2 min, 4 min, and 10 min over 3 more days. The 10 min postinfusion timeout was chosen to minimize psychostimulant effects of cocaine infusion on the next seeking component (Olmstead et al., 2000).

Pre-long-access infusions. Once the animals had acquired the task, the first set of four infusions was conducted over 8 d; two infusions (PBS or bac/mus) into the dorsolateral striatum, and two more infusions (PBS or bac/mus) into the midlateral striatum. Infusions were always preceded by an infusion-free baseline day to allow for recovery. The order of the experimental and control infusions, and of the DLS and MLS infusions, was counterbalanced at all stages, but the two infusions for one structure were always conducted sequentially to minimize potential effects of baseline drift in relevant comparisons.

Long-access cocaine self-administration. Subsequently, the animals were given 12 daily sessions of *ad libitum* cocaine self-administration in which only the taking lever was presented, and pressing that lever resulted in a cocaine infusion and the standard 20 s timeout. The sessions terminated after 6 h, or earlier if 150 infusions had been earned.

Post-long-access infusions. After one re-baseline session under the seeking (RI 120 s)/taking (FR 1) with 10 min timeout schedule, the second set of four infusions was conducted over another 8 d, again with two infusions (PBS or bac/mus) into the dorsolateral striatum, and two infusions (PBS or bac/mus) into the midlateral striatum. The procedures were identical to the pre-long-access infusions, except that the order of infusions was newly counterbalanced.

Introduction of punishment. Next, intermittent and unpredictable contingent punishment of the seeking response was introduced, which resulted in the emergence of compulsive drug seeking (Pelloux et al., 2007). During each punishment session, half of the cycles contained no punishment and terminated with access to the taking lever and cocaine availability. In the remaining half of the cycles, the seeking response was punished: the first response that met the RI requirement in the seeking link delivered the foot shock (0.5 s, 0.5 mA) and led to a direct transition to the timeout period without the taking link. Reinforced and punished cycles were presented randomly within the daily sessions, except that no more than two sequential cycles were punished. Three punishment sessions were run before the last infusions phase (see Infusions during punished responding), as previous experiments have shown that re-

