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DORSOMEDIAL STRIATUM LESIONS AFFECT ADJUSTMENT TO REWARD UNCERTAINTY, BUT NOT TO REWARD DEVALUATION OR OMISSION

CARMEN TORRES,[a] AMANDA C. GLUECK,[b] SHANNON E. CONRAD,[b] IGNACIO MORÓN[c] AND MAURICIO R. PAPINI[b]*

[a] *Department of Psychology, University of Jaén, 23071-Jaén, Spain*

[b] *Department of Psychology, Texas Christian University, Fort Worth, TX 76129, USA*

[c] *Department of Psychobiology, University of Granada, 18071-Granada, Spain*

Abstract—The dorsomedial striatum (DMS) has been implicated in the acquisition of reward representations, a proposal leading to the hypothesis that it should play a role in situations involving reward loss. We report the results of an experiment in which the effects of DMS excitotoxic lesions were tested in consummatory successive negative contrast (reward devaluation), autoshaping training with partial vs. continuous reinforcement (reward uncertainty), and appetitive extinction (reward omission). Animals with DMS lesions exhibited reduced lever pressing responding, but enhanced goal entries, during partial reinforcement training in autoshaping. However, they showed normal negative contrast, acquisition under continuous reinforcement (CR), appetitive extinction, and response facilitation in early extinction trials. Open-field testing also indicated normal motor behavior. Thus, DMS lesions selectively affected the behavioral adjustment to a situation involving reward uncertainty, producing a behavioral reorganization according to which goal tracking (goal entries) became predominant at the expense of sign tracking (lever pressing). This pattern of results shows that the function of the DMS in situations involving reward loss is not general, but restricted to reward uncertainty. We suggest that a nonassociative, drive-related process induced by reward uncertainty requires normal output from DMS neurons.

Key words: reward devaluation, reward omission, reward uncertainty, successive negative contrast, partial reinforcement, extinction spike.

*Corresponding author.
E-mail addresses: mctorres@ujaen.es (C. Torres), glueckphd@gmail.com (A. C. Glueck), shannon.conrad@tcu.edu (S. E. Conrad), imoron@ugr.es (I. Morón), m.papini@tcu.edu (M. R. Papini).

Abbreviations: CR, continuous reinforcement; cSNC, consummatory successive negative contrast; DLS, dorsolateral striatum; DMS, dorsomedial striatum; ERK, extracellular signal-related kinase; PBS, phosphate buffered saline; pCREB, phosphorylated cyclic adenosine monophosphate response element-binding protein; PR, partial reinforcement; PRAE, partial reinforcement acquisition effect; PREE, partial reinforcement extinction effect.

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INTRODUCTION

There are theoretical and empirical reasons to think that the adjustment to situations involving reward devaluation (e.g., successive negative contrast), reward uncertainty (e.g., partial reinforcement), and reward omission (e.g., appetitive extinction) share a common set of mechanisms (Daly and Daly, 1982; Amsel, 1992; Flaherty, 1996; Gray and McNaughton, 2000; Papini, 2014; Papini et al., 2015; Anselme, 2015, 2016). Amsel's (1992) behavioral theory, for example, suggests that the devaluation or omission of an otherwise expected reward unconditionally induces an aversive emotional state (called primary frustration), which can then be associatively reactivated by the presentation of stimuli that were present at the time of the loss event (called secondary frustration). In the consummatory successive negative contrast (cSNC) situation, devaluation from a large to a small reward (e.g., 32% to 4% sucrose) is accompanied by the release of stress hormones (Mitchell and Flaherty, 1998; Pecoraro et al., 2009), influenced by anxiolytic (Flaherty et al., 1986; Kamenetzky et al., 2008; Ortega et al., 2014a) and opioid treatments (Pellegrini et al., 2005; Wood et al., 2005, 2008), followed by preference for substances with addictive potential (Manzo et al., 2015a,b), modulated by genetic influences (Torres and Sabariego, 2014), dependent on the integrity of brain structures involved in emotion (Ortega et al., 2011; Kawasaki et al., 2015), and affected by the post-training administration of memory enhancing drugs (Bentosela et al., 2006; Ruetti et al., 2009; Norris et al., 2011). Many of these features are also present in appetitive extinction and reward uncertainty situations based on instrumental training procedures (Feldon and Gray, 1981; Coe et al., 1983; Kawasaki and Iwasaki, 1997; Thomas and Papini, 2001; Rosas et al., 2007; Gómez et al., 2008, 2009; Shaw et al., 2009; Cuenya et al., 2012; Manzo et al., 2014, 2015a,b). Thus, reward loss (herein denoting reward devaluation, uncertainty, and omission) involves emotional activation and the development of aversive emotional memories (Papini and Dudley, 1997; Papini, 2003; Papini et al., 2015). However, these neurobehavioral factors are usually studied separately in various reward-loss situations.

The goal of the present experiment was to determine the role of the dorsomedial striatum (DMS) in reward

devaluation, uncertainty, and omission in the same animals (see Glossary for task descriptions). A similar design to that employed here was used before in two other studies. Ortega et al. (2013) trained animals with lesions of orbital or medial prefrontal cortex in a cSNC task followed by an autoshaping task involving either continuous or partial reinforcement (CR, PR). In that study, lesions of the orbital cortex attenuated cSNC and also eliminated the enhancement of autoshaped lever pressing responding during PR training, relative to CR training (the partial reinforcement acquisition effect, PRAE). Unlike in this case, lesions of the medial prefrontal cortex affected neither task. Similarly, Ortega et al. (2014b) reported that after six generations, animals selectively bred for fast recovery from a 32-to-4% sucrose downshift exhibited a reduced cSNC effect; however, no change was observed in a line of animals selected for slow recovery or in a randomly paired control line. Interestingly, fast recovery animals also displayed no evidence of the PRAE or of the PREE (i.e., partial reinforcement extinction effect, i.e., increased persistence of lever pressing during extinction after PR training; Boughner and Papini, 2006). None of these correlated effects were observed in either slow-recovery or randomly selected animals. In both cases the authors (Ortega et al., 2013; Ortega et al., 2014b) concluded that the attenuation of the cSNC and PRAE/PREE was consistent with a common neural mechanism activated by exposure to episodes involving reward loss, whether in terms of devaluation, omission, or uncertainty.

Here we sought to extend this approach to lesions of the DMS. The DMS was selected based on four sources of evidence. First, the DMS has been shown to be critical in reward devaluation situations. For example, DMS expression levels of phosphorylated cyclic adenosine monophosphate response element-binding protein (pCREB, a marker of synaptic plasticity) were higher after the first devaluation session than after the second devaluation in the cSNC situation (Glueck et al., 2015). Comparable results were obtained with the extracellular signal-related kinase (ERK, also a marker for cellular plasticity). Shiflett et al. (2010) reported that infusion of the ERK inhibitor U0126 into the posterior region of the DMS abolished the reduction in instrumental behavior induced by reward devaluation based on presession feeding. These data suggest a role of the DMS in situations involving reward devaluation.

Second, using instrumental training procedures and the presession feeding devaluation technique, Yin et al. (2005) reported that lesions of the posterior DMS after limited amounts of training abolished the reward-devaluation effect. Interestingly, similar lesions in the dorsolateral striatum (DLS) induced the reward-devaluation effect after extensive training, an effect absent in sham animals (Yin et al., 2004). These results provide support for the hypothesis that different sections of the dorsal striatum (DMS, DLS) are involved in the transition from the acquisition of instrumental actions to the performance of instrumental habits (Gasbarri et al., 2014; Hart et al., 2014).

Third, the DMS has been implicated in decision making, specifically involving choice behavior under risky/uncertain conditions in humans (e.g., Brevers et al., 2015), and choice after serial discrimination reversals in rats (Castañé et al., 2010). Paradoxically, DMS lesions did not impair extinction performance assessed after the last reversal, despite disrupting reversal performance as noted above (Castañé et al., 2010). Tasks such as serial discrimination reversals not only involve reward uncertainty, but they require a choice between competing alternatives and a degree of behavioral flexibility that may promote learning-set formation (Bushnell and Stanton, 1991; Ragozzino, 2007; Floresco et al., 2009).

Fourth, although the involvement of the DMS in reward-loss situations is largely unknown, its afferent-efferent connections (Voorn et al., 2004; Striedter, 2016) point to structures known to regulate actions triggered by worse-than-expected outcomes. Evidence from structures that send inputs to the DMS, whether directly or indirectly (mediated by ventral striatum and thalamus), include the prelimbic cortex, which expresses pCREB during cSNC (Glueck et al., 2015), the orbitofrontal cortex, whose lesion attenuates the cSNC effect (Ortega et al., 2013), the anterior cingulate cortex, whose lesion prolongs the cSNC effect (Ortega et al., 2011), the amygdala, whose reversible inactivation attenuates the cSNC effect (Kawasaki et al., 2015), and the nucleus accumbens, whose neurons show reduced dopamine release during reward devaluation and omission (Genn et al., 2004; Biesdorf et al., 2015). Outputs from the dorsal striatum also reach the lateral habenula, which inhibits dopaminergic neurons of the mesostriatal reward pathway (Christoph et al., 1986) and whose lesion retards extinction of lever pressing after sucrose reinforcement (Friedman et al., 2011). Altogether, these sources of evidence pointed to a key role of the DMS in situations involving reward loss such as those studied in the present experiment.

