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Dorsolateral striatum is critical for the expression of surprise-induced enhancements in cue associability

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Abstract

The dorsolateral striatum (DLS) is frequently implicated in sensory-motor integration, including the performance of sensory orienting responses (ORs) and learned stimulus–response habits. Our laboratory previously identified a role for the DLS in rats' performance of conditioned ORs to Pavlovian cues for food delivery. Here, we considered whether DLS is also critical to another aspect of attention in associative learning, the surprise-induced enhancement of cue associability. A large behavioral literature shows that a cue present when an expected event is omitted enters into new associations more rapidly when that cue is subsequently paired with food. Research from our laboratory has shown that both cue associability enhancements and conditioned ORs depend on the function of a circuit that includes the amygdala central nucleus and the substantia nigra pars compacta. In three experiments, we explored the involvement of DLS in surprise-induced associability enhancements, using a three-stage serial prediction task that permitted separation of DLS function in registering surprise (prediction error) and enhancing cue associability, and in using that increased associability to learn more rapidly about that cue later. The results showed that DLS is critical to the expression, but not the establishment, of the enhanced cue associability normally produced by surprise in this task. They extend the role of DLS and the amygdalo-nigro-striatal circuit underlying learned orienting to more subtle aspects of attention in associative learning, but are consistent with the general notion that DLS is more important in the expression of previously acquired tendencies than in their acquisition.

Introduction

Over the past decade, the dorsolateral striatum (DLS) has frequently been implicated in the performance of well-learned, automated responses or 'habits' (e.g. Yin *et al.*, 2006; Smith & Graybiel, 2014), characterized by their rigid, relatively inflexible nature, and their insensitivity to post-training modulation of the value of the reinforcer. Earlier, many researchers, noting its strong connectivity with sensory and motor cortices, described more general roles for the DLS in sensory-motor integration, including stimulus–response learning (McDonald & White, 1993) and the integration of sensory information with motor systems in the performance of orienting responses (ORs; Carli *et al.*, 1985, 1989).

Han *et al.* (1997) identified a role for the DLS in the performance of appetitively conditioned ORs in rats. Typically, presentation of a salient auditory or visual stimulus produces an unconditioned stimulus-specific OR, which habituates rapidly with repeated stimulus presentation. However, formation of associations between that stimulus and food often results in the re-emergence or potentiation of that OR (e.g. Holland, 1977). Unlike conditioned responses (CRs) related to the food reinforcer (e.g. food-source approach), the acquisition of conditioned ORs depends on normal function of the amygdala central nucleus (CeA; Gallagher *et al.*, 1990; McDannald *et al.*, 2004). Using a disconnection lesion/inactivation design, Han *et al.* (1997) found that the performance, but not the initial acquisition, of these conditioned ORs depended on convergence of processing by CeA and DLS. Food-related CRs were unaffected by the lack of CeA–DLS convergence.

Han *et al.*'s (1997) observations are consistent with the common idea that the DLS is more important for performance than for learning (e.g. Attalah *et al.*, 2007), and with Carli *et al.*'s (1985) suggestion that the DLS subserves the integration of sensory information with motor behavior in action, but not sensory attention itself. Indeed, there is little evidence that DLS neurons respond to visual or auditory stimuli in the absence of motor responses to those stimuli (e.g. Root *et al.*, 2010).

By contrast, Holland & Gallagher (1999) suggested that conditioned ORs might be construed as one of many alterations in attention that occur in associative learning. Here we considered whether the DLS might be more broadly involved in attention by examining its role in the enhancement of cue associability (ease of entering into new associations) after surprising omissions of an expected event, assessed independently of the performance of ORs or other CRs known to rely on DLS function.

According to many models of associative learning (e.g. Pearce & Hall, 1980; LePelley, 2004), the induction of surprise (prediction error) in a learning trial enhances attention to cues present on that trial, as reflected in the rate at which those cues subsequently enter

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into associations. Here we examined effects of permanent or transient disruptions of DLS function on rats' performance in a three-stage serial prediction task (Table 1; Wilson *et al.*, 1992) that permitted separation of function in registering prediction error and enhancing cue associability, and in using that increased associability to learn more rapidly about that cue later.

Methods and materials

Experimental design

This study was conducted as three experiments, which differed in the nature and timing of DLS manipulations, but which used identical behavioral training procedures. In an initial 'expectancy' phase, rats first received consistent serial light→tone pairings to establish the light as a highly valid predictor of the tone. Next, in a 'surprise' phase, for experimental rats the tone was omitted on half of the trials, whereas other, control rats received additional consistent light→tone pairings. Finally, the associability of the light was assessed in a test phase in which the light was directly paired with food. Within the Pearce–Hall model (1980), as the light comes to predict the tone in the expectancy phase, its associability decreases, whereas violation of that prediction in the surprise phase restores or enhances that associability. Rats for which the tone was unexpectedly omitted in the surprise phase routinely show substantially more rapid learning of the new light–food relationship in the final test phase than control rats that received consistent light→tone pairings in the surprise phase (reviewed by Holland & Maddux, 2010).

To determine if an intact DLS is necessary for normal performance in this task, in experiment 1 we examined the effects of bilateral lesions of the DLS made prior to any experimental training. To assess the necessity of normal DLS activity for the detection of surprise or the formation of an enhanced associability memory at the time of surprise itself, in experiment 2 we examined the effects of temporarily disrupting DLS function by lidocaine infusions prior to sessions in the surprise phase. To examine the importance of intact DLS function for the expression of that enhanced associability as more rapid learning, in experiment 3 we infused lidocaine prior to sessions in the test phase. Each experiment was conducted in two (experiments 2 and 3) or three (experiment 1) replications, with all conditions represented similarly in each replication.

Subjects

The subjects were 126 (42, 43 and 41 rats in experiments 1, 2 and 3, respectively) male Long-Evans rats (Charles River Laboratories, Raleigh, NC, USA), which weighed 300–325 g on arrival to the laboratory vivarium. Rats were individually housed in a colony room with a 12:12-h light–dark cycle. They received about 1 week of free access to food and water prior to lesion (experiment 1) or cannula implantation (experiments 2 and 3) surgery. Surgery was followed by 10–14 days of recovery before behavioral training. During the recovery period, the rats were handled daily. For the rats in experiment 1, 5 days before the beginning of behavioral training, their access to food was restricted, such that their weights reached and were then maintained at 85% of their free feeding weights. The rats in the initial replications of experiments 2 and 3 first participated in a study of the effects of DLS lidocaine infusions on the acquisition of a submerged water maze task (Asem & Holland, 2015). In that experiment, each of these rats received four prior lidocaine or saline infusions into the DLS, using the same parameters as specified later for the present experiments. The rats in the second replications of experiments 2 and 3 were experimentally naïve. For all experiments, behavioral training sessions were conducted during the light portion of the light–dark cycle. The care and experimental treatment of rats was conducted according to the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals*, and protocols were approved by the Johns Hopkins University Animal Care and Use Committee.