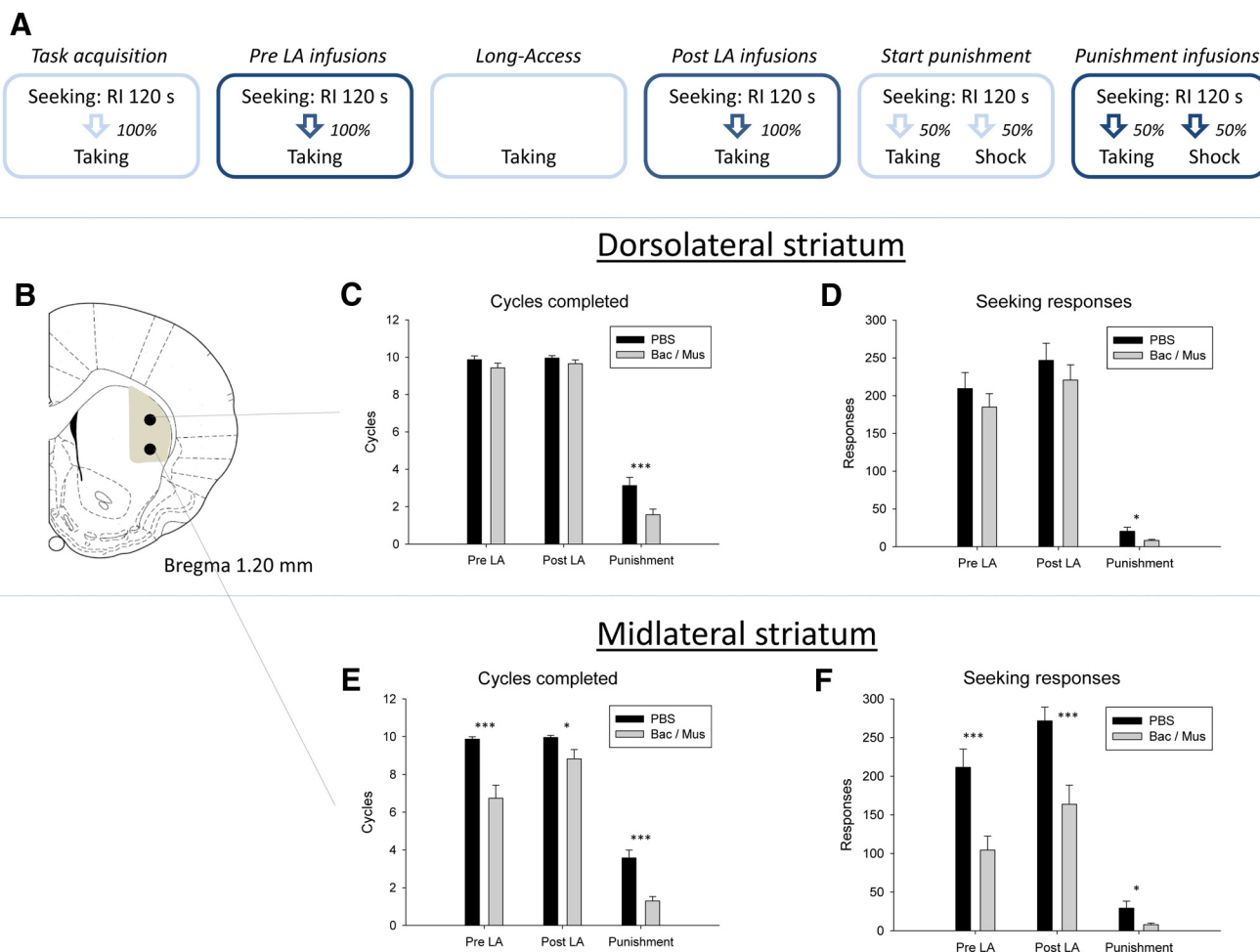


Figure 1. Cocaine seeking and taking task and effect of inactivating the dorsolateral and midlateral striatum on compulsive cocaine seeking. **A**, Experimental procedures and instrumental contingencies. Each infusion block involved PBS and baclofen/muscimol (0.3/0.03 nmol per side) infusion into the DLS and MLS. RI, Random Interval schedule. **B**, Neuroanatomical representation of cortical forelimb projection area in the lateral striatum (gray shaded area) and definition of the DLS and MLS (black dots). **C**, Mean (\pm SEM) seeking cycles completed after inactivation of the DLS at the three time points. Inactivation of the DLS affected responding under punishment but not baseline responding. **D**, Mean (\pm SEM) seeking responses after inactivation of the DLS at the three time points. **E**, Mean (\pm SEM) seeking cycles completed after inactivation of the MLS at the three time points. Inactivation of the MLS affected responding at all stages. **F**, Mean (\pm SEM) seeking responses after inactivation of the MLS at the three time points. *** $p < 0.001$, * $p < 0.05$. For all comparisons, $N = 23$.

sponding of both punishment-sensitive and -resistant (compulsive) subgroups stabilized after three punishment sessions (Pelloux et al., 2007).

Infusions during punished responding. After stabilization of responding under punishment, the third set of four infusions was conducted over another 8 d, again with two infusions (PBS or bac/mus) into the dorsolateral striatum, and two infusions (PBS or bac/mus) into the midlateral striatum. The procedures were identical to the earlier infusions, except that an additional postinfusion session was conducted the day after the last infusion to obtain complete postinfusion data.