The approach implemented here was to compare the effects of DMS lesions in three tasks administered in succession: cSNC, PR vs. CR training, and appetitive extinction, the last two based on autoshaping training. The cSNC task evaluated the role of the DMS in reward devaluation in a consummatory response situation (i.e., licking for sucrose). We assessed reward uncertainty in terms of the PRAE (PR vs. CR during acquisition) and PREE (PR vs. CR in extinction) using the autoshaping situation. The transition from acquisition to extinction provided two sources of evidence on the role of the DMS on reward omission: the extinction spike and extinction rate. The extinction spike (or burst) refers to a tendency in the autoshaping preparation for lever pressing to increase early in extinction relative to the terminal acquisition level of responding (Thomas and Papini, 2001). The extinction spike has not been reported after PR training in acquisition. Appetitive extinction after CR training was used to evaluate the effects of DMS lesions on reward omission. Serial reversal learning and similar tasks including risky/uncertain reward conditions involve choice between alternatives as well as shifts in

reward conditions (Castañé et al., 2010; Brevers et al., 2015). Unlike in these tasks, the reward-loss situations included here do not involve choice between alternatives and therefore do not demand any obvious degree of behavioral flexibility beyond what is required for simple acquisition and extinction. As a result, the effects detected in these tasks would suggest that the function of the DMS is more related to reward loss than to choice and flexibility, since reward downshifts are present in all of them. Finally, animals were also tested in the open field under light and dark conditions, assessing locomotion in the central vs. peripheral area. This test was included to determine whether DMS lesions affected motor behavior and also anxiety levels (Prut and Belzung, 2003).

Based on the evidence reviewed above, we expected the DMS lesion to reduce or eliminate the cSNC effect, the PRAE, the PREE, and the extinction spike, and we predicted that extinction after CR training would be retarded. Although the predictions for all these effects, except for cSNC, are based on autoshaped lever pressing, we simultaneously assessed goal entries. Available evidence suggests that there are individual differences in the tendency to approach the lever vs. the goal (i.e., sign vs. goal trackers; Boakes, 1977). Open-field testing was expected to help assess the alternative hypothesis that the predicted effects were attributable to changes in activity or anxiety-related behavior.

EXPERIMENTAL PROCEDURES

Subjects

Fifty-two male Wistar rats, approximately 90 days old, and experimentally naive were prepared for surgery. These animals were derived from breeders purchased at Harlan Labs (Indianapolis, IN), but were reared and maintained at the TCU colony. Animals were weaned around postnatal day 21, maintained in groups of 2–4 housed in polycarbonate cages, and around 40 days of age were moved to individual housing in wire-bottom cages. During training, weights were maintained within 81–84% of the *ad lib* weight for each animal by providing the appropriate amount of food each day, at least 15 min after the end of the daily training session. Animals were housed under a 12-h light/12-h dark cycle (lights on at 07:00 h) in a room with constant temperature (22–23 °C) and humidity (40–65%).

Surgery

Surgeries were performed over a period of 4 weeks. As a result, animals started behavioral testing at different times. As animals became available for surgical treatment, they were randomly assigned to the DMS lesion or sham condition. In preparation for surgery, animals were anesthetized (5%) and maintained (1–2%) with isoflurane inhalation. Once anesthetized, the animal's head was shaved and cleaned with betadine and alcohol (70%). To prevent eye dryness, a drop of mineral oil was applied to each eye. Animals were then set in a stereotaxic instrument (Vernier Stereotaxic with Manual Fine Drive, Leica Biosystems, Buffalo Grove, IL, USA), a midline incision was made, the skull was scraped clean of connective tissue, and bregma was located. Quinolinic acid (20 μg/μl) dissolved in a 10% phosphate buffered saline (PBS) solution, titrated to pH 7.4 with sodium hydroxide, was used as the neurotoxin and administered with an infusion pump (KDScientific, Model KDS 232 CE, Holliston, MA, USA). There were four infusions in each hemisphere at two different A/P and D/V coordinates: A/P: +0.2, +1.2; M/L: ±2.00; and D/V: −4.5, −3.5 (Paxinos and Watson, 2007). Thus, the infusions were designed to produce damage in the anterior and posterior sections of the DMS. The neurotoxin was infused in a volume of 0.175 μl, at a rate of 0.1 μl/min, and over a period of 100 s within each hemisphere. Following surgery, all animals received a dose of buprenorphine (0.4 mg/kg, 2.0 μl dose, sc) to alleviate pain induced by the surgery. Animals were left undisturbed in a breeder cage for 2 days before being returned to their home cage for 5–8 days. During this period of recovery from surgery, their weight was gradually brought to the target 81–84% deprivation relative to their *ad lib* weight.

Phase 1: cSNC

cSNC took place in eight conditioning boxes (MED Associates, St. Albans VT, USA) constructed of aluminum and Plexiglas, and measuring 29.4 × 28.9 × 24.7 cm (L × H × W). The floor was made of steel rods 0.5 cm in diameter and 1.2 cm apart (from center to center) running perpendicular to the feeder wall. A tray filled with corncob bedding was placed below the floor to collect fecal pellets and urine. Two elliptical holes, 1 × 1 cm (W × H), 3.5 cm from the floor, and separated by 6.5 cm, were located against the feeder wall. A sipper tube, 1 cm in diameter, was inserted through the middle hole (the lateral hole for a second sipper tube was not used in this experiment). When fully inserted, the sipper tube was flush against the outer wall of the apparatus, such that the rats could only reach the tubes with their tongues. Sucrose solutions were delivered via this sipper tube. The solutions were prepared weight by weight by mixing sucrose with distilled water (32 or 4 g of sucrose for every 78 or 96 g of water, for 32% and 4% sucrose concentrations). A computer located in an adjacent room controlled the presentation and retraction of the sipper tube, and detected contact with the sipper tube via a circuit involving the steel rods in the floor. Such circuit was used to record licking responses. Each conditioning box was enclosed in a sound-attenuating chamber that contained a house light (GE 1820), a speaker that delivered white noise, and a fan for ventilation. Together, the speaker and fan produced noise with an intensity of 80.1 dB, SPL, Scale C (Digital Sound Lever Meter, Extech, Waltham MA, USA).

cSNC training (Phase 1) started once animals had recovered from surgery and had reached their deprivation weight, about 11–14 days after surgery. Animals with sham or DMS lesions were matched for weight as far as possible and randomly assigned to one of two training groups based on the sucrose

concentration, 32% or 4%, delivered during the 10 preshift sessions. Group labels were: 32/Sham, 4/Sham, 32/DMS, and 4/DMS. Preshift was followed by 5 postshift sessions in which all animals received access to 4% sucrose. Each session started with a 30-s variable interval (range: 15–45 s) designed to attenuate the posteffects of handling and transport on consummatory behavior. At the end of this interval, the sipper tube was automatically presented. The session proper lasted 5 min from the first detected contact with the drinking spout. A 30-s variable interval (range: 15–45 s) followed at the end of the session and before the animal was placed back into its home cage.

Phase 2: autoshaping

Autoshaping training was carried out in four standard operant chambers (MED Associates, St. Albans VT, USA), each enclosed in a sound-attenuating chamber. Each box was 20.1 × 28 × 20.5 cm (W × L × H), with a grid floor consisting of stainless steel bars 0.4 cm in diameter and spaced 1.6 cm apart (from center to center). Underneath the grid floor was a pan filled with corncob bedding. Two retractable levers were located 1 cm to the right and left of the feeder, and 6 cm above the floor. Only one lever, located to the left of the magazine hole, was used in this experiment. This lever was 4.8 cm wide and when fully inserted protruded 1.9 cm into the chamber. It took 0.2 s for the lever to be fully inserted or retracted. The lever was adjusted so that a minimum forced applied on it would be detected. A food cup was located inside a hole in the front wall of the chamber, 2 cm above the floor. A photocell placed 1.1 cm inside this hole and above the food cup detected head entries into this area. Pellet dispensers delivered 45-mg food pellets (Bio-Serv, Frenchtown NJ, USA). Each food pellet contained protein (18.8%), fat (5.0%), carbohydrate (61.5%), fiber (4.6%), ash (4.4%), and moisture (5.0%), and provided 3.68 kcal/g. The sound-attenuating chambers were equipped with a light (GE 1820) that provided diffuse illumination, a speaker that administered white noise, and a fan for air circulation. Background masking noise (speaker and fan) registered 80.1 dB, SPL, scale C (Digital Sound Lever Meter, Extech, Waltham MA, USA). A computer located in an adjacent room recorded lever presses and goal entries, and also controlled the protraction and retraction of the lever, and the pellet dispenser.

Although rats did not have to press the lever to obtain food (i.e., a Pavlovian training procedure), they nonetheless approached and made contact with the lever (a phenomenon called ‘‘autoshaping”). Autoshaping training (Phase 2) started a day after the last cSNC session. Animals were matched for assignment to the cSNC task and then semi-randomly allocated to either the CR or PR condition based on the cSNC behavior. The goal was to equate PR and CR groups as much as possible in terms of prior consummatory behavior and sucrose condition. There were 10 sessions of acquisition, each consisting of 10 trials. In each trial the lever was presented for 10 s. Trials were separated by variable intervals averaging 90 s (range: 60–120 s). During CR acquisition, each lever presentation ended with the delivery of five 45-mg precision food pellets at a rate of one every 0.2 s. During PR acquisition, 50% of the lever trials ended with the delivery of five 45-mg pellets, one every 0.2 s, and the rest of the trials ended without food delivery. Acquisition was followed by 10 extinction sessions with the same training parameters, except that no pellets were delivered at the end of each trial (i.e., as in nonrewarded trials in the PR condition).

