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Effects of sensitization on the detection of an instrumental contingency ☆

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ABSTRACT

While prior exposure to drugs of abuse permanently changes many behaviors, the underlying psychological mechanisms are relatively obscure. Here, the effects of sensitization on the detection of an action–outcome relationship were assessed, using a particularly stringent contingency degradation procedure. Rats were trained to leverpress until the probability of reinforcement for a response on one lever, or alternative reinforcement for a response on a second lever was reduced to 0.05 per second. Sensitization was then carried out (1 mg/kg *d*-amphetamine/day for 7 days). Then, one reinforcer was also made available for a lack of response on either lever ($p = 0.05$/s), maintaining its contiguity with the original response but eliminating its contingent relationship. Sensitized animals were more active, particularly early in the contingency degradation phase, but reduced responding directed at the degraded action–outcome contingency at a similar rate as controls. However, controls also reduced responding directed at the nondegraded contingency until very late in training, while sensitized animals maintained nondegraded responding at baseline levels. It was suggested that the relatively specific response shown by sensitized animals may reflect either improved action–outcome utilization or discrimination of relevant task features.

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1. Introduction

Although preexposure to drugs of abuse is widely known to enhance their subsequent locomotor-stimulant properties (Braga et al., 2009; Jackson and Nutt, 1993; Stewart and Vezina, 1989; Vezina et al., 1987), it is possibly the facilitation of drug self-administration that accounts for the sheer intensity of interest in the phenomenon of sensitization (Hooks et al., 1994; Horger et al., 1990, 1992; Morgan et al., 2005; Phillips and Di Ciano, 1996; Piazza et al., 1990, 1991; Samaha et al., 2002; Vezina, 2004; Woolverton et al., 1984; Yap and Miczek, 2007; Zapata et al., 2003; Zhao and Becker, 2009). However, precisely why sensitization might enhance the rewarding properties of drugs of abuse remains open to debate. Drug self-administration requires the performance of a specific response, typically the depression of a lever, following which the drug outcome is delivered. While an apparently straightforward behavior, there are many conceivable governing factors. Aside from the perceived value of the reinforcer (cf. Wise, 1978, 2008), other possible associative mechanisms include the encoding or retrieval of action–outcome, outcome–action or stimulus–stimulus Pavlovian associations, which may be purely excitatory/inhibitory in nature or perhaps take on discriminative or occasion setting features (Colwill and Rescorla, 1986; Hall, 2002; Rescorla, 1988, 1992; Schmajuk and Holland, 1998).

While mesocorticolimbic dopamine is well-known to play an important role in associative learning, significant controversy remains over whether this role is relatively indirect, e.g. in enhancing the consolidation of recent learning (Dalley et al., 2005; see also Discussion: Phillips and Hitchcott, 2009), or whether brain dopamine plays a more direct role in signaling stimulus prediction error (Rescorla and Wagner, 1972; Schultz, 2002, 2007; Schultz et al., 2008; Tobler et al., 2003), and whether this role is causative in strengthening associative learning or merely a signal of its occurrence again remains the subject of debate (Berridge, 2007). Alternatively, mesolimbic dopamine's most pertinent function may be to enhance the 'incentive-salience' of stimuli of acquired motivational significance, and to modify the degree to which such conditioned stimuli are "wanted" or act as "motivational magnets" (Berridge, 2001; Berridge et al., 2009; Robinson and Berridge, 2008). A third point of view emphasizes the activational value of mesocorticolimbic dopamine prior to an anticipated goal, and in modifying the intensity of conditioned reinforcement (Horvitz, 2002; Robbins and Everitt, 1987b, 1992; Robbins and Everitt, 1996, 2007) or the degree of effort expended in carrying out a conditioned motivational task (Salamone, 2009; Salamone et al., 2007).