Histology

Following the completion of the experiment, subjects were anesthetized with a lethal dose of sodium pentobarbitone (Euthatal, 200 mg/ml; Genus Express) and perfused transcardially with 0.01 M PBS followed by 4% paraformaldehyde. The brains were removed and postfixed in paraformaldehyde. Before being sectioned, the brains were transferred to 20% sucrose in 0.2 M phosphate buffer and left overnight. Coronal sections were cut at 60 μ m on a freezing microtome and stained with cresyl violet. Cannulae locations were mapped onto standardized sections of the rat brain (Paxinos and Watson, 1998), and investigated for any signs of tissue damage.

Statistics

Statistical analysis was based on analysis of the number of cycles completed and seeking responses per session for each infusion. The data were

analyzed using ANOVAs with appropriate between- and within-subject factors. All statistical tests used an α level of $p < 0.05$ for the rejection of the null hypothesis.

Results

Twenty-three rats completed the entire experiment, and the cannulae locations were mapped onto standardized sections of the rat brain (Paxinos and Watson, 1998). The cannulae placements of all 23 rats fell within the dorsolateral and midlateral striatum (Fig. 2) and there was no evidence for gross damage to the striatum beyond the location of the guide and infusion cannulae. The data were analyzed at the group level, including all subjects ($N = 23$) and including all sessions with a preceding intracranial infusion. Drug seeking was quantified by two measures: the number of seeking cycles completed and the number of seeking responses per session.

The overall analysis of the cycles completed showed that inactivation of the MLS produced a greater reduction in responding than inactivation of the DLS, and that inactivation of the DLS reduced the number of seeking cycles completed under punishment, but not in the baseline task either before or after long-access cocaine self-administration (Fig. 1C,E). Thus,

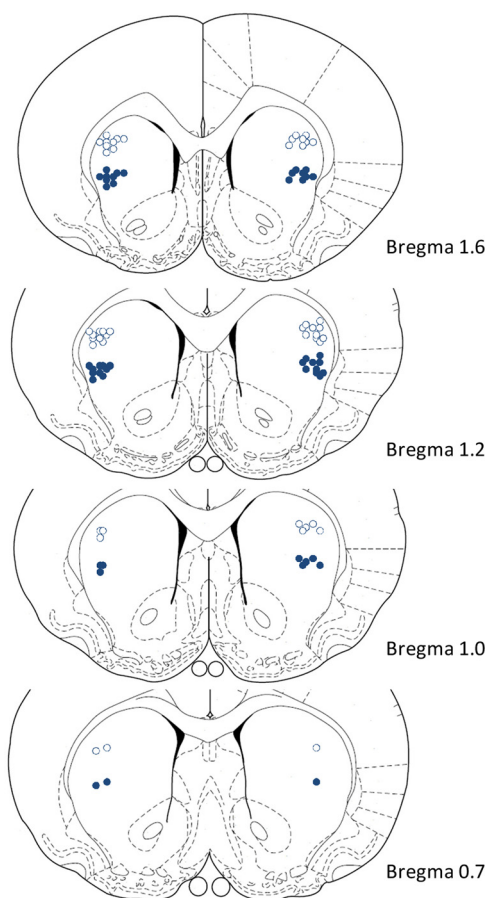


Figure 2. Neuroanatomical representation of cannulae placements. Open circles represent the dorsolateral striatum and closed circles represent the midlateral striatum ($N = 23$ for both regions). Sections at various distances from bregma in mm.

the three-way ANOVA of the number of cycles completed revealed significant main effects of inactivation ($F_{(3,20)} = 39.5, p < 0.001$), test ($F_{(3,20)} = 244.3, p < 0.001$), and striatal site ($F_{(3,20)} = 7.6, p = 0.012$), significant two-way interactions between inactivation and test ($F_{(3,20)} = 5.5, p = 0.012$), and inactivation and striatal site ($F_{(3,20)} = 16.3, p = 0.001$), and a three-way interaction between inactivation, test, and striatal site ($F_{(3,20)} = 3.514, p = 0.048$). Separate one-way ANOVAs revealed a significant effect of inactivating the DLS on punished responding ($F_{(1,22)} = 29.8, p < 0.001$), but not unpunished responding pre-long-access (pre-LA; $F_{(1,22)} = 2.6, p > 0.05$) or post-long-access (post-LA; $F_{(1,22)} = 1.9, p > 0.05$). The same analyses for the MLS revealed significant effects of inactivation at the pre-LA ($F_{(1,22)} = 16.7, p < 0.001$), post-LA ($F_{(1,22)} = 5.3, p = 0.032$), and punishment ($F_{(1,22)} = 25.8, p < 0.001$) stages.