Phase 3: open field

The open-field test was carried out in three boxes (MED Associates, St. Albans VT, USA), each measuring 43 × 30 × 43 cm (L × H × W). Each box was visually isolated with a cardboard screen. A light (60 W, GE Reveal) placed on top of each field provided bright illumination. A computer located in an adjacent room recorded the distance traveled, in centimeters, in 1-min bins, and separately for the central area and the peripheral area surrounding the walls. Open-field testing (Phase 3) started a day after the last extinction session in autoshaping. Each animal received two 20-min sessions of open-field testing in two successive days, one with the box illuminated and the other with the box in the dark. The order of light and dark sessions was counterbalanced across animals. At the start of each session, the rat was placed in the center of the open field.

In these three phases of training, animals received one session per day, seven days per week, beginning at approximately the same time each day (between at 9:00 and 16:00 h), during the light portion of the daily cycle. In each phase, rats were always tested in the same box across days. Boxes were wiped after each session with a wet paper towel and feces were removed when necessary. Squads were kept constant within each phase, but the order in which they were run was randomized across days.

HISTOLOGY

A day after the final open-field test, animals were sacrificed with an overdose of CO_2 and the brains were immediately extracted and embedded in a 4% paraformaldehyde solution for at least 3 days. Brains were then immersed in 30% sucrose for at least 2 days, mounted in a 3% agarose/PBS solution, and sectioned with a vibratome (LEICA VT1000S, Leica Biosystems, Richmond IL, USA) in 70-μm slices. Most of the slices were stained with Cresyl-Violet (see below) and photographed with an Olympus CX41 light microscope with Q-Color 3 digital camera. Excitotoxic lesions of the DMS result in a significant alteration of brain tissue and a correlated increase in ventricle size (Lindgren et al., 2013). Based on this fact, we used an objective measure of ventricle size to select animals for this study. Image-Pro Express and ImageJ were used for image capture, analysis, and ventricle size calculation. Images were analyzed by an observer blind to behavioral assignments of the animals. The images shown in Fig. 1, bottom panels, were taken with an Olympus BH2 microscope equipped

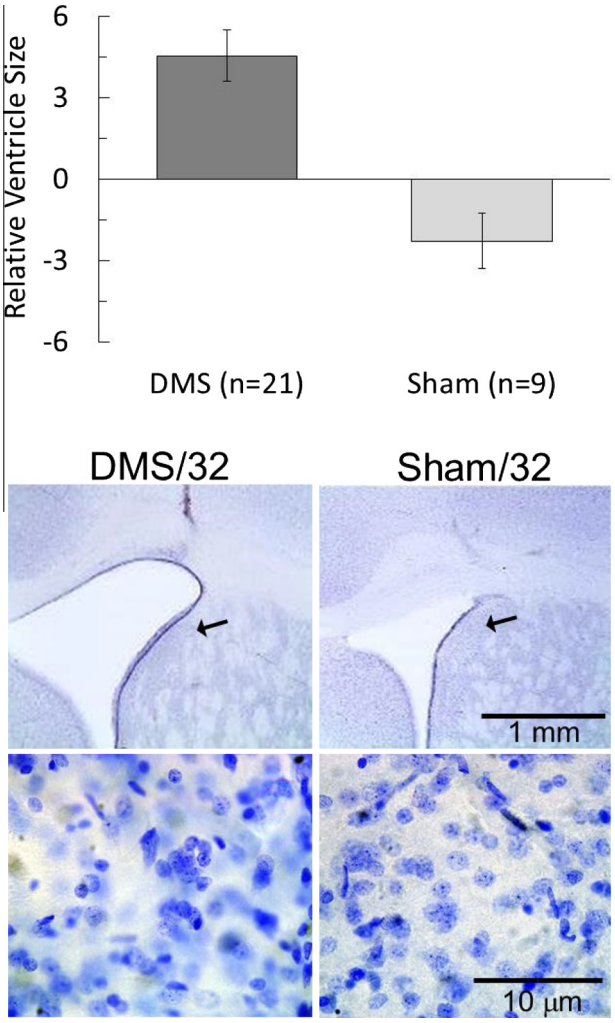

Fig. 1. Top: Mean (± SEM) of relative ventricle size for groups of rats that were given DMS chemical lesions or sham lesions. A value of zero indicates that ventricle size is equal to the mean plus one standard deviation value of sham animals (see text for details). Bottom: Photomicrographs of coronal sections stained with Cresyl Violet. Representative brain slices from an animal with DMS lesion (left panels) and a sham-lesioned animal (right panels) are shown, both exposed to reward downshift in Phase 1. The top images allow for a comparison of ventricle size (×2). The arrow points to the region shown below in an enlarged image (×100).

with a Jenoptic Prog Res CT3 digital camera (×2) and with an Olympus BX51 microscope equipped with an Olympus DP70 digital camera (×100).

STATISTICAL ANALYSIS

The Shapiro–Wilk test for normality yielded significant deviations in 7 of 60 tests in Phase 1 data (cSNC). Similar results were observed in terms of deviations from homogeneity of variance, assessed with the Levene test; only session 5, out of 15 sessions deviated from homogeneity of variance across groups in Phase 1. Concerning the analysis of the extinction spike and response bias in Phase 2 (autoshaping), the same tests detected 1 and 11 deviations from normality out of 8 and 80 tests, respectively, and no violations of homogeneity of variance in either data set. Given the relatively low level of deviations from these assumptions, the results from cSNC (Phase 1), the extinction spike (Phase 2), and response bias (Phase 2) were subjected to analysis of variance. However, a substantially larger percentage of deviations were observed in data from Phase 2 (autoshaping), especially during extinction sessions in both lever pressing and goal entries, and from the open-field test. Therefore, data from autoshaping acquisition and extinction (Phase 2), and from the open-field test (Phase 3) were also analyzed using nonparametric Mann–Whitney tests for independent samples based on average data across sessions or 1-min bins (i.e., eliminating the repeated-measure factor of sessions or bin). The results were identical with those obtained with parametric tests. Moreover, substantial deviations from normality were found in training periods where both parametric and nonparametric analyses yielded nonsignificant lesion effects (e.g., extinction of lever pressing and goal entries, activity in the open-field test), so Type I error was not compromised. For consistency of analysis across phases, only the results of parametric statistics are presented below for all phases of the experiment. IBM SPSS Statistics 23 software was used to compute all statistical tests. The alpha value was set at the 0.05 level. When appropriate, LSD pairwise comparisons derived from the main analysis were used to determine the source of significant interactions.

RESULTS

Histology and sample size

From the initial 52 rats, one was eliminated after five sessions in Phase 1 because of poor health and four were eliminated because they failed to acquire licking behavior during preshift sessions in Phase 1. The remaining 47 brains were treated with Cresyl Violet for staining cell bodies. Four sham brains were also treated with NueN staining for neuronal nuclei, but these images are not shown here because they add no information. Four brains from Group 4/Sham were lost in histology; because there was no indication in the behavior of these animals that they had suffered a lesion, their behavioral data were included in the analyses. The remaining 43 brains were included in the analysis of ventricle size at different A/P coordinates as an index of DMS lesion. The following selection criteria were applied to these 43 brains. First, the mean (standard deviation) size for each coordinate was computed for sham animals. Second, the largest value for each animal was selected for analysis and the corresponding A/P coordinate for that value was noted. Second, DMS rats with a ventricle size score equal or larger than the mean plus one standard deviation of the sham group for each A/P coordinate were selected. Moreover, sham animals with a ventricle size score above the mean plus one standard deviation of their group were also eliminated. Third, as a result of this selection, 8 animals with relatively small ventricle size in the DMS condition were eliminated on the assumption

that the neurotoxin had not produced a sufficiently large lesion. Moreover, 5 animals in the sham condition with relatively large ventricle size were eliminated on the assumption that cannulation had produced damage to the DMS. Fig. 1, top panel, shows the results for the remaining animals, 21 with DMS lesions and 9 with sham lesions. This figure plots, for each rat, ventricle size minus the mean plus one standard deviation of the sham group for the equivalent A/P coordinate. A difference score equal to zero indicates that the two values were equal. Selected rats with excitotoxic lesions of the DMS had larger ventricles than rats with sham lesions, $F(1, 28) = 18.27$, $p < 0.001$. One-sample t-Tests indicated that the ventricles of DMS rats were also significantly larger than zero, $t(20) = 4.80$, $p < 0.001$. However, the ventricles of sham animals were not significantly different from zero, $t(8) = -2.25$, $p = 0.054$. Slices treated with Cresyl Violet are shown in Fig. 1, bottom panel. The histological examination revealed that the quinolinic acid infusion produced a circumscribed and moderated gliosis and neuronal loss, in addition to ventricular alterations and striatal shrinkage. Control brains with vehicle infusions showed no degenerative alterations except those corresponding to the cannula track.

Table 1 shows the assignment of selected animals to each phase of behavioral testing. Although an attempt was made to counterbalance for prior experience, the selection of animals based on the histology and animals eliminated because of health or behavioral issues resulted in a somewhat distorted assignment.