TABLE 1. Outline of behavioral training procedures

Group	Expectancy phase	Surprise phase	Test phase
Shift	light→tone→food light→tone→empty	light→tone→food light→empty	light→food
Consistent	light→tone→food light→tone→empty	light→tone→food light→tone→empty	light→food

Apparatus

The behavioral training apparatus consisted of eight individual chambers (20.5 × 22.0 × 22.5 cm) with stainless steel front and back walls, clear acrylic sides, and a floor made of 0.48-cm stainless steel rods spaced 1.9 cm apart. An illuminated clear acrylic food cup was recessed in a 5.0 × 5.0 cm opening in the front wall, and photocells at the front of the food cup recorded entries and time spent in the cup. Sucrose pellets (45 mg; Formula 5TUT, Test Diets, Richmond, IN, USA) were delivered to the food cups by pellet feeders (Coulbourn H14-22, Allentown, PA, USA). A 1-W lamp was mounted behind a perforated steel hemisphere on the front wall, 10 cm above the food cup; illumination of this lamp served as the 'light' stimulus. An infrared activity monitor (Coulbourn H24-61) and a bank of infrared LEDs to provide illumination for clear video recordings were mounted on the top of each chamber. Each chamber was enclosed inside a sound-attenuating shell. A piezoelectric device for presenting an intermittent (3 Hz) 79-dB, 1900-Hz tone was mounted on the side wall of the shell. A video camera mounted near that device allowed for television viewing and behavioral scoring (not reported here). Constant dim illumination visible to the rats was provided by a 1-W lamp mounted behind a red lens mounted near the piezoelectric device, and ventilation fans provided masking noise (70 dB).

Surgery

Stereotaxic (Kopf Model 902, Tujunga, CA, USA) surgery was conducted under aseptic conditions. For both lesion and cannula implantation surgery, rats were maintained under anesthesia with 2–3% isoflurane mixed with oxygen. In experiment 1, bilateral DLS lesions were made using 0.2 μL of 15 mg/mL quinolinic acid (Sigma, St. Louis, MO, USA) in phosphate-buffered saline (PBS) solution infused into each of two sites in each hemisphere with a 2.0-μL Hamilton syringe over a 4-min period. The injectors remained in place for 3 min after infusions before they were removed, to allow diffusion away from the tip. The coordinates used were 0.2 mm anterior to bregma and 3.8 mm right or left of the midline, with infusions at a depth of 5.0 mm from the skull surface for one site, and 1.6, 3.0 and 5.5 mm, respectively, for the other site. Sham lesions were made by infusing PBS alone in the same manner.

For cannula implantations in experiments 2 and 3, four 1/8-inch self-tapping mounting screws were installed into the skull. Then, a 26-gauge guide cannula (PlasticsOne, Roanoke, VA, USA) was

implanted into each DLS at 0.26 mm posterior and ±4.2 mm lateral to bregma, with the guide tip at a depth of 2.0 mm below the skull surface. Cannulae were held in place with dental acrylic and fitted with dummy injectors that were cut to match the length of the guide.

After both types of surgery, the incision was closed with surgical staples and topical antibiotic ointment was applied to the wound edges. After removal from the stereotaxic apparatus, each rat received a single 0.3-mL subcutaneous injection of 0.02 mg/mL buprenorphine hydrochloride (Sigma) for amelioration of pain, and was allowed to recover from surgery for 7–10 days before beginning behavioral training.

Drugs and infusion procedures (experiments 2 and 3)

Injector cannulas (33 gauge) that extended 2.0 mm below the tip of the guides (to 4.0 mm below the skull surface) were connected by PE50 tubing to separate 10-μL Hamilton syringes in a multiple-syringe pump (KD Scientific, Holliston, MA, USA). The pump simultaneously administered 0.5 μL of 2% lidocaine or PBS vehicle infusate bilaterally into DLS, over 1 min. After infusion, the injector was left in place for an additional 1 min. After removal of the injectors, the dummy injectors were reinserted. Infusions were delivered within 10 min prior to each of the two surprise sessions (experiment 2) or each of the first three test sessions (experiment 3).

Behavioral training procedures

Table 1 provides an outline of the behavioral training procedures. Once their weights reached 85%, rats were first given 10–20 sucrose pellets in their home cages, to familiarize them with the reinforcer. Each training session in each phase of the experiments included 16 trials, distributed across random intertrial intervals, which averaged 4 min (range = 2–6 min). The rats were first trained to eat sucrose pellets from the recessed food cups, in one or two (as needed) sessions, each including 16 unsignaled reinforcer deliveries. Then, to establish a strong light–tone association during the expectancy phase, all rats received trials consisting of a 10-s light → 10-s tone serial compound. In each session of this phase, the light→tone compound was reinforced with sucrose pellets on eight trials and non-reinforced on eight trials. Trial order in each session was randomly determined. After ten sessions of expectancy training, rats received two surprise phase sessions. During each surprise session, light→tone prediction error was induced for rats in the shift group by omitting the tone on the eight non-reinforced trials, whereas rats in the consistent group had their light→tone expectancies confirmed through continuation of the expectancy protocol. Finally, in each of the five sessions in the test phase, all rats received 16 presentations of the light conditioned stimulus (CS) alone followed immediately by sucrose pellet reinforcement. More rapid acquisition of food cup CRs to the light CS was taken as evidence of enhanced associability of that CS.

Histological procedures

After completion of behavioral testing, the rats were deeply anesthetized with isoflurane and perfused intracardially with 0.9% saline followed by either 3.7% formalin (26 rats in experiment 1, all rats in experiment 2 and 31 rats in experiment 3) or cold 4% paraformaldehyde in 0.1 M phosphate buffer (PB) solutions (16 rats in experiment 1 and ten rats in experiment 3). Brains perfused with formalin were removed and stored at 4 °C in 3.7% formalin + 12% sucrose solution; brains perfused with paraformaldehyde were removed, post-fixed and cryoprotected overnight in 4% paraformaldehyde in 0.1 M PB containing 12% sucrose, frozen with powdered dry ice, and stored at −80 °C. A freezing microtome was used to take 40-μm sections from each brain. Of every three consecutive sections, the first was mounted on glass slides, dehydrated in ascending concentrations of alcohol, defatted in xylene and Nissl-stained with thionin for evaluation of lesions or cannula placements. For 16 rats in experiment 1, the second and third sections were processed for NeuN and tyrosine hydroxylase (TH) immunocytochemistry, respectively. For ten rats in experiment 3, the second section was processed for FOS immunocytochemistry (data not reported here).