The overall analysis of the seeking responses gave nearly identical results (Fig. 1D,F). Thus, three-way ANOVA of the number of seeking responses per session revealed significant main effects of inactivation ($F_{(3,20)} = 22.7, p < 0.001$) and test ($F_{(3,20)} = 93.9, p < 0.001$), and significant two-way interactions between inactivation and test ($F_{(3,20)} = 4.7, p = 0.021$) and inactivation and striatal site ($F_{(3,20)} = 15.0, p = 0.001$), and a three-way interaction between inactivation, test, and striatal site ($F_{(3,20)} = 5.5, p = 0.012$). Separate one-way ANOVAs revealed a significant effect of inactivating the DLS on punished responding ($F_{(1,22)} = 7.1, p = 0.014$), but not pre-LA ($F_{(1,22)} = 1.3, p > 0.05$) or post-LA ($F_{(1,22)} = 1.0, p > 0.05$) responding. The same analyses for the

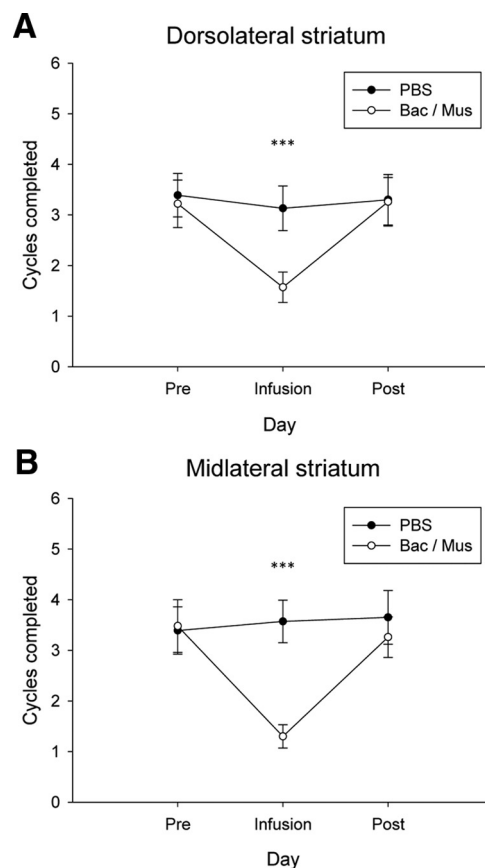
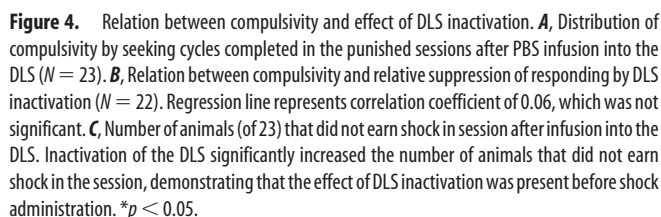


Figure 3. Effect of inactivating lateral striatal subregions on cocaine seeking under punishment the day after baclofen/muscimol infusion. **A**, Mean (\pm SEM) seeking cycles completed after inactivation of the DLS the day before infusion, the day of infusion, and the day after infusion. Inactivation of the DLS only affected responding on the day of infusion. **B**, Mean (\pm SEM) seeking cycles completed after inactivation of the MLS the day before infusion, the day of infusion, and the day after infusion. Inactivation of the MLS only affected responding on the day of infusion. *** $p < 0.001$. For all comparisons, $N = 23$.