Certainly, preexposure to *d*-amphetamine is well-known to enhance the acquisition of both excitatory (Harmer and Phillips, 1998, 1999b) and inhibitory Pavlovian conditioning (Harmer and Phillips, 1999a), as measured *via* a goal-tracking conditioned approach response. These

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effects relied on a close temporal relationship between the arbitrary stimulus and unconditioned stimulus, and resulted in a correspondingly elevated dopamine efflux in a variety of terminal regions of the mesocorticolimbic dopamine system (Harmer et al., 1997; Harmer and Phillips, 1999b; Phillips et al., 2003b,c). The acquisition of Pavlovian conditioned approach may be enhanced by post-session *d*-amphetamine in the shell, but not core of the nucleus accumbens (Di Chiara et al., 2004; Phillips et al., 2003a), and the facilitatory effects of sensitization on conditioned approach may be eliminated by D2/3 dopamine receptor blockade within the amygdala (Phillips et al., 2002). The majority of these studies depended on the observation of a skeletomotor goal-tracking response as an indirect measure of Pavlovian learning (Boakes, 1977; Farwell and Ayres, 1979; Mackintosh, 1974, p.4), which appears relatively late in the development of a typical association between appropriate elements. However, a more recent study confirmed the important role of amygdala dopamine in the very earliest, 'emotional' phase of Pavlovian conditioning (see also Konorski, 1967; Lennartz and Weinberger, 1992; Mintz and Wang-Ninio, 2001; Wagner, 2008; Wagner and Brandon, 1989), before the development of a conditioned approach response (Phillips et al., 2010).

The role of the mesocorticolimbic dopamine system in instrumental learning is less well understood. While Pavlovian learning typically depends on the temporal or spatial association of relevant environmental stimuli, instrumental learning may require additional knowledge of the relationship between an action and its outcome (e.g. Dickinson, 1994). Hence, while it is certainly the case that instrumental responding governed by appetitive conditioned reinforcers is increased by intra-accumbens *d*-amphetamine (Taylor and Robbins, 1984; Taylor and Robbins, 1986; Wyvell and Berridge, 2000), and may also be facilitated at a later date following repeated exposure to *d*-amphetamine (Wyvell and Berridge, 2001) or heroin (Ranaldi et al., 2009), the extent to which sensitization of mesolimbic dopamine affects such behaviors through modification of Pavlovian activational vs. instrumentally contingent features of the respective tasks is relatively unclear (Di Ciano and Everitt, 2003; Ito et al., 2000, 2002). Hence, the current study assessed the effects of sensitization on the ability specifically to detect a change in instrumental contingency.

While the term 'contingency' in this context is meant to indicate knowledge on the part of the animal of the relationship between an action and its outcome (Dickinson, 1994), modifying the contingent relationship between and an action and its outcome while maintaining their Pavlovian features is quite a challenge, and so the current procedure used to assess this knowledge very specifically maintained the temporal relationships between two leverpressing responses and their respective reinforcers, and so Pavlovian contiguity between responses and stimuli was maintained at all times (Dickinson and Mulatero, 1989). Following sensitization with *d*-amphetamine, responses on each lever continued to deliver the relevant reinforcement at the same rate as before, however one outcome was now also made available for a lack of responding. The temporal contiguity between this outcome and associated stimuli (e.g. lever) was unchanged then, but the contingent relationship between action and outcome reduced to zero. In other words, animals were now as likely to receive the 'degraded' outcome for failing to press the respective lever as for actually pressing it (zero contingency), while nevertheless leverpresses were as likely as before to result in reinforcement (maintained contiguity).

Reduced responding for the 'degraded' outcome may then reflect the appropriate detection that a particular action no longer had a meaningful effect on the probability of its outcome. A particularly stringent aspect of the procedure used here was to present both levers and outcome within the same sessions rather than in alternating sessions as more commonly carried out (Dickinson and Mulatero, 1989). This enabled the concurrent assessment of discriminative task features, e.g. the ability to tell the difference between actions (left vs. right levers) or outcomes (pellets vs. sucrose solution), and so the specificity of any change in responding maintained by the 'degraded' outcome by comparison with the nondegraded, 'control' outcome was taken as a measure of an animal's ability to discriminate between appropriate response-outcome features of the task environment.

2. Material and methods

2.1. Subjects

A total of 24 male Lister hooded rats took part in these experiments (Charles Rivers, Margate, Kent, UK). Animals were housed in pairs under a 12 h:12 h light/dark cycle (lights on 08.00 h) at a constant temperature of 22 °C. Experiments were carried out between 10.00 and 17.00 h. Body weights were reduced to 85% of free-feeding weight throughout the course of this study by restricting access to food. Water was available ad libitum. All experimental procedures were carried out under the Animals (Scientific Procedures) Act 1986, and were subject to UK Home Office approval (Project License PPL 50/01257).