Immunocytochemistry procedures

Standard immunohistochemical protocols were used (e.g. Lee *et al.*, 2005). The primary antibodies used were for FOS (SC-32; Santa Cruz Biotechnology, Santa Cruz, CA, USA), NeuN (AB153; Millipore, Temecula, CA, USA) or TH (Immunostar, Hudson, WI, USA), and the secondary antibody was biotinylated goat anti-rabbit IgG (Vector, Burlingame, CA, USA). Sections were incubated in avidin–biotin peroxidase conjugate (Vector) and reacted with diaminobenzidrine-$NiCl_2$ to visualize cells immunoreactive for FOS, NeuN or TH. Sections were mounted on slides, dehydrated in ascending concentrations of alcohol and coverslipped with Permount.

Lesion evaluation

DLS lesions were evaluated from photographs of the Nissl-stained sections at six coronal planes of DLS (+1.70, +1.20, +0.70, +0.20, −0.30 and −0.80 relative to bregma). Outlines of the lesion extents were drawn on digital images from Paxinos & Watson (1998) using Adobe Photoshop 11.0.2. Calculation of percentage damage was performed in Photoshop by comparing the area of the intersection of lesion and region extent with the area within the region's borders. The lesion outlines for each rat at each plane were then filled in Photoshop with an opacity of 5% (100% divided by 20, the number of lesions represented) and stacked onto a single atlas section image, such that the darkness of an area reflected the number of lesions that included that area.

Behavioral measure and analysis

The behavioral response measure was the percentage of time spent in the food cup in each trial epoch, as assessed by interruption of the infrared photobeam. Trial epochs were defined as a 5-s stimulus-free pre-CS period (immediately prior to the light CS), the first 5 s of the light CS, the second 5 s of the light CS, the first 5 s of the tone CS, the last 5 s of the tone CS and the 5 s initiated by reinforcer delivery. Conditioned food cup responding was assessed during the latter half of CS presentations because in that epoch food cup CRs are more frequent and less contaminated by conditioned ORs (e.g. Holland, 1977).

CRs during the pre-CS, light and tone (when applicable) periods were each analysed with separate analyses of variance (ANOVAS) with replication, treatment (shift or consistent) and DLS state (excitotoxic or sham lesion in experiment 1, lidocaine or saline infusions in experiments 2 and 3) as between-subject variables, and (when applicable) repeated measures on the within-subjects variable of sessions. When the within-subject sessions variable was included, the

Greenhouse–Geisser procedure was used to compensate for potential violations of sphericity assumptions. In the test phase, the ANOVAS were followed by planned contrasts to evaluate the hypotheses that control rats in the shift condition would show greater responding than both the control rats in the consistent condition and lesion/lidocaine rats in the shift condition.

Results

Histological results

Lesions (experiment 1)

Two rats' lesions were judged as too small. Those rats were excluded from all analyses of lesions and behavioral data, leaving ten rats in each of the four treatment–lesion combinations. Figure 1A shows drawings of the extents of each rat's lesion at six rostrocaudal levels of DLS, and Fig. 1B–G show representative sham and quinolinic acid lesions, in Nissl- and NeuN-stained sections. A small number of DLS lesions extended into portions of the dorsocentral (as defined by Reep & Corwin, 2009) and/or more ventral potions of the lateral striatum, but none included significant portions of the dorsomedial striatum (as sampled, for example, by Furlong *et al.*, 2014) nor any portion of the nucleus accumbens. DLS lesion areas averaged 2.62 ± 0.2 mm^2 per section among the rats in the shift condition, and 2.75 ± 0.16 mm^2 per section among rats in the consistent condition. A replication × treatment ANOVA of these lesion areas showed no significant effects or interactions ($P > 0.532$). Among the eight DLS-lesioned and eight sham-lesioned rats also processed for TH immunochemistry, the density of TH staining in both DLS itself and its major dopaminergic afferent, the substantia nigra pars compacta (SNc), did not differ as a function of lesion ($P = 0.676$). Thus, the excitotoxic lesions of DLS did not appear to damage SNc or its dopaminergic innervation of DLS. Although this analysis was conducted on only a subset of rats in experiment 1, its results are consistent with those of a more extensive analysis after identical lesions in another study (Esber *et al.*, 2015).

Cannulae placements

Cannulae were located in the dorsolateral striatum, ranging from 0.20 mm anterior to bregma to 0.40 mm posterior to bregma. Across experiments 2 and 3, 11 rats were excluded from the analysis because of poor cannula placement ($n = 6$) or because they lost their cannula headsets before the completion of behavioral testing ($n = 5$). Figure 2 shows cannula locations for all rats accepted for inclusion in experiments 2 and 3.

Notably, our cannulations and lesions may have affected somewhat different portions of the DLS. Our lesions were designed to damage DLS throughout its rostrocaudal extent, whereas our cannula placements were those we have used successfully in other studies of DLS function (Asem & Holland, 2015). From unpublished assessment of the spread of dyes and alterations in FOS expression after our DLS lidocaine infusions, we believe that the two DLS manipulations encompassed similar medial–lateral and dorsal–ventral extents, but that the inactivations probably spared function in more rostral portions of DLS, compared with the lesions.

Behavioral results

Five of the experienced rats and one of the naïve rats used in experiments 2 and 3 (of the 73 rats with proper cannula implants) failed to acquire food cup responding to any cue in the expectancy phase, and were excluded from all analyses. We have no explanation for this comparatively high rate of exclusion (e.g. no rats were excluded from experiment 1 on the basis of failure to learn), but casual observation suggested that some of these rats may have avoided the food cup to minimize aversive consequences of striking the food cup walls with their cannula headsets. In experiment 2, the final numbers of rats in the shift-lidocaine, shift-saline, consistent-lidocaine and consistent-saline conditions were eight, ten, eight and nine, respectively. In experiment 3, those sample sizes were eight, eight, nine and seven, respectively.