MLS revealed significant effects of inactivation at the pre-LA ($F_{(1,22)} = 22.2, p < 0.001$), post-LA ($F_{(1,22)} = 22.1, p < 0.01$), and punishment ($F_{(1,22)} = 5.8, p = 0.025$) stages.

Subsequently, it was investigated whether the effect of striatal inactivation in the punishment phase also carried over to the day after the infusion. To this end, the number of seeking cycles completed per session on the day before infusion, the day of infusion, and the day after infusion was investigated. The overall analysis showed that for inactivation of both the DLS and MLS, responding under punishment was lower immediately after infusion, but not on the days before or after infusion (Fig. 3A,B). Thus, in the two-way ANOVA of the DLS inactivation, there was a significant interaction between day and inactivation ($F_{(2,21)} = 6.2, p = 0.004$), with a significant effect on the day of infusion ($F_{(1,22)} = 29.8, p < 0.001$), but not the day before ($F_{(1,22)} = 0.4, p > 0.05$) or after ($F_{(1,22)} = 0.0, p > 0.05$). In the two-way ANOVA of the MLS inactivation, there was a significant interaction between day and inactivation ($F_{(2,21)} = 9.2, p < 0.001$), with a significant effect on the day of infusion ($F_{(1,22)} = 25.8, p < 0.001$), but not the day before ($F_{(1,22)} = 0.6, p > 0.05$) or after ($F_{(1,22)} = 1.0, p > 0.05$).

Next, the relationship between baseline compulsivity and the effect of inactivating the DLS was investigated. Based on the distribution of the average number of seeking–taking cycles completed under punishment after PBS infusion into the DLS (Fig. 4A), the relative level of compulsive responding was compared



Together, these findings suggest a model whereby activity in the MLS is always necessary for reinforced lever pressing, while the

DLS comes to control a selective aspect of responding after overtraining. Apparently, activity in the DLS is not necessary for responding under normal (unpunished) conditions, as activity in the MLS is presumably sufficient to drive normal responding. However, the role of the DLS is unmasked in conditions where an inhibitory response drive that was more recently acquired is superimposed on the excitatory response drive. Although there are only limited data on the differential afferent projections to the MLS and DLS regions, one possible explanation for the selective role of the MLS in reinforced responding could be the considerably denser primary forelimb motor cortex (caudal forelimb area, CFA) projection into the MLS (Rouiller et al., 1993).

Dorsolateral striatum and compulsive drug seeking

Contrary to our expectations, there was no evidence for a selective effect of DLS inactivation on responding under punishment in highly compulsive animals, as the proportional suppression of responding after DLS inactivation was unrelated to the level of compulsivity. Thus, these results do not provide an explanation for the differential levels of compulsivity that were previously observed after an extended history of cocaine self-administration (Deroche-Gamonet et al., 2004; Pelloux et al., 2007). Nevertheless, the present results do demonstrate that the DLS is a neural structure that exerts a strong influence on drug seeking under threat of punishment. Therefore, it remains possible that inter-individual variability in the response of the DLS to extended cocaine self-administration is related to the variability in behavioral compulsivity. This hypothesis would be consistent with human (Volkow et al., 2006), macaque monkey (Letchworth et al., 2001; Porrino et al., 2004), and rodent studies (Welch et al., 2007; Im et al., 2010; Peça et al., 2011) implicating the dorsal striatum in compulsive behavior, and deserves further investigation in the future.

In conclusion, these results show that inactivation of the dorsolateral striatum does not affect cocaine seeking, even after overtraining. Instead, it is selectively important for punished drug seeking. Activity in the DLS after extended cocaine self-administration seems to drive punished responding by reducing the influence of threat of intermittent and unpredictable contingent shock on response output. Furthermore, the results show that the midlateral striatum mediates instrumental responding at all stages of training, thereby suggesting a novel differentiation in the functions of the sensorimotor striatum.

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