Phase 1: downshifted vs. unshifted

Performance of these animals in the cSNC task yielded the following results. Preshift consummatory performance increased significantly across sessions 1–10, $F(9, 270) = 22.71$, $p < 0.001$. All other main and interaction effects were nonsignificant, Fs < 1.16, ps > 0.32. An analysis of the last preshift session, session 10, also failed to detect any differences, Fs < 1. Thus, these four groups were equated before the downshift.

A downshift from 32% to 4% sucrose produced a sharp, but transient decline in licking responses. Although animals with a DMS lesion performed somewhat below sham animals, the difference was not large (Fig. 2). Because the cSNC effect was short lived, an analysis involving all five postshift sessions yielded only a significant change across sessions, $F(4, 120) = 2.74$, $p < 0.04$. All other effects were nonsignificant, Fs < 3.14, ps > 0.08. An analysis restricted to the first and last postshift sessions (11 and 15, respectively) yielded a significant contrast by session interaction, $F(1, 30) = 7.56$, $p < 0.02$, and a significant session effect, $F(1, 30) = 11.07$, $p < 0.003$. All other effects: Fs < 3.23, ps > 0.08. Pairwise LSD comparisons derived from the main analysis indicated that the contrast by session interaction was due to a lower response level in groups exposed to the 32-to-4% sucrose downshift relative to unshifted controls on session 11, $F(1, 30) = 6.72$, $p < 0.02$. No evidence of the cSNC effect was found on session 15, $F < 1$.The main conclusion from Phase 1 is that there was a significant cSNC effect, but no evidence that the DMS lesion affected either the contrast effect or consummatory performance in general.

Table 1. Assignment of animals to the three phases of behavioral testing

		Phase 1		Phase 2		Phase 3	
Lesion	$n=$	cSNC	$n=$	AS	$n=$	OF	$n=$
DMS	21	32–4% sucrose	10	CR	6	Dark/light	21
				PR	4	Dark/light	
		4% sucrose	11	CR	6	Dark/light	
				PR	5	Dark/light	
Sham	13	32–4% sucrose	7	CR	4	Dark/light	13
				PR	3	Dark/light	
		4% sucrose	6	CR	2	Dark/light	
				PR	4	Dark/light	

Note. In Phase 2, animals with the same schedule treatment were pooled. For example, Group CR/DMS had an $n = 12$; 6 rats were downshifted and 6 rats were unshifted during Phase 1. In Phase 3, the dark/light conditions were common to all the animals (i.e., a within-subject manipulation), although their administration was counterbalanced across subjects. AS, autoshaping; CR, continuous reinforcement; cSNC, consummatory successive negative contrast; DMS, dorsomedial striatum; Dark/light, sequence of open-field treatments; OF, open field; PR: 50% partial reinforcement.

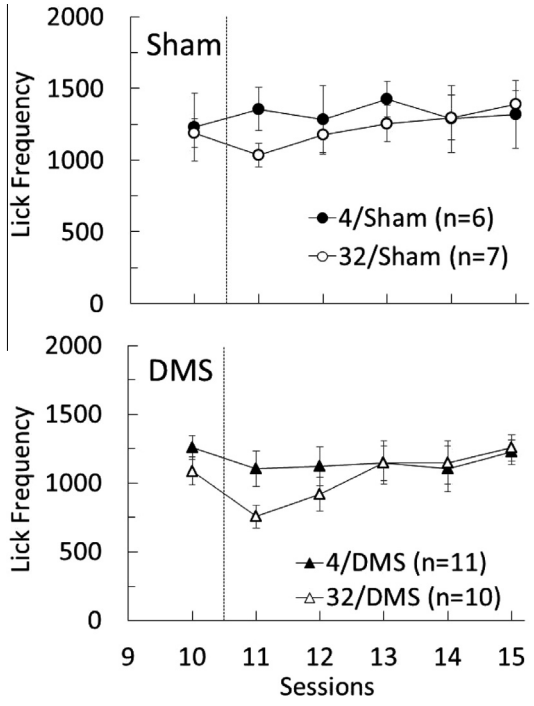

Fig. 2. Mean (±SEM) lick frequency in animals receiving access to 32% or 4% sucrose during 10 daily session. During the last 5 sessions, both groups received access to 4% sucrose. The suppression of licking in 32-to-4% sucrose downshifted animals on Session 11 is referred to as consummatory successive negative contrast (cSNC). Top: sham-operated animals. Bottom: animals with DMS lesions. Data from Phase 1.

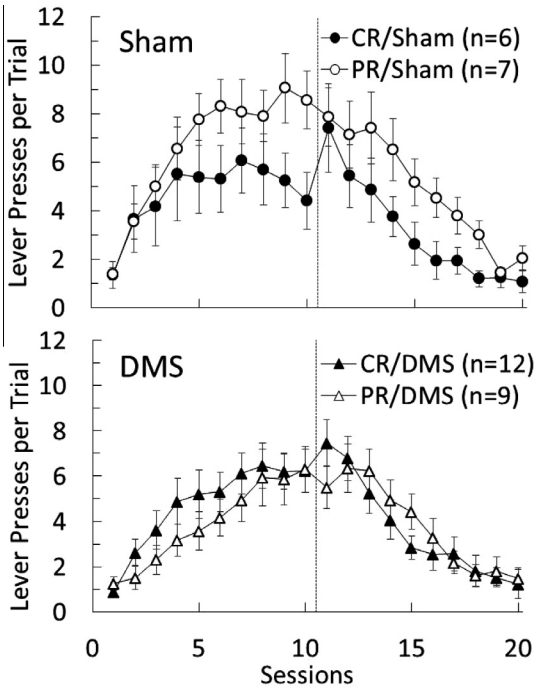

Fig. 3. Mean (±SEM) lever pressing in the autoshaping situation of animals receiving 50% partial reinforcement (PR) or continuous reinforcement (CR) during acquisition sessions (1–10). Rewards were withheld during extinction sessions (11–20). Top: sham-operated animals. Bottom: animals with DMS lesions. Data from Phase 2.

Phase 2: acquisition during PR vs. CR

Figs. 3 (lever pressing), 4 (goal entries), and 5 (response bias), show the results of acquisition and extinction. The statistical results for extinction are presented in the following section. Within each figure, the top panel shows the results for Sham groups, whereas the bottom panel shows the results for DMS groups. Consider first the acquisition results for *lever pressing*.

Fig. 3 suggests that the higher lever pressing under PR than CR in sham animals (the PRAE) was not present in DMS animals. A Lesion × Schedule × Session (1–10) analysis yielded a significant schedule by session interaction, $F(9, 270) = 2.11$, $p < 0.03$, and an increase in lever pressing across sessions, $F(9, 270) = 36.04$, $p < 0.001$. All other effects were not significant, Fs < 2.54, ps > 0.12. Separate Schedule × Session analyses were calculated for sham and DMS groups to determine whether the apparent effect observed in Fig. 3 had statistical support. Sham groups showed a clear PRAE in lever pressing, that is, higher lever pressing under PR training than under CR training. The effect was observed in terms of a significant schedule by session interaction, $F(9, 99) = 2.14$, $p < 0.04$. By contrast, there was no evidence of a PRAE in groups with a DMS lesion, either in terms of an interaction or a main effect of schedule, Fs < 1. Separate Lesion × Session analyses were also computed on DMS vs. Sham groups receiving CR or PR acquisition training. For PR animals, there was a significant interaction, $F(9, 126) = 1.99$, $p < 0.05$; PR/Sham animals lever pressed significantly above PR/DMS animals, $F(1, 14) = 5.96$, $p < 0.03$. The same analysis for CR animals failed to detect any lesion effect whether as an interaction or as a main effect, Fs < 1.01, ps > 0.44. The acquisition effect was significant in both analyses, Fs > 13.16, ps < 0.001. Thus, the DMS lesion modified the adjustment of lever pressing to the reward uncertainty introduced by a schedule of PR, thus abolishing the PRAE.

Consider now the results for *goal entries*. Sham and DMS groups were reversed in terms of goal entries in PR and CR groups (top vs. bottom panels, Fig. 4). Groups were also reversed in goal entries relative to the results for lever pressing (compare acquisition in Figs. 3 and 4). A Lesion × Schedule × Session (1–10) showed a significant interaction between lesion and schedule, $F(1, 30) = 5.01$, $p < 0.04$. There was also a significant session effect, $F(9, 270) = 21.48$, $p < 0.001$. All other factors were nonsignificant, Fs < 1.91, ps > 0.08. LSD pairwise analysis of the lesion by schedule interaction showed that the source of this effect was a difference between sham and DMS animals trained under PR, $F(1, 30) = 6.50$, $p < 0.02$. Other pairwise comparisons were nonsignificant, Fs < 2.61, ps > 0.11. This effect was also detected in terms of separate Lesion × Session analyses for PR and CR groups. Thus, goal entries during acquisition were significantly higher in PR/DMS than in PR/Sham animals, $F(1, 14) = 10.80$, $p < 0.006$. This difference was not observed in CR/DMS vs. CR/Sham animals, either as an interaction or a main effect, Fs < 1. The change across sessions was significant in both analyses, Fs > 8.86, ps < 0.001.