Expectancy phase

In the expectancy phase, in which all rats in all three experiments were treated identically, the rats acquired considerable conditioned food-cup responding to the tone, and showed little food-cup responding to the light or during the pre-CS periods (left portions of each panel in Fig. 3). Initial ANOVAS performed on the data from each measurement epoch (pre-CS, light and tone periods) showed no significant main effects or interactions of replication ($P > 0.120$), so that variable was dropped from the analyses. The main effect of sessions was significant for responding to the tone in all three experiments ($P < 0.001$), for responding to the light in experiment 1 ($P = 0.010$) but not experiments 2 or 3 ($P = 0.644$, 0.076), and for pre-CS responding in experiments 1 and 2 ($P < 0.002$) but not experiment 3 ($P = 0.170$). There were no significant effects of any other variable, nor any significant interactions ($P > 0.157$). Additional replication × treatment × DLS manipulation ANOVAS of performance over the final two sessions of the expectancy phase also showed no significant main effects or interactions ($P > 0.201$). Thus, within each experiment, rats in all groups entered the surprise phase with similar levels of responding.

Surprise phase

Food-cup responding in the two surprise phase sessions for each experiment is shown in the right portions of each panel in Fig. 3. As in the expectancy phase, none of the main effects or interactions involving replication was significant, so that variable was dropped from the analyses. Importantly, there were no significant effects of behavioral treatment, DLS manipulation or their interaction for any measure in experiments 1 ($P > 0.312$), 2 ($P > 0.182$) or 3 ($P > 0.294$). Importantly, in experiment 2, rats in the shift-lidocaine and consistent-lidocaine conditions received infusions of lidocaine into DLS prior to each of these sessions. Thus, neither disruptions in DLS function produced by lesion (experiment 1) nor those produced by temporary perturbation (experiment 2) affected the rats' behavior in sessions in which surprise was induced in shift rats.

Test phase

Figure 4 shows the primary data of this study, the acquisition of food-cup responding to the light during the test phase. For experiments 1 and 2, initial replication × treatment × DLS manipulation × sessions ANOVAS for responding during the light and pre-CS periods all showed no main effects or interactions involving replication ($P > 0.465$), so that variable was dropped for subsequent analyses. In experiment 3, the main effect of replication was significant for both light ($F_{1,24} = 6.37$, $P = 0.019$) and pre-CS ($F_{1,24} = 8.49$, $P = 0.008$) responding. However, because replication did not

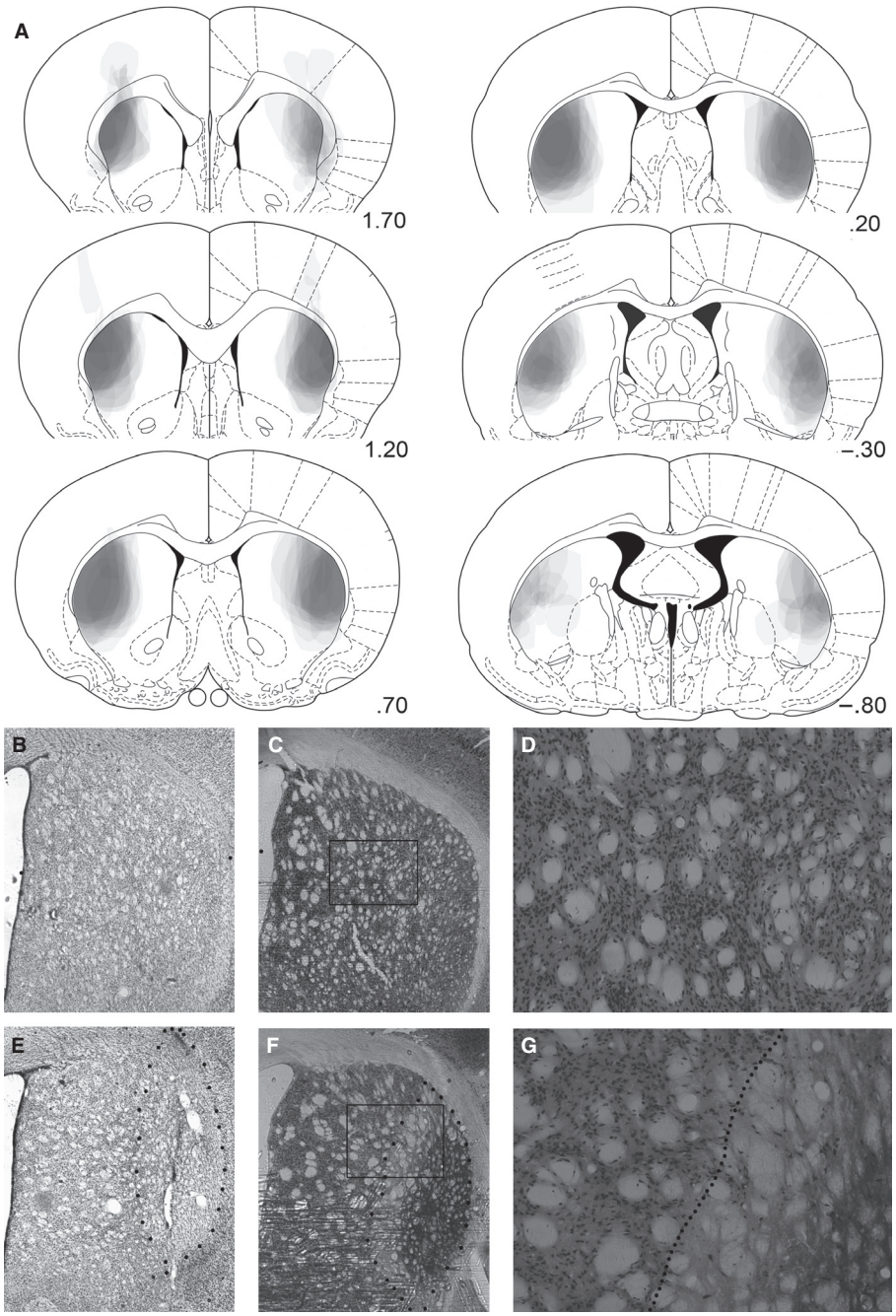

FIG. 1. Dorsolateral striatal lesions in experiment 1. (A) Extent of lesions at six anterio-posterior planes. Each lesion is represented; the darker an area, the more lesions included that area (see text for details). The lesions are drawn on sections from Paxinos & Watson (1998), and are used by permission of Elsevier. The numbers to the right of each section indicate distance (mm) anterior or posterior (−) to bregma. (B–D) A representative sham lesion; (E–G) a representative quinolinic acid lesion. (B,E) Nissl-stained sections, (C,F) NeuN-stained sections, (D,G) higher magnification views of the areas outlined in C and F. Lesion borders are indicated by dotted lines.

interact with treatment or DLS state for either measure ($F_{1,24} < 1.35$, $P > 0.257$), we dropped that variable in the experiment 3 ANOVAS as well.