2.2. Apparatus

Testing was carried out in eight experimental chambers (31 cm wide × 24 cm deep × 29 cm high); Med Associates Inc, St Albans, VT, USA). Each chamber was equipped with a dual liquid/pellet receptacle (5 cm wide × 5 cm high × 3 cm deep) located immediately above the floor halfway along the righthand wall, which was used for presentations of 15% w/v sucrose solution *via* a dipper (Model ENV-202, Med Associates; cup capacity 0.06 ml) which was made up fresh everyday and allowed to reach room temperature before the session, or 45 mg food pellets (Noyes, Lancaster, NH; Improved Formula A) *via* a pellet dispenser (Model ENV-203, Med Associates). Two retractable levers each 5 cm wide, were positioned symmetrically upon this wall 12 cm apart and 7 cm above the grid floor, either side of the dual receptacle. The operant chamber could be illuminated by a white 15 W houselight located at the top of wall opposite. Each chamber was also equipped with two white stimulus lights 15 W, positioned directly above each retractable lever 18 cm above the grid floor, and a 75 dB SonAlert sinusoidal tone (2.9 kHz) generator. The operant chamber was housed in a sound-attenuating box and a ventilating fan mounted on the side of the box masked external noise further.

Each chamber was also fitted with a number of active photobeams for the measurement of activity. Four photobeams recorded horizontal activity, and were positioned 4 cm above the grid floor. They were aligned from front to back at 4 cm, 11 cm, 19 cm and 27 cm from the wall with the reinforcer receptacle. A fifth photobeam was located in the sidewalls of the dual receptacle recess and was used to monitor alcove approach behavior. The apparatus was controlled, and the data collected, by a standard IBM compatible 386 PC with appropriate software platform (Med Associates Inc, St Albans, VT, USA).

2.3. Drugs

d-amphetamine sulfate (Sigma Chemical Co., Poole, UK) was dissolved in sterile phosphate buffered saline, which also served as the vehicle. Doses of *d*-amphetamine sulfate were calculated as the salt.

2.4. Procedure

2.4.1. US approach training

Rats were initially trained to consume the sucrose solution or food pellets during two sessions in which each US was alternately presented 25 times/session according to a variable time 60 s (VT-60 s) schedule (50 possible intervals generated using the progression sequence of Fleshler and Hoffman, 1962).

2.4.2. Instrumental pretraining

Two session types were repeatedly presented in alternating sequence: Session Type I in which depression of one lever might result in delivery of the sucrose solution, and Session Type II in which the alternative lever was made available, and depression of this lever instead could result in delivery of a food pellet (see Table 1). Sessions were of 1000 s duration. The specific lever (left or right)–reinforcer (sucrose or pellet) association was counterbalanced across animals. Reinforcement schedules were suspended following delivery of a reinforcer, until withdrawal from the alcove was detected. Initially, the probability of reinforcement following a response in any 1 s was set at 1.00, and typically 5 sessions of each Session Type were presented at this level of contingency. Reinforcer probability gradually declined thereafter, until the probability of reinforcement following a response in any 1 s reached 0.05. Ten sessions of each Session Type were typically presented at this contingency level.

2.4.3. Baseline sessions

Sessions took the same form as instrumental pretraining above, except that the two levers were now presented concurrently rather than across alternating sessions. Sessions were therefore of 2000 s duration, and there were six baseline sessions in all.

2.4.4. Sensitization

Subjects were carefully divided into two groups, matched for response rates on the two levers, alcove approaches and locomotor activity. One group was administered 1 mg/kg *d*-amphetamine once per day for 7 consecutive days, the other received vehicle. All animals remained in their homecages for a further 7 days following completion of drug treatment, and were maintained at 85% B.W. at all times.

2.4.5. Degraded contingency phase

Sessions were of the same format as baseline sessions above, except that one of the two possible reinforcers was now delivered with a probability of 0.05 following each second with no presses on either lever (cf. the more stringent 'N–N' condition: Dickinson and Mulatero, 1989). Animals were allocated to one of the two possible conditions according to their baseline leverpress and alcove approach rates, and locomotor activity. There were 18 sessions in all.