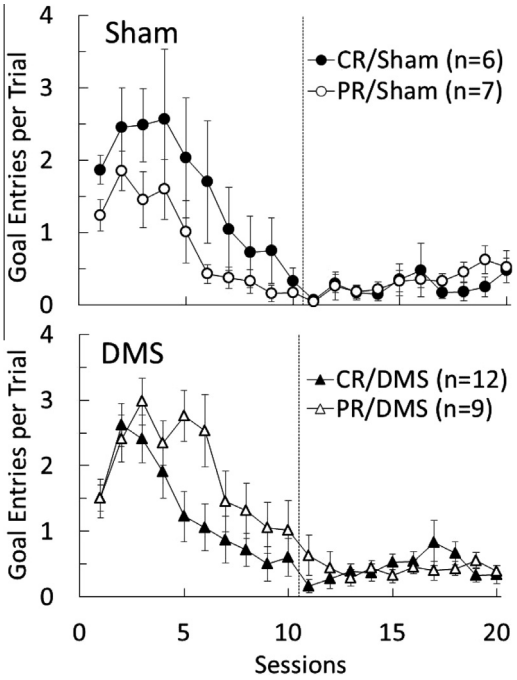

Fig. 4. Mean (±SEM) goal entries during lever presentations in the autoshaping situation of animals receiving 50% partial reinforcement (PR) or continuous reinforcement (CR) during acquisition sessions (1–10). Rewards were withheld during extinction sessions (11–20). Top: sham-operated animals. Bottom: animals with DMS lesions. Data from Phase 2.

These results showed that DMS lesions produced a reorganization of conditioned responding in the PR condition, but had no detectable effect on behavior in the CR condition. This reorganization involved reduced lever pressing and increased goal entries in animals with DMS lesions, that is, a shift from sign- to goal-tracking during acquisition sessions. Such reorganization can be illustrated in terms of *response bias*, a measure that pits tendencies to respond to the lever and goal against each other. Response bias, calculated as (lever presses per trial minus goal entries per trial) is a component of the formula commonly used to assess the animal's propensity for sign tracking vs. goal tracking (e.g., Flagel et al., 2011). A positive response bias indicates predominance of sign tracking, whereas a negative response bias indicates a prevalence of goal tracking. As shown in Fig. 5, apart from an occasional negative group average during the initial acquisition sessions, these rats were predominantly sign trackers. Nonetheless, a sign-tracking bias was least pronounced in PR/DMS rats throughout acquisition. A Lesion × Schedule × Session (1–10) analysis indicated only a significant increase across sessions, $F(9, 270) = 36.40$, $p < 0.001$; all other effects were not significant, Fs < 3.53, ps > 0.06. Separate Lesion × Session analyses comparing PR and CR groups showed a significant interaction for PR animals, $F(9, 126) = 2.41$, $p < 0.02$, and significantly higher lever pressing for sham than for DMS animals, $F(1, 14) = 8.03$, $p < 0.02$, but none of these effects for CR animals, Fs < 1. LSD pairwise comparisons indicated that the source of the significant interaction between Groups PR/DMS vs. PR/Sham was reduced lever pressing in the former on sessions 2–7, Fs(1, 14) > 4.87, ps < 0.05.

Altogether, the results from autoshaping acquisition suggest that the DMS lesion shifted the performance of animals exposed to PR away from sign tracking and toward goal tracking. There was no evidence of such response reorganization in continuously reinforced animals. Thus, these results were selective for the condition involving reward uncertainty.

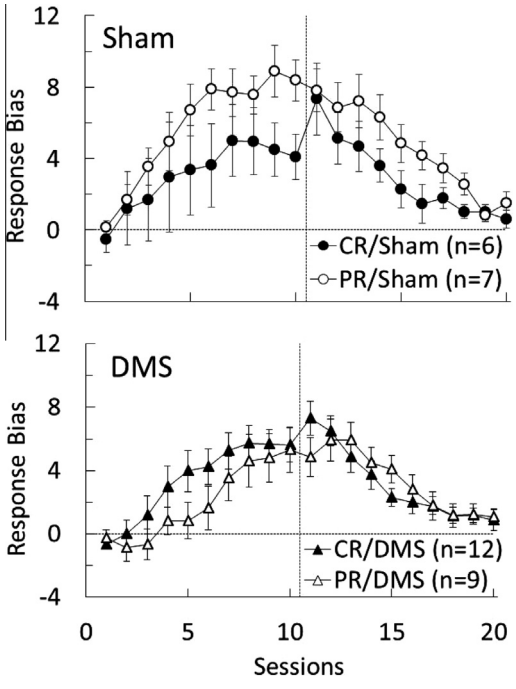

Fig. 5. Mean (±SEM) response bias, computed as the difference between lever pressings per trial (sign tracking) minus goal entries per trial (goal tracking) for each group during autoshaping acquisition and extinction. Top: sham-operated animals. Bottom: animals with DMS lesions. Data from Phase 2.

Phase 2: extinction after PR vs. CR

Figs. 3–5 also show the results for extinction. In terms of *lever pressing* (Fig. 3), the initial extinction performance shows a discrepant result. CR groups increased performance during the initial extinction session, relative to the terminal performance in acquisition, but this extinction spike was not observed in PR groups. The DMS lesion may have reduced the extinction spike, but it did not prevent it. A Lesion × Schedule × Session (10 vs. 11) analysis revealed an interaction between schedule and session, $F(1, 30) = 16.34$, $p < 0.001$. The change across sessions was marginally nonsignificant, $F(1, 30) = 3.66$, $p = 0.065$. All other effects were also nonsignificant, Fs < 2.11, ps > 0.15.

Independently of acquisition performance, the extinction of lever pressing showed the familiar PREE in both sham and DMS groups. Statistically, the PREE resulted in a significant interaction between schedule and session, $F(9, 270) = 2.64$, $p < 0.007$. The reduction of lever pressing across sessions was also significant, $F(9, 270) = 59.98$, $p < 0.001$. All other effects, including lesion effects, were nonsignificant, Fs < 1.65, ps > 0.20. Separate Lesion × Session analysis for PR and CR groups indicated that the DMS lesion had no detectable effects on extinction performance, either in terms of an interaction or a main effect, Fs < 1.24, ps > 0.28. The reduction in lever pressing during extinction sessions was significant in both comparisons, Fs > 28.13, ps < 0.001.

In terms of *goal entries* (Fig. 4), extinction performance seemed to exhibit a trend toward an increase, but this effect was not different across conditions (both lesion and schedule) and it failed to achieve significance, all Fs < 2.73, ps > 0.10. Session × Lesion analyses for PR and CR groups also yielded nonsignificant results for all factors, Fs < 1.07, ps > 0.11. Thus, DMS lesions did not significantly affect either extinction of lever pressing or of goal entries.

In terms of *response bias*, two main results are reflected in Fig. 5. First, sign tracking continued to predominate over goal tracking during extinction sessions, in the absence of reward, as it had been the case during acquisition sessions. Despite a slight increase in goal entries during extinction (see Fig. 4), none of the group means were negative during extinction. Second, despite the opposite effects of PR on acquisition for sham and DMS groups, the extinction functions were very similar, showing for both conditions somewhat greater persistence after PR than after CR. A Lesion × Schedule × Session (11–20) analysis indicated

a significant interaction between schedule and session, $F(9, 270) = 2.88$, $p < 0.004$. There was also a significant reduction in performance across extinction sessions, $F(9, 270)$, 56.48, $p < 0.001$, but none of the other factors reached a significant level, Fs < 1.42, ps > 0.24. Pairwise LSD comparisons indicated that PR groups performed significantly above CR groups on session 15, $F(1, 30) = 6.78$, $p < 0.02$. As with previous dependent variables, we calculated separate Schedule × Session analyses for sham and DMS groups. In both cases, the extinction effect was significant, Fs > 26.06, ps < 0.001; however, none of the factors involving the schedule of reinforcement was significant, Fs < 1.36, ps > 0.26. Therefore, there was no evidence that the DMS lesion affected any aspect of extinction, including the extinction spike, the PREE, and the extinction performance of PR and CR groups taken separately.

Phase 3: open-field testing

Fig. 6 shows the results of the open-field test under either dark (top panel) or light (bottom panel) conditions. The distance traveled in each 1-min bin in the central and peripheral areas of the open field are presented in each of these panels. Independent Lesion (DMS, Sham) × Area (Central, Peripheral) × 1-min Bin (1–20) analyses were computed for the dark and light sessions, with repeated measures for Area and Bin. Both analyses yielded the same results. Animals traveled a greater distance in the periphery than in the central area of the open field, Fs(1, 32) > 82.05, ps < 0.001, but the difference between these areas decreased across 1-min bins, as shown by significant interactions, Fs(19, 608) > 5.56, ps < 0.001. In both cases the reduction in activity across 1-min bins was significant, Fs(19, 608) > 38.51, ps < 0.001. Importantly, none of the factors involving Lesion achieved significance in either analysis, Fs < 1.43, ps > 0.10. An inspection of Fig. 6 appears to show a lesion effect only during the first minute of the open-field test, so analyses of these data were computed for both dark and light sessions. Only the area effects were significant, Fs(1, 32) > 79.88, ps < 0.001. Again, the main effect of lesion and the area by lesion interaction were not significant, Fs < 2.79, ps > 0.10.

Thus, there was no evidence that the DMS lesion altered patterns of activity in the open field under two different conditions of illumination.