In experiment 1 (Fig. 4A), sham-lesioned control rats in the shift condition acquired conditioning to the light faster than control rats in the consistent condition, but no such difference was observed for DLS-lesioned rats. This assertion is supported by a significant treatment × lesion interaction ($F_{1,36} = 13.30$, $P < 0.001$). Furthermore, sham-lesioned rats in the shift condition showed significantly greater responding than either sham-lesioned rats in the consistent condition ($P = 0.002$) or DLS-lesioned rats in the shift condition ($P = 0.027$). Thus, DLS lesions disrupted the shift condition advantage in learning that was observed in control rats, attributable to surprise-induced enhancements of cue associability (Wilson *et al.*, 1992; Holland & Maddux, 2010).

In experiment 2 (Fig. 4B), lidocaine infusions prior to each surprise phase session had no effect on test performance: rats in the shift condition learned more rapidly than the rats in the consistent

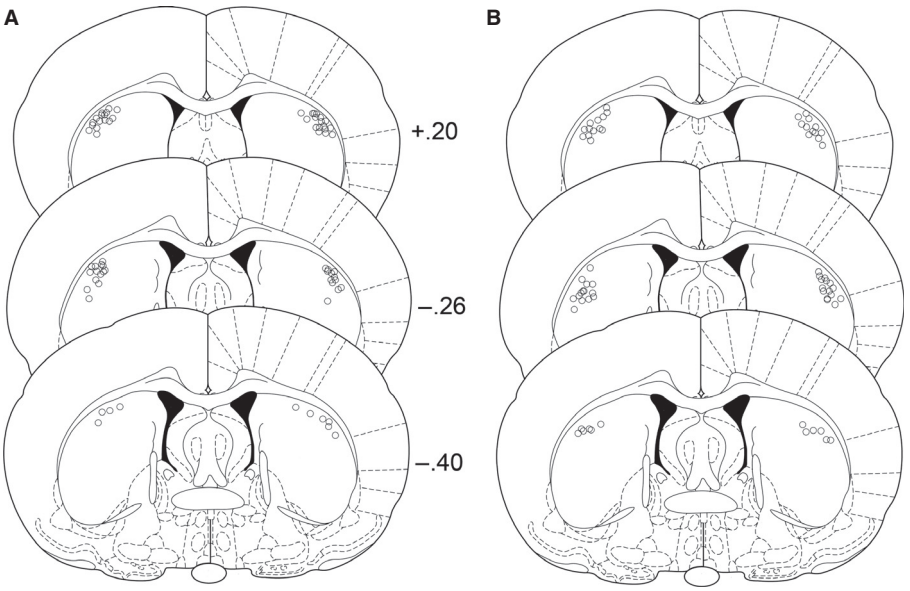

FIG. 2. Cannula tip placements in experiments 2 (A) and 3 (B). Atlas sections indicate distance (mm) anterior (+) or posterior (−) to bregma. Tips found between +0.20 and −0.16 are shown on the top section, those between −0.16 and −0.36 on the center section, and those between 0.36 and 0.40 on the bottom section. Atlas sections are from Paxinos & Watson (1998), and are used by permission of Elsevier.

condition regardless of whether they received lidocaine or saline infusions. ANOVA showed significant main effects of treatment ($F_{1,31}$ = 7.93, P = 0.008) and sessions ($F_{4,124}$ = 52.56, P < 0.001), and a significant treatment × sessions interaction ($F_{4,124}$ = 2.65, P = 0.036). However, neither the main effect of drug nor the treatment × drug interaction was significant (F < 1, P > 0.787). Responding was significantly greater in the shift condition than in the consistent condition, among both saline- (P = 0.027) and lidocaine-infused (P = 0.035) rats. Responding of saline- and lidocaine-infused rats in the shift condition did not differ from each other (P = 0.846).

In experiment 3 (Fig. 4C), lidocaine infusions prior to each of the first three test sessions abolished the shift advantage that was observed in saline-infused control rats. As in experiment 1, the treatment × DLS manipulation (drug) interaction was significant ($F_{1,28}$ = 4.36, P = 0.046). Furthermore, saline-infused rats in the shift condition showed significantly greater responding than either saline-infused rats in the consistent condition (P = 0.014) or lidocaine-infused rats in the shift condition (P = 0.028), whereas no difference between infusion groups was observed in the consistent condition (P = 0.670). Thus, infusing lidocaine prior to each of the first three test sessions did not generally disrupt the acquisition or expression of food cup responding, but instead only affected the enhanced rate of acquisition found among saline-infused rats in the shift condition. Importantly, disruption of the normal shift advantage persisted into the fourth and fifth test sessions, which were conducted without prior infusions. This persistence shows that lidocaine did not simply suppress the expression of food cup behavior. Instead, lidocaine infusions prevented more rapid learning in the shift condition, ostensibly by precluding expression of the enhanced associability memory established during the surprise phase. We consider the importance of this observation further in the Discussion.

Analyses of pre-CS food cup responding in the test phase (Fig. 4) showed significant main effects of sessions in experiments 2 ($F_{4,124}$ = 4.91, P = 0.001) and 3 ($F_{4,112}$ = 4.11, P = 0.004), but no significant main effects or interactions of any other variable (P > 0.154) in any experiment.

Discussion

Taken together, the results of experiments 1–3 suggest that the DLS is critical to the expression, but not the establishment, of the enhanced cue associability normally found after surprise in this task. Although DLS function was essential for the more rapid test phase learning consequent to enhanced cue associability, it was unnecessary for either the coding of prediction error or using that prediction error to adjust cue associability in the surprise phase.