2.4.6. Extinction test

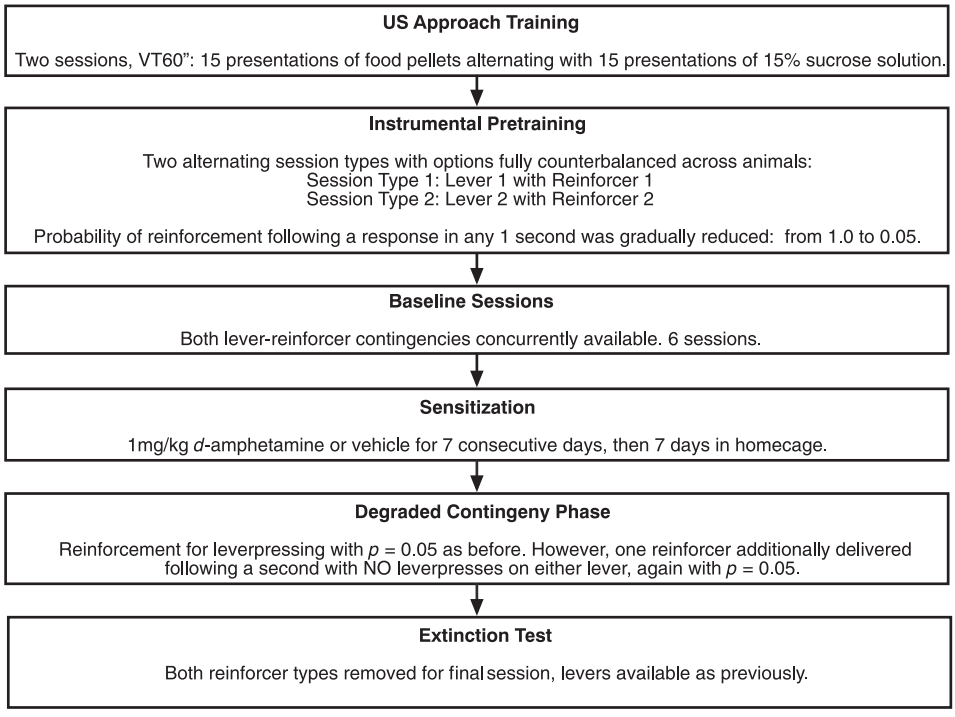
Both reinforcer types were removed for a final session, and response rates by sensitized and control groups recorded.

2.5. Statistical Analysis

Data were analyzed initially using parametric analyses of variance, and given statistically significant interaction terms within-factor comparisons were analyzed subsequently using simple main effect analyses of variance or appropriate *post hoc* tests (Winer, 1971). Baselines were subjected to 2-way analyses of variance (Independent variable: Group [Sensitized, Controls] × Contingency [Positive, Zero]) where appropriate. Total leverpresses and alcove approaches per contingent reinforcement during the differential contingency task were subjected initially to three-way analyses of variance (Independent variable: Group [Sensitized, Controls] × Session [Baseline: 'B', 3-Session Blocks 1–6] × Contingency [Positive, Zero]), and subsequently analyzed as two-way fully repeated measures analyses of variance for each group separately. Within-session leverpresses were analyzed using three-way repeated measures analyses of variance (Session [1–9, 10–18] × Reinforcer [3-Reinforcer Blocks 1–3] × Contingency [Positive, Zero]) for Sensitized and Control Groups. Response rates during the final contingency session and subsequent extinction test were analyzed using a three-way analysis of variance (Independent variable: Group [Sensitized, Controls] × Session [Session 18, Extinction] × Contingency [Positive, Zero]). Reinforcers earned or delivered during acquisition of the differential contingency task were subjected to two-way analyses of variance (Independent variable: Group [Sensitized, Controls] × Session [3-Session Blocks 1–6]).

Table 1

Sequence of procedural events from initial US approach training to final extinction session. Following the establishment of robust leverpressing on each lever (Instrumental pretraining) and the later completion of final baseline sessions during which both levers were available concurrently, subjects were divided into two matched groups. They were then subjected during the Sensitization procedure either to 1 mg/kg/day *d*-amphetamine or vehicle for 7 consecutive days, and left in the homecages for a further 7 days. All subjects then entered the Degraded Contingency Phase, in which one lever-reinforcer outcome contingency was reduced to zero. Following adjustment to this condition, a final Extinction Test was carried out.



Locomotor activity was analyzed initially as two-way split plot analyses of variance (Group [Sensitized, Controls] × Session [Baseline: 'B', 3-Session Blocks 1–6]) for Chamber Total (Beams 1–4), Lever/alcove side (Beams 3–4) and Opposite side to levers and alcove (Beams 1–2). Within-session locomotor activity scores were subjected to a three-way analysis of variance (Independent variable: Group [Sensitized, Controls] × Session [1–9, 10–18] × Reinforcer [3-Reinforcer Blocks 1–3]) and followed up with appropriate two-way analyses and simple main effects.