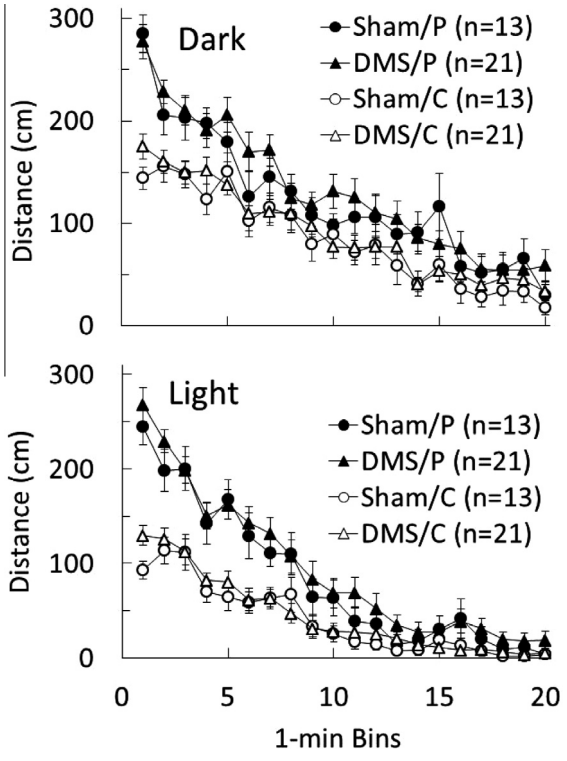

Fig. 6. Mean (±SEM) distance (cm) traveled in the open field expressed in 1-min bins and segregated according to the central or peripheral areas, in animals with either sham or DMS lesions. Top: testing under dark conditions. Bottom: testing under light conditions. Data from Phase 3.

DISCUSSION

The goal of this research was to analyze the role of the DMS in situations involving reward devaluation, uncertainty, and omission. The results can be summarized as follows. First, there was no evidence that the DMS lesion affected behavior in situations involving reward devaluation or omission. Thus, animals with either DMS or sham lesions displayed similar cSNC effects in Phase 1 and extinction spikes in Phase 2. Second, the DMS lesion selectively reduced lever pressing and increase goal entries during autoshaping acquisition under PR, but it did not affect either behavior when autoshaping training involved CR. Interestingly, the DMS lesion did not influence the PREE or extinction rates after CR training. Third, there was no evidence that DMS lesions affected motor activity or anxiety levels in the open field. Habituation of locomotor activity was not influenced by the lesion and animals displayed the usually higher activity levels in the periphery of the open field than in the central area, whether under dark or light conditions. Therefore, these results provide little support for the hypothesis that the behavioral effects dependent upon reward loss share a common brain circuit. Rather, they suggest that the adjustment to situations involving reward uncertainty is uniquely dependent upon the integrity of DMS neurons.

There were empirical precedents suggesting that DMS lesions should affect behavior in all the tasks involving reward downshifts included in this experiment: cSNC, PRAE, extinction spike, PREE, and extinction rates. Thus, pretraining lesions, posttraining lesions, and temporal inactivation of the posterior DMS abolish the impact of outcome devaluation on instrumental performance (Yin et al., 2005; Balleine et al., 2007). Consistent with these results, blocking ERK activation by infusing the inhibitor U0126 also into the posterior DMS also disrupted the effect of outcome devaluation via pre-session feeding (Shiflett et al., 2010), and pCREB expression was enhanced after the first reward devaluation

session in the cSNC situation (Glueck et al., 2015). Furthermore, factors affecting cSNC had also affected the PRAE in two previous experiments following a design similar to that used here: ventrolateral lesions of the orbital cortex (Ortega et al., 2013) and artificial selection for fast recovery from reward downshift (Ortega et al., 2014b). There is also evidence that areas providing indirect input to the DMS, such as the nucleus accumbens (Hart et al., 2014), respond to reward devaluation and omission. For example, microdialysis studies showed a reduction in dopamine efflux in the nucleus accumbens during reward devaluation (Genn et al., 2004) and in the accumbens core, but not shell, during reward omission (Biesdorf et al., 2015). Based on this evidence, the DMS lesion should have at least alleviated the suppression of sucrose intake observed in the cSNC task and, because of the covariation observed in previous experiments, this lesion should have also disrupted performance under partial reinforcement conditions, both in acquisition (PRAE) and extinction (PREE). However, only the PRAE was affected.

These empirical precedents suggested a role for the DMS in associative processes activated by reward-loss events—a role that found no support in the present data. However, some theories also include a nonassociative factor related to the response invigoration properties of reward uncertainty. Such a nonassociative factor may be thought of as having an activating (motivational, emotional) role on behavior. Two nonassociative factors potentially relevant for reward loss are incentive hope (Anselme, 2015, 2016) and drive induction (Amsel, 1992). In Anselme's (2015) model, a cue signaling an uncertain reward accrues additional motivational value, called incentive hope (nonassociative factor), independently of the reward expectation it may elicit (associative factor). Incentive hope adds to the motivational value of a reward signal as if the organism were responding for a larger reward. This additional motivational value is connected to dopamine release in the nucleus accumbens core (Cardinal and Howes, 2005).

In Amsel's (1992) model, negative expectancy violations lead to the conditioning of secondary frustration (associative factor), but are also drive inducing, invigorating dominant responses (nonassociative factor). Thus, for example, whereas the PRAE (which in the runway situation occurs far from the goal; Goodrich, 1959) would reflect response invigoration induced by secondary frustration (a nonassociative factor resulting from anticipating goal frustration), the extinction spike would reflect invigoration triggered by primary frustration (reacting to goal frustration; Dudley and Papini, 1995, 1997; Stout et al., 2003; Thomas and Papini, 2001). Experiments involving lesions of limbic structures provided some supporting evidence for the distinction between secondary vs. primary frustration (Henke, 1973, 1977; Henke and Maxwell, 1973). For example, Henke (1977) reported that lesions of the amygdala eliminated response invigoration immediately after surprising nonreward (the frustration effect in double-runway procedure, analogous to the extinction spike), but did not affect the PREE (dependent upon anticipatory frustration and thus analogous to the PRAE); by contrast, septal lesions did not affect response invigoration, but they eliminated the PREE. These findings are consistent with the idea that these two behavioral effects that developed from the same reward-loss event were supported by different neural circuits, but they do not implicate the dorsal striatum explicitly. Could the distinction between associative and nonassociative factors help explain the effects of the DMS lesion in the present study?

One interpretation of the present results would suggest that the disruption of the PRAE by DMS lesions reflects a selective interference with the nonassociative effects of anticipating uncertain reward (incentive hope) or goal frustration (drive induction) during reward uncertainty training. There are two problems with these nonassociative explanations. First, if the DMS lesion eliminated the PRAE by lowering the nonassociative impact of the reward signal, as suggested by the incentive hope hypothesis (Anselme, 2015), then the extinction spike should have been present in the transition from acquisition to extinction after either CR or PR training and the DMS lesion should have reduced the extinction spike. In fact, the extinction spike was observed after CR training, but not after PR training, and there was no evidence that the DMS lesion reduced its size. Although its underlying mechanism is poorly understood, the extinction spike that occurs in the autoshaping situation is known to be eliminated by adrenalectomy (Thomas and Papini, 2001), a result pointing to its connection with emotional activation.

A second problem with nonassociative interpretations is that the DMS lesion did not simply reduce lever pressing during PR training, but it also enhanced goal entries (see Figs. 3 and 4). In a sense, while the lesion eliminated the PRAE in lever pressing, it induced a PRAE in goal entries. The autoshaping procedure allows for a clear visualization of this behavioral reorganization because of the simultaneous recording of sign-tracking (lever pressing) and goal tracking (goal entries) responses, two behaviors that appear to be based upon different mechanisms (e.g., Tomie et al., 2000; Morrison et al., 2015). Boakes (1977) first reported that there is a tendency for some rats to show a bias for lever pressing (sign trackers), whereas others show a tendency toward goal entry (goal trackers). Such clear cut distinction was not observed in the present experiment.

The reasons for the absence of stable goal trackers in the present experiment are not clear. Experiments in which sign and goal tracking are stable individual differences have allowed a neurobiological characterization of these phenotypes. For example, the posterior sections of DMS and DLS, and the nucleus accumbens core and shell are differentially activated in sign trackers, as measured in terms of c-Fos mRNA expression; by contrast, none of the areas explored in the prefrontal cortex, striatum, habenula, and thalamus show activation in goal trackers (Flagel et al., 2011). If PR training mimics the ''spontaneous'' tendency for sign tracking exhibited by some rats, then the DMS lesion should lead to a reduction of lever pressing, as observed in the present experiment; but, of course, by the same token, the lesion should have also reduced lever pressing in CR animals, a result that was not observed here.

The present findings concerning goal entries in the autoshaping situation deserve a special discussion. When goal entries are measured in the absence of lever presentations their frequency tends to increase monotonically during training (e.g., Harris et al., 2013). This fact has led to its widespread use as a measure of Pavlovian conditioning. By contrast, the autoshaping data reported here show that goal entries display a sharp early increase followed by a rapid decrease to a steady, low level (see Fig. 4). Response competition may be a factor for the reduction of goal entries during late acquisition, but it is not an entirely satisfactory account because both lever pressing and goal entries increased rapidly early in acquisition without signs of competition, and also goal entries did not change in extinction despite a rapid reduction in lever pressing. Still, the reversal in the frequency of goal entries in DMS vs. Sham animals trained under PR vs. CR conditions requires an explanation. One possibility is to view such behavioral reorganization as a passive byproduct of drive levels for lever pressing. Thus, in acquisition, lever pressing in PR/Sham animals is at such a high level that goal entries suffer from intense competition and are thus at a low level compared to CR/Sham animals. If the DMS lesion reduces drive affecting lever pressing, then one would have to assume that drive levels controlling goal entries in PR/DMS animals were heightened by activity in some other brain region. This speculation is consistent with the fact that sign and goal tracking are controlled by different mechanisms. As mentioned above, neural activation in the dorsal striatum occurs in sign trackers, but not in goal trackers (Flagel et al., 2011).