Within the Pearce–Hall (1980) model, the rate of associative learning is a function of both the potency of the reinforcer and the associability of the cue. In turn, cue associability is determined in part by the magnitude of prior prediction errors, i.e. the absolute value of the discrepancy between the expected and experienced values of the reinforcer on previous trials. As cue–reinforcer associations are formed, the prediction error, and hence cue associability, declines, such that the cue enters into future associations less readily. However, if the expected reinforcer is omitted, the induction of a large prediction error restores or enhances cue associability. Considerable behavioral data support these claims (reviewed by Holland & Maddux, 2010; Pearce & Mackintosh, 2010). In the three-phase serial prediction task used here, as consistent light–tone pairings in the expectancy phase establish strong light–tone associations, the associability of the light decreases, but the subsequent surprise-phase omission of the tone in the shift condition enhances that associability. Thus, when the light was directly paired with food in the final test phase, intact rats in the shift condition initially learned about it more rapidly than rats in the consistent condition.

As predicted by this model, among control rats with intact DLS function (those with sham lesions in experiment 1 and those with saline infusions in experiments 2 and 3), rats in the shift condition showed more rapid learning about the light cue in the test phase than those in the consistent condition. By contrast, no such superiority was observed among rats with bilateral lesions of DLS (experiment 1) or test phase bilateral infusions of lidocaine into DLS (experiment 3): regardless of prior surprise phase treatment, learning of DLS-manipulated rats was comparable to that of control rats in

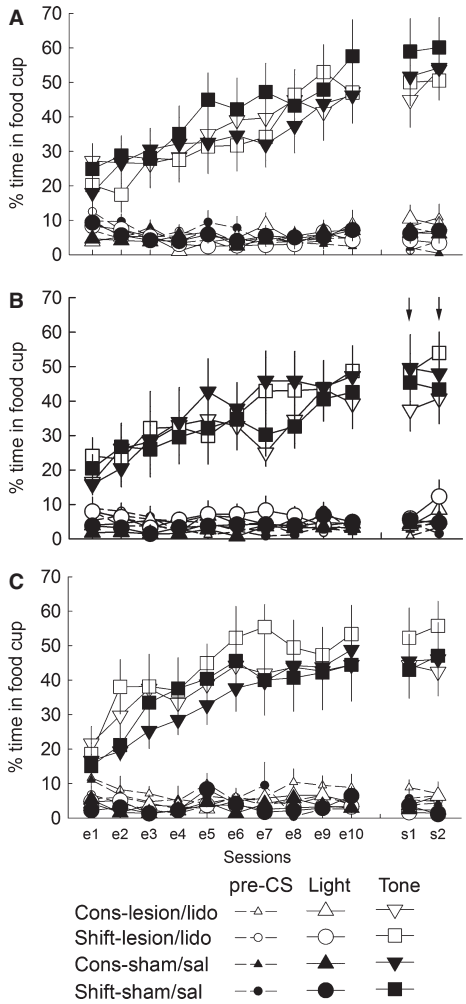

FIG. 3. Food cup conditioned responding during the expectancy (e; left portions) and surprise (s; right portions) of all three experiments. (A) Responding of lesioned and sham-lesioned rats in experiment 1, (B) responding of rats that received infusions of either lidocaine (lido) or saline (sal) before each surprise session (indicated by arrows) and (C) responding of rats that received infusions of either lidocaine (lido) or saline (sal) in the final test phase. Cons (consistent) and shift refer to the training conditions (Table 1).

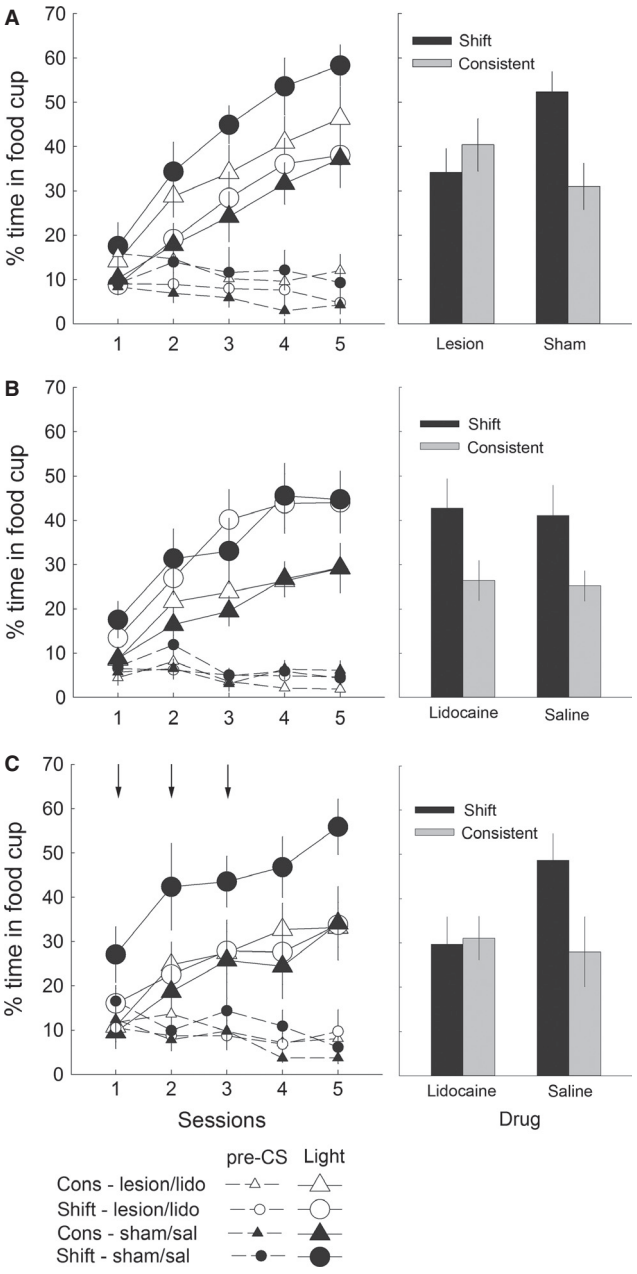

FIG. 4. Food cup conditioned responding in the final test phase of all three experiments. The line graphs show acquisition session-by-session and the bar graphs show responding collapsed across all test sessions. (A) Responding of lesioned and sham-lesioned rats in experiment 1, (B) responding of rats that received infusions of either lidocaine (lido) or saline (sal) before each surprise session, and (C) responding rats that received infusions of either lidocaine (lido) or saline (sal) before sessions 1–3 in the final test phase (indicated by arrows). Cons (consistent) and shift refer to the training conditions (Table 1).

the consistent condition. Furthermore, it is unlikely that these failures to observe enhanced learning in the shift condition reflect deficits in motoric or motivational function, or in the ability to express conditioned responses more generally. First, the DLS manipulations did not affect test phase learning among rats in the consistent condition, and second, when DLS function was restored later in the test phase in experiment 3, the previously inactivated rats in the shift condition continued to lag control rats in that condition.