3. Results

3.1. Total leverpressing rates

Response rates during the final baseline session were very comparable across matched groups and levers (see Fig. 1, upper panels; Group × Contingency interaction: $F(1,22) = 1.4$, N.S.; Group: $F(1,22) = 0.3$, N.S.; Contingency: $F(1,22) = 1.3$, N.S.). By contrast, subsequent sensitization of one group resulted in a very different response to elimination of the response–outcome contingency for one of the levers (Group x Contingency × Session interaction: $F(6,132) = 2.3$, $p<0.05$; Group × Contingency interaction: $F(1,22) = 10.4$, $p<0.01$; Group × Session interaction: $F(6,132) = 4.3$, $p<0.001$; Group: $F(1,22) = 2.6$, N.S.; Contingency: $F(1,22) = 26.4$, $p<0.001$; Session: $F(6,132) = 83.5$, $p<0.001$). Thus, the response of sensitized animals to the introduction of the degraded contingency phase was very selective, and so responding was maintained on the contingent lever at levels comparable with baseline rates throughout the degraded contingency phase, but nevertheless responding rapidly declined on the zero contingency lever (Fig. 1, upper left panel; Contingency × Session interaction: $F(6,66) = 9.5$, $p<0.001$; Contingency: $F(1,11) = 41.3$, $p<0.001$; Session: $F(6,66) = 23.4$, $p<0.001$). The response of controls across the two lever contingencies was far less selective, and so a specific deficit on the zero contingency lever was only observed in this group by the final 3-session block of the degraded contingency phase (Fig. 1, upper right panel; Contingency × Session interaction: $F(6,66) = 3.7$, $p<0.01$; Contingency: $F(1,11) = 1.6$, N.S.; Session: $F(6,66) = 70.7$, $p<0.001$).

However, while the selectivity of response shown by the two groups differed considerably, sensitized and control animals exhibited at least one important feature in common: there was no difference between sensitized and control groups in their rate of reduction in response on the zero contingency lever (Group × Session interaction: $F(6,132) = 0.1$, N.S.; Group: $F(1,22) = 0.4$, N.S.; Session: $F(6,132) = 66.9$, $p<0.001$).

3.2. Total alcove approaches

Subsequent alcove approaches showed a similar, though less marked pattern as leverpressing reported earlier. Thus, while baseline rates were very comparable (Fig. 1, lower panels; Group × Contingency interaction: $F(1,22) = 0.3$ N.S.; Group: $F(1,22) = 0.004$, N.S.; Contingency: $F(1,22) = 0.02$, N.S.), sensitized animals gradually developed a differential alcove approach (Group × Contingency × Session interaction: $F(6,132) = 3.7$, $p<0.01$; Group × Contingency interaction: $F(1,22) = 3.3$, $p<0.05$; Group × Session interaction: $F(6,132) = 0.8$, N.S.; Group: $F(1,22) = 1.6$,