A paradoxical finding in the present experiment was that the effects of the DMS lesion were inconsistent across reward loss tasks. Especially striking is the fact that while DMS animals exhibited no evidence of the PRAE in lever pressing, the same animals went on to produce evidence of the PREE in subsequent sessions. A similar result was reported by Castañé et al. (2010); in their case, although DMS lesions impaired successive discrimination reversals, they had no detectable effect in a series of extinction trials that followed the last reversal. The results reported here suggest that PRAE and PREE in lever pressing are dependent upon different mechanisms as response invigoration during exposure to reward uncertainty does not appear to be a prerequisite for response persistence during extinction. Moreover, goal entries did not exhibit the PREE, whether after evidence of the PRAE (in DMS animals) or of a reversed PRAE (in sham animals). Therefore, the PRAE and PREE were effectively dissociated in the present results. Amsel's (1992) model can accommodate lever pressing results more comfortably than it deals with goal tracking results. In terms of lever pressing, Amsel's model assumes that the PRAE is a nonassociative effect resulting from the drive inducing properties of secondary frustration, whereas the PREE is an associative process arising from the counterconditioning of secondary frustration during occasional pairings with reward in acquisition trials. This model could also account for the lack of a lesion effect on the extinction spike by assuming that this effect reflects drive induction from primary frustration—an unconditioned emotional state induced by exposure to a negative discrepancy between obtained and expected rewards (Amsel, 1992; Dudley and Papini, 1997).

CONCLUSION

We suggest that the motivational/emotional activation arising from anticipatory frustration in situations involving exposure to reward uncertainty and influencing autoshaped lever pressing requires output from DMS neurons. There was no evidence in these data that DMS output is necessary for the behavioral adjustment to reward devaluation or omission. An understanding of goal-entry dynamics under reward uncertainty in autoshaping will require additional research.

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REFERENCES

Amsel A (1992) Frustration theory. Cambridge, UK: Cambridge University Press.

Anselme P (2015) Incentive salience attribution under reward uncertainty: a Pavlovian model. Behav Proc 111:6–18.

Anselme P (2016) Motivational control of sign-tracking behavior: a theoretical framework. Neurosci Biobehav Rev 65:1–20.

Balleine BW, Delgado MR, Hikosaka O (2007) The role of dorsal striatum in reward and decision-making. J Neurosci 27:8161–8165.

Bentosela M, Ruetti E, Muzio RN, Mustaca AE, Papini MR (2006) Administration of corticosterone after the first downshift session enhances consummatory successive negative contrast. Behav Neurosci 120:371–376.

Biesdorf C, Wang AL, Topic B, Petri D, Milani H, Huston JP, de Souza Silva MA (2015) Dopamine in the nucleus accumbens core, but not shell, increases during signaled food reward and decreases during delayed extinction. Neurobiol Learn Mem 123:125–139.

Boakes R (1977) Performance on learning to associate a stimulus with positive reinforcement. In: Davis H, Hurwitz H, editors. Operant-pavlovian interactions. Hillsdale, NJ: Erlbaum. p. 67–97.

Boughner RL, Papini MR (2006) Survival of the partial reinforcement extinction effect after contextual shifts. Learn Motiv 37:304–323.

Brevers D, Bechara A, Hermoye L, Divano L, Kornreich C, Verbanck P, Noël X (2015) Comfort for uncertainty in pathological gamblers: a fMRI study. Behav Brain Res 278:262–270.

Bushnell PJ, Stanton ME (1991) Serial spatial reversal learning in rats: comparison of instrumental and automaintenance procedures. Physiol Behav 50:1145–1151.

Cardinal RN, Howes NJ (2005) Effects of lesions of the nucleus accumbens core on choice between small certain rewards and large uncertain rewards in rats. BMC Neurosci 6:37.

Castañé A, Theobald DEH, Robbins TW (2010) Selective lesions of the dorsomedial striatum impair serial spatial reversal learning in rats. Behav Brain Res 210:74–83.

Christoph GR, Leonzio RJ, Wilcox KS (1986) Stimulation of the lateral habenula inhibits dopamine-containing neurons in the substantia nigra and ventral tegmental area of the rat. J Neurosci 6:613–619.

Coe CL, Stanton ME, Levine S (1983) Adrenal responses to reinforcement and extinction: role of expectancy versus instrumental responding. Behav Neurosci 97:654–657.
Cuenya L, Sabariego M, Donaire R, Fernández-Teruel A, Tobeña A, Gómez MJ, Mustaca AE, Torres C (2012) The effect of partial reinforcement on instrumental successive negative contrast in inbred Roman high- (RHA-I) and low- (RLA-I)avoidance rats. Physiol Behav 105:1112–1116.
Daly HB, Daly JT (1982) A mathematical model of reward and aversive nonreward: its application in over 30 appetitive learning situations. J Exp Psychol Gen 111:441–480.
Dudley RT, Papini MR (1995) Pavlovian performance of rats following unexpected reward omissions. Learn Motiv 26:63–82.
Dudley RT, Papini MR (1997) Amsel's frustration effect: a replication with control for frequency and distribution of rewards. Physiol Behav 61:627–629.
Feldon J, Gray JA (1981) The partial reinforcement extinction effect after treatment with chlordiazepoxide. Psychopharmacology 73:269–275.
Flagel SB, Cameron CM, Pickup KN, Watson SJ, Akil H, Robinson TE (2011) A food predictive cue must be attributed with incentive salience for it to induce c-Fos mRNA expression in cortico-striatal-thalamic brain regions. Neuroscience 196:80–96.
Flaherty CF (1996) Incentive relativity. Cambridge, UK: Cambridge University Press.
Flaherty CF, Grigson PS, Rowan GA (1986) Chlordiazepoxide and the determinants of contrast. Anim Learn Behav 14:315–321.
Floresco SB, Zhang Y, Enomoto T (2009) Neural circuits subserving behavioral flexibility and their relevance to schizophrenia. Behav Brain Res 204:396–409.
Friedman A, Lax E, Dikshtein Y, Abraham L, Flaumenhaft Y, Sudai E, Ben-Tzion M, Yadid G (2011) Electrical stimulation of the lateral habenula produces an inhibitory effect on sucrose self-administration. Neuropharmacology 60:381–387.
Gasbarri A, Pompili A, Packard MG, Tomaz C (2014) Habit learning and memory in mammals: behavioral and neural characteristics. Neurobiol Learn Mem 114:198–208.
Genn RF, Ahn S, Phillips AG (2004) Attenuated dopamine efflux in the rat nucleus accumbens during successive negative contrast. Behav Neurosci 118:869–873.
Glueck AC, Dennis T, Perrotti L, Torres C, Papini MR (2015) Brain expression of pCREB in rats exposed to reward devaluation. Neurosci Lett 587:93–97.
Gómez MJ, de la Torre L, Callejas-Aguilera JE, Lerma-Cabrera JM, Rosas JM, Escarabajal MD, Agüero A, Tobeña A, Fernández-Teruel A, Torres C (2008) The partial reinforcement extinction effect (PREE) in female Roman high- (RHA-I) and low-avoidance (RLA-I) rats. Behav Brain Res 194:187–192.
Gómez MJ, de la Torre L, Callejas-Aguilera JE, Rosas JM, Escarabajal MD, Agüero Á, Tobeña A, Fernández-Teruel A, Torres C (2009) Differences in extinction of an appetitive instrumental response in female inbred roman high- (RHA-I) and low- (RLA-I) avoidance rats. Psicológica 30:181–188.
Goodrich KP (1959) Performance in different segments of an instrumental response chain as a function of reinforcement schedule. J Exp Psychol 57:57–63.
Gray JA, McNaughton N (2000) The neuropsychology of anxiety. An enquiry into the functions of the septo-hippocampal system. 2nd ed. Oxford, UK: Oxford University Press.
Harris JA, Andrew BJ, Kwok DWS (2013) Magazine approach during a signal for food depends on Pavlovian, not instrumental, conditioning. J Exp Psychol: Anim Behav Proc 39:107–116.
Hart G, Leung BK, Balleine BW (2014) Dorsal and ventral streams: the distinct role of striatal subregions in the acquisition and performance of goal-directed action. Neurobiol Learn Mem 108:104–118.
Henke PG (1973) Effects of reinforcement omission on rats with lesions in the amygdala. J Comp Physiol Psychol 84:187–193.
Henke PG (1977) Dissociation of the frustration effect and the partial reinforcement extinction effect after limbic lesions in rats. J Comp Physiol Psychol 91:1032–1038.
Henke PG, Maxwell D (1973) Lesions in the amygdala and the frustration effect. Physiol Behav 10:647–650.
Kamenetzky GV, Mustaca AE, Papini MR (2008) An analysis of the anxiolytic effects of ethanol on consummatory successive negative contrast. Adv Lat Am Psychol 26:135–144.
Kawasaki K, Iwasaki T (1997) Corticosterone levels during extinction of runway response in rats. Life Sci 61:1721–1728.
Kawasaki K, Glueck AC, Annicchiarico I, Papini MR (2015) Function of the centromedial amygdala in reward devaluation and open field activity. Neuroscience 303:73–81.
Lindgren HS, Wickens R, Tait DS, Brown VJ, Dunnet SB (2013) Lesions of the dorsomedial striatum impair formation of attentional set in rats. Neuropharmacology 71:148–153.
Manzo L, Gómez MJ, Callejas-Aguilera JE, Fernández-Teruel A, Papini MR, Torres C (2014) Anti-anxiety self-medication induced by incentive loss in rats. Physiol Behav 123:86–92.
Manzo L, Donaire R, Sabariego M, Papini MR, Torres C (2015a) Anti-anxiety self-medication in rats: oral consumption of chlordiazepoxide and ethanol after reward devaluation. Behav Brain Res 278:90–97.
Manzo L, Gomez MJ, Callejas-Aguilera JE, Fernandez-Teruel A, Papini MR, Torres C (2015b) Partial reinforcement reduces vulnerability to anti-anxiety self-medication during appetitive extinction. Int J Comp Psychol 28:1–8.
Mitchell C, Flaherty CF (1998) Temporal dynamics of corticosterone elevation in successive negative contrast. Physiol Behav 64:287–292.
Morrison SE, Bamkole MA, Nicola SM (2015) Sign tracking, but not goal tracking, is resistant to outcome devaluation. Front Neurosci 9:1–12.
Norris JN, Ortega LA, Papini MR (2011) Postsession D-cycloserine enhances the emotional memory of an incentive downshift event. Behav Brain Res 223:348–355.
Ortega LA, Uhelski M, Fuchs PN, Papini MR (2011) Impairment of recovery from incentive downshift after lesions of the anterior cingulate cortex: Emotional or cognitive deficits? Behav Neurosci 125:988–995.
Ortega LA, Glueck AC, Uhelski M, Fuchs PN, Papini MR (2013) Role of the ventrolateral orbital cortex and medial prefrontal cortex in incentive downshift situations. Behav Brain Res 244:120–129.
Ortega LA, Glueck AC, Daniel AM, Prado-Rivera MA, White MM, Papini MR (2014a) Memory interfering effects of chlordiazepoxide on consummatory successive negative contrast. Pharmacol Biochem Behav 116:96–106.
Ortega LA, Norris JN, Lopez-Seal MF, Ramos T, Papini MR (2014b) Correlates of recovery from incentive downshift: a preliminary selective breeding study. Int J Comp Psychol 27:160–186.
Papini MR (2003) Comparative psychology of surprising nonreward. Brain Behav Evol 62:83–95.
Papini MR (2014) Diversity of adjustments to reward downshifts in vertebrates. Int J Comp Psychol 27:420–445.
Papini MR, Dudley RT (1997) Consequences of surprising reward omissions. RevGen Psychol 1:175–197.
Papini MR, Fuchs PN, Torres C (2015) Behavioral neuroscience of psychological pain. Neurosci Biobehav Rev 48:53–69.
Paxinos G, Watson C (2007) The rat brain in stereotaxic coordinates. 6th ed. New York: Academic Press.
Pecoraro N, de Jong H, Dallman MF (2009) An unexpected reduction in sucrose concentration activates the HPA axis on successive post shift days without attenuation by discriminative contextual stimuli. Physiol Behav 96:651–661.
Pellegrini S, Wood MD, Daniel AM, Papini MR (2005) Opioid receptors modulate recovery from consummatory successive negative contrast. Behav Brain Res 16:239–249.
Prut L, Belzung C (2003) The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. Eur J Pharmacol 463:3–33.
Ragozzino ME (2007) The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. Ann NY Acad Sci 1121:355–375.