If DLS inactivation in the first three test sessions of experiment 3 acted only by suppressing performance of CRs, then restoration of DLS function before the final two test sessions would have resulted in an immediate recovery of performance in the shift-lidocaine rats to levels comparable to those observed in the shift-saline rats, as Han *et al.* (1997) noted in the performance of conditioned ORs after the restoration of previously impaired DLS function in a simple conditioning procedure. By contrast, if lidocaine inactivation of DLS during the test sessions interfered with the expression of enhanced cue associability, the lack of such a recovery is anticipated by the Pearce–Hall (1980) model. After three sessions of learning at a faster rate, the associative strength of the light would be considerably greater in the shift-saline rats than in the shift-lidocaine rats. Thus, restoring the light's associability to its enhanced level would not result in an immediate enhancement of conditioned responding. Moreover, within this model, after restoration of DLS function, the rate of learning in the shift-lidocaine rats would not be expected to be as rapid as was initially observed in the shift-saline rats. Because the light was a consistent predictor of the food reinforcer for all rats

in the test sessions, its associability would be driven lower as these sessions proceeded and the reward prediction error declined. Therefore, when DLS function was restored in test session 4, the light's associability would already have been recalculated to similar, lower levels in all rats. Although the light's associability was high in the shift-saline rats in test sessions 1 and 2, permitting rapid initial learning, it would be low in the shift-lidocaine rats when DLS function was restored in test sessions 4 and 5. All in all, it is unlikely that DLS inactivation in test sessions simply prevented the expression of higher levels of conditioned responding. Instead, DLS function appears to be critical to the expression of the altered cue associability itself at the time of new learning.

Importantly, rats' test phase learning was unaffected by lidocaine infusions when they were administered only during the surprise phase. Hence, perturbed DLS function did not affect the coding of prediction error or the recalculation of an enhanced cue associability that occurs in the surprise phase, consistent with a recent electrophysiological recording experiment that found units encoding prediction errors in the dorsomedial striatum of rats, but not in DLS (Stalnaker *et al.*, 2012). Instead, perturbed DLS function appeared to affect only rats' ability to use a previously enhanced cue associability parameter to establish faster learning in the test phase. Although these observations are consistent with the common notion that DLS is more important in performance than in learning (e.g. Attalah *et al.*, 2007) or the coding of prediction errors (e.g. Haruno & Kawato, 2006), it is important to note that there is ample evidence from functional magnetic imaging experiments that in humans prediction errors are indeed encoded in the dorsal striatum (e.g. Valentin & O'Doherty, 2009; Cooper *et al.*, 2011), including regions of dorsal putamen most comparable to rat DLS (e.g. Garrison *et al.*, 2013). Furthermore, as noted earlier, the effects of DLS inactivation we observed in experiment 3 are not strictly 'performance' effects because they were expressed as alterations in learning itself, not just the performance of previously learned CRs.

DLS dysfunction also did not appear to interfere with the expression of the reductions in cue associability that the Pearce–Hall (1980) model predicts should occur among rats in the consistent condition, as strong light–tone associations were formed. Interference with these reductions among rats given the consistent treatment would be reflected in *faster* test phase learning in lesioned rats (experiment 1) or rats infused with lidocaine (experiment 3) than in control rats. Previously, we found such rapid learning among consistently treated rats with lesions of hippocampus (Han *et al.*, 1995) or its basal forebrain cholinergic innervation (Baxter *et al.*, 1997). Nevertheless, although there was a hint of such an effect in experiment 1, there was clearly no such effect in experiment 3. Of course, the design of these experiments did not permit an independent assessment of cue associability reductions in the consistent condition, so it is difficult to make this assertion confidently. However, it is notable that in our previous research, manipulations of brain regions that interfered with enhancements of cue associability had no effect on associability reductions (e.g. Holland & Gallagher, 1993a,b; Chiba *et al.*, 1995; Bucci *et al.*, 1998).

The involvement of DLS in surprise-induced enhancement of cue associability appears to have much in common with its role in conditioned ORs. First, perturbation of DLS function affected only the expression of previously altered cue associability (experiment 3) and previously acquired conditioned ORs (Han *et al.*, 1997), but not the alteration of cue associability at the time of surprise (experiment 2) or the acquisition of the associations responsible for conditioned ORs (Han *et al.*, 1997). Second, both attentional functions engage circuitry that includes the CeA and SNc, the major source of dopaminergic projections to the DLS. Both conditioned ORs and surprise-induced enhancement of cue associability are impaired after asymmetric 'disconnection' lesions that prevent the normal convergence of information processing of CeA and SNc, or that of CeA and DLS. Lee *et al.* (2005, 2006) made unilateral lesions of CeA and SNc, either contralaterally, which disrupted interactions between those structures, or ipsilaterally, which produced comparable damage to each structure but permitted interactions between them in one hemisphere. Rats with ipsilateral lesions of CeA and SNc showed normal conditioned ORs (Lee *et al.*, 2005) and normal associability enhancements in the serial prediction task (Lee *et al.*, 2006), but rats with contralateral lesions of those structures did not. Similarly, we found that contralateral lesions of CeA and DLS disrupted both conditioned ORs (Han *et al.*, 1997) and surprise-induced associability enhancements (Esber *et al.*, 2015).

Nevertheless, regional dissociations between these two attentional phenomena exist. For example, although associability enhancements depend on the function of the substantia innominata (SI) (Chiba *et al.*, 1995; Han *et al.*, 1999; Holland & Gallagher, 2006) and posterior parietal cortex (PPC) (Schiffino *et al.*, 2014a), conditioned ORs do not (Chiba *et al.*, 1995; Bucci & Chess, 2005). Similarly, although both the acquisition and the expression of conditioned ORs depend on SNc function (El-Amamy & Holland, 2006), only the adjustment of cue associability itself is affected by SNc dysfunction in the serial prediction task (Lee *et al.*, 2008). Perturbation of SNc function by infusions of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite-type glutamate receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX) at the time of surprise eliminated the shift advantage in subsequent drug-free testing, but such infusions given only at the time of test did not differentially affect test learning of rats that had previously received shift or consistent treatments (Lee *et al.*, 2008).