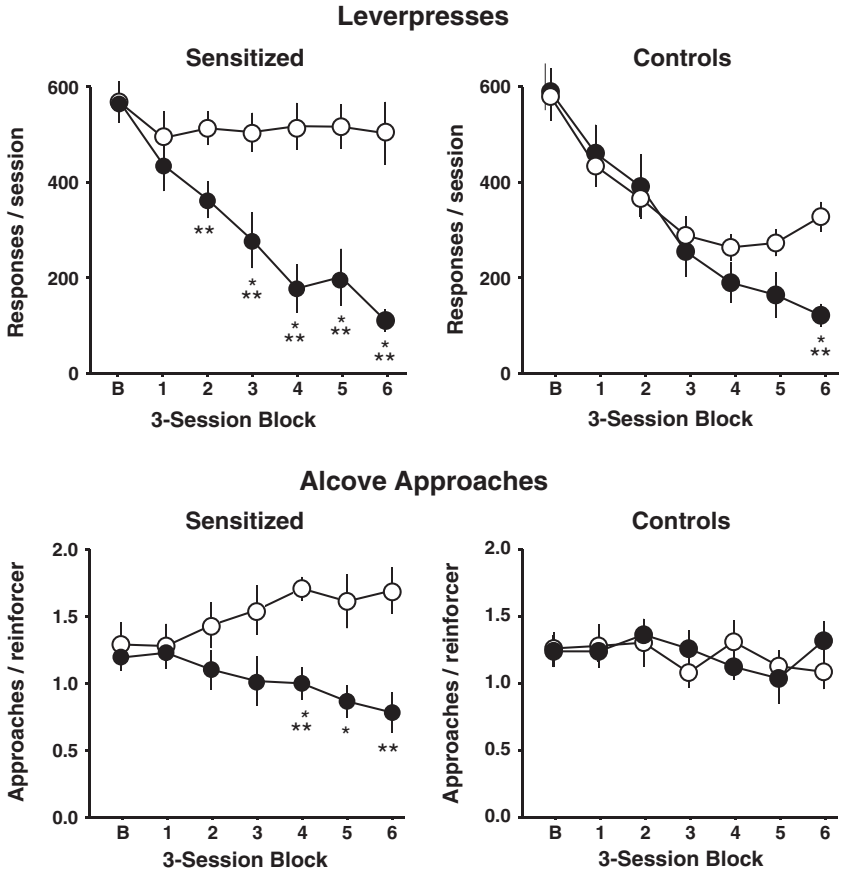


Fig. 1. Effects of sensitization on response to a degraded instrumental contingency. Subjects were trained to press one lever for one reinforcer (food pellets or sucrose solution), and a second lever for the alternative reinforcer. The final probability of reinforcer delivery in 1 s was 0.05 ($p = 0.05$/s). Then, one group received *d*-amphetamine (Sensitized; 1 mg/kg/day for 7 days), and a second group received vehicle (Controls). During the test phase shown above, reinforcers continued to be delivered as before, but one reinforcer was now also available following the absence of a response on either lever ($p = 0.05$/s), maintaining response–outcome contiguity on that lever but eliminating its contingent relationship with the outcome (Filled circles). Both relationships were maintained at all times on the alternative lever (Open circles), but reduced to zero on the alternate lever. Graphs show leverpressing (Upper panels); or subsequent alcove approach (Lower panels). Values are mean (±1SEM) responses per session, for final baseline ('B') and subsequent 3-session blocks. Stars indicate statistically significant comparisons with the nondegraded performance, * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

N.S.; Contingency: F(1,22) = 2.8, N.S.; Session: F(6,132) = 0.9, N.S.), and as the degraded contingency sessions progressed they developed a somewhat lower rate of response to the delivery of the zero contingency reinforcer by comparison with the positive contingency outcome (Fig. 1, lower left panel; Contingency × Session interaction: F(6,66) = 4.4, p<0.001; Contingency: F(1,11) = 6.0, p<0.05; Session: F(6,66) = 0.4, N.S.). By contrast, controls failed to develop a differential approach response at any time (Fig. 1, lower right panel; Contingency × Session interaction: F(6,66) = 1.4, N.S.; Contingency: F(1,11) = 0.01, N.S.; Session: F(6,66) = 1.3, N.S.).

3.3. Within-session response rates

Both sensitized and control groups tended to begin sessions throughout exposure to the degraded contingency task by responding on the two levers at broadly equivalent levels (see Fig. 2; First 3-Reinforcer block, largest interaction term, Group x Session F(1,22) = 2.9, N.S.; Group F(1,22) = 0.07, N.S.; Session F(1,22) = 3.9, N.S.; Contingency F(1,22) = 1.6, N.S.). However, sensitized animals developed an appropriate differential response on the two levers later in sessions (Contingency × Reinforcer interaction: F(2,22) = 13.1, p<0.001; Contingency × Session interaction: F(1,11) = 5.0, p<0.05; Reinforcer: F(2,22) = 17.0, p<0.001; Contingency: F(1,11) = 35.2, p<0.001; Session: F(1,11) = 32.3, p<0.001), and this tendency developed further as the degraded contingency training schedule progressed (see Fig. 2, left panels. Sessions 1–9: Contingency × Reinforcer interaction: F(2,22) = 6.2, p<0.01; Contingency F(1,11) = 5.9, p<0.05; Reinforcer F(2,22) = 12.2, p<0.001; Sessions 10–18: Contingency × Reinforcer interaction: F(2,22) = 15.3, p<0.001; Contingency F(1,11) = 41.9, p<0.001; v Reinforcer