Rosas JM, Callejas-Aguilera JE, Escarabajal MD, Gómez MJ, de la Torre L, Agüero Á, Tobeña A, Fernández-Teruel A, Torres C (2007) Successive negative contrast effect in instrumental runway behaviour: a study with Roman high- (RHA) and Roman low- (RLA) avoidance rats. Behav Brain Res 185:1–8.

Ruetti E, Justel N, Mustaca AE, Papini MR (2009) Postsession corticosterone administration enhances the effects of incentive downshift: exploring the boundaries of this effect. Behav Neurosci 123:127–144.

Shaw D, Norwood K, Sharp K, Quigley L, McGovern SF, Leslie JC (2009) Facilitation of extinction of operant behaviour in mice by D-cycloserine. Psychopharmacology 202:397–402.

Shiflett MW, Brown RA, Balleine BW (2010) Acquisition and performance of goal-directed instrumental actions depends on ERK signaling in distinct regions of dorsal striatum in rats. J Neurosci 30:2951–2959.

Stout S, Boughner RL, Papini MR (2003) Reexamining the frustration effect in rats: aftereffects of surprising reinforcement and nonreinforcement. Learn Motiv 34:437–456.

Striedter GF (2016) Neurobiology. A functional approach. Oxford, UK: Oxford University Press.

Thomas B, Papini MR (2001) Adrenalectomy eliminates the extinction spike in autoshaping with rats. Physiol Behav 62:543–547.

Tomie A, Aguado AS, Pohorecky LA, Benjamin D (2000) Individual differences in Pavlovian autoshaping of lever-pressing in rats predict stress-induced corticosterone release and mesolimbic levels of monoamines. Pharmacol Biochem Behav 65:509–517.

Torres C, Sabariego M (2014) Incentive relativity: gene–environment interactions. Int J Comp Psychol 27:446–458.

Voorn P, Vanderschuren LJMJ, Groenewegen HJ, Robbins HJ, Pennartz CMA (2004) Putting a spin on the dorsal–ventral divide of the striatum. Trends Neurosci 27:468–474.

Wood MD, Daniel AM, Papini MR (2005) Selective effects of the delta opioid receptor agonist DPDPE on consummatory successive negative contrast. Behav Neurosci 119:446–454.

Wood MD, Norris JN, Daniel AM, Papini MR (2008) Trial-selective effects ofU50,488H, a kappa opioid receptor agonist, on consummatory successive negative contrast. Behav Brain Res 193:28–36.

Yin HH, Knowlton BJ, Balleine BW (2004) Lesions of the dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental conditioning. Eur J Neurosci 19:181–189.

Yin HH, Ostlund SB, Knowlton BJ, Balleine BW (2005) The role of the dorsomedial striatum in instrumental conditioning. Eur J Neurosci 22:513–523.

GLOSSARY

Autoshaping: In rats, presentation of a retractable lever for a few seconds is followed, upon lever retraction, with the response-independent delivery of a reward. It is a Pavlovian procedure, but rats typically develop approach, contact, and other behaviors directed at the lever.

Consummatory successive negative contrast (cSNC): A consummatory task involving a single session per day. Access to a large reward (e.g., 32% sucrose) during several daily sessions is followed by access to a small reward (e.g., 4% sucrose). The behavior of downshifted animals is compared to that of unshifted controls always receiving access to the small reward. During these final sessions, although both groups receive the same reward magnitude, downshifted animals exhibit a significant reduction in consummatory behavior relative to unshifted controls.

Dorsomedial striatum (DMS): In the rat brain, an extended region in the anterior–posterior axis located ventro-medially with respect to the lateral ventricles, whose major afferents arrive from various regions of the prefrontal cortex and substantia nigra pars compacta, and whose major efferents connect it to the dorsal pallidum and the external globus pallidus. The DMS is part of a corticostriatal loop involved in behavioral plasticity associated to conditioning processes.

Extinction spike or burst: In the autoshaping situation, an increase in lever pressing during early extinction trials, relative to the level exhibited during terminal acquisition trials.

Goal tracking: In the autoshaping situation, a tendency to approach the site where the reward will be delivered during the reward signal.

Open-field task: A task usually administered in one or two sessions. The animal is released in an empty arena where it can move freely while its behavior is monitored. Rodents typically stay closed to the peripheral walls, a behavior called thigmotaxis, and avoid the central area of the field. Treatments that increase activity, especially in the central area, are usually interpreted as reducing unconditioned fear, anxiety, or conflict. There is a tendency for activity to be higher under dark conditions than when the field is lighted.

Partial reinforcement acquisition effect (PRAE): In the autoshaping situation, the tendency to increase lever-pressing responses during partial reinforcement acquisition training, relative to a group given continuous reinforcement training. Partial reinforcement refers to the proportion of signals followed by reward.

Partial reinforcement extinction effect (PREE): In the autoshaping situation, the tendency for slower extinction after acquisition under partial, rather than continuous reinforcement. Partial and continuous reinforcement refer to the proportion of signals followed by reward.

Reward devaluation: A procedure involving a (usually unexpected) reduction to a nonzero reward magnitude. Provided the reduction is significant, such devaluation induces signs of negative emotion, including disruption of goal approach.

Reward omission: A situation in which a reward signal is not followed by reward, such as in appetitive extinction.

Reward uncertainty: A situation in which two reward conditions are combined in an unpredictable fashion, such as in partial reinforcement training (i.e., reward and nonreward).

Sign tracking: In the autoshaping situation, a tendency to approach the signal for reward presentation.

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