These observations suggest that the coding of surprise for the enhancement of cue associability requires information processing by CeA and SNc, and that the consequences of such processing are conveyed elsewhere for the storage and subsequent expression of a memory for enhanced cue associability. At first glance it seems reasonable to suggest that information could be conveyed from SNc to DLS through its rich direct projections (Beckstead *et al.*, 1979; Matsuda *et al.*, 2009). Storage of the altered cue associability memory in DLS itself is consistent with our observation of impaired learning in the shift-lidocaine rats in Experiment 3. However, that possibility is made less likely by our observations that in the serial prediction task, DLS is needed *only* at the time of expression, and SNc function is needed *only* at the time of surprise (Lee *et al.*, 2008). One might expect that the two regions would need to be simultaneously active at some point in the task for information coded in SNc to be registered as an increased associability parameter in DLS. One possible solution to this problem is that there is some post-session replay of surprise information permitting systems consolidation (McGaugh, 2004) of an altered associability memory in DLS itself after the effects of lidocaine inactivation dissipate (e.g. Holland & Gallagher, 2006). Another possibility is that enhanced associability is produced and stored elsewhere in the brain, but such information must converge with enhanced 'sensory drive' provided by DLS processing of the cue at the time of new learning. From this perspective, plasticity in the DLS is not induced by surprise, but rather DLS processing is needed at the time of expression of cue associability to amplify altered associability signal inputs from other brain regions. This amplification might occur in the DLS itself, requiring DLS afferents from regions that code associability information, or in those associability-coding regions themselves, requiring DLS

efferents to those regions, or in some other region that receives converging information from DLS and associability-coding regions.

Recently, Schiffino *et al.* (2014a) identified PPC as a strong candidate for the storage of altered associability information. Using the three-stage serial prediction task, Schiffino *et al.* (2014a) found that perturbation of PPC function by administration of NBQX at either the time of surprise or the time of test, or by administration of the protein-synthesis inhibitor anisomycin immediately after surprise sessions, all prevented surprise-induced enhancement of cue associability. Furthermore, using single-unit electrophysiology during a two-step reversal task, Schiffino *et al.* (2014b) identified PPC neurons that exhibited activity during presentations of visual cues that was consistent with the associability changes predicted by the Pearce–Hall (1980) model. Thus, on cue presentation, efferents from PPC might provide this enhanced associability information to DLS, amplifying that signal further over the course of learning in the test.

We can only speculate on the route by which associability information from PPC might be conveyed to DLS. Although lateral portions of PPC and other cortical areas that communicate with PPC, such as lateral and medial agranular cortex, project directly to DLS (e.g. Reep *et al.*, 2003; Wu *et al.*, 2009), PPC projections to dorsal striatum appear to primarily target dorsocentral striatum (Cheatwood *et al.*, 2002) and dorsomedial striatum more broadly (Liljeholm & O'Doherty, 2012), which was undamaged in experiment 1 (and distant from the cannula placements in experiments 2 and 3). Enthusiasm for a cortico-striatal route (e.g. Reig & Silberberg, 2014) is further tempered by Esber *et al.*'s (2015) observation that rats with unilateral lesions of DLS contralateral to CeA lesions failed to show associability enhancements. Although, because of their CeA lesions, rats in that study may have coded altered cue associability information in PPC unilaterally, that information could nevertheless be made available to both hemispheres of DLS, because many cortical neurons project to dorsal striatum bilaterally (e.g. Wilson, 1987, 2014; Wu *et al.*, 2009). On the other hand, associability information in cortex may not engage bilateral projection neurons, but instead may preferentially involve neurons whose striatal projections are unilateral. Thus, at this point, the role of direct cortical activation of DLS as opposed to, for example, thalamic afferents or efferents of DLS (e.g. Matsumoto *et al.*, 2001; Doig *et al.*, 2014), which are almost exclusively unilateral, is entirely conjectural.

Similarly, the relation of the present data to previous findings, which show the expression of surprise-induced associability enhancements to depend on the functional integrity of SI (Holland & Gallagher, 2006) and cholinergic projections from SI to PPC (Bucci *et al.*, 1998), remains an open question. Evidence suggests comparable amplification roles for SI and DLS in this task: for both regions, perturbations of function at the time of test eliminate the shift advantage, but perturbations at the time of surprise have no effect. Because direct cholinergic projections from SI to PPC are identified contributors to performance in this task (Bucci *et al.*, 1998), one could imagine those projections amplifying PPC-stored associability information in PPC itself. However, as Schiffino *et al.* (2014a) noted, the network supporting the expression of enhanced cue associability in faster learning may be quite extensive, encompassing amygdalo-nigro-striatal and thalamo-striato-cortical loops, as well as such direct connections (see Reep & Corwin, 2009, for an excellent summary of potential sources of interaction among cortical, thalamic and striatal areas for attention in rats).

Regardless of the circuitry by which DLS is involved in surprise-induced associability enhancements, our data add to a growing trend to construe dorsal striatum not just as a 'sensory hub' (Reig & Silberberg, 2014) or mediator of habits (Smith & Graybiel, 2014) and motor control (e.g. Pawlak *et al.*, 2010; Root *et al.*, 2010; Reig & Silberberg, 2014), but more broadly as an integrator of reinforcement processing, executive control, decision and attention (e.g. Balleine *et al.*, 2007; Liljeholm & O'Doherty, 2012). Indeed, it is worth considering whether DLS is involved in the expression of other learning functions that depend on the processing of prediction errors, but are typically thought to engage variations in reward processing rather than in cue processing. Unfortunately, we are unaware of any systematic investigation of DLS function in such functions. However, given known interactions between DLS and CeA in the serial prediction task (Esber *et al.*, 2015), it is notable that although performances in the serial prediction task, unblocking with reward downshifts, and other tasks thought to involve variations in cue processing are disrupted by lesions of the CeA (e.g. Holland & Gallagher, 1993a,b; Holland *et al.*, 2000; Wheeler & Holland, 2011), performances in tasks thought to engage prediction-error-induced alterations in reward processing, such as blocking, unblocking with reinforcer upshifts and conditioned inhibition, are typically unaffected by those lesions (e.g. Holland & Gallagher, 1993b; Holland *et al.*, 2000; Holland, 2006). All told, although the study of the striatum has emphasized its sensory-motor properties, its functions may eventually be revealed to be as diverse as those of cortex (Wilson, 2014).

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Abbreviations

ANOVA, analysis of variance; CeA, amygdala central nucleus; CR, conditioned response; DLS, dorsolateral striatum; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione; OR, orienting response; PB, phosphate buffer; PBS, phosphate-buffered saline; PPC, posterior parietal cortex; SI, substantia innominata; SNc, substantia nigra, pars compacta; TH, tyrosine hydroxylase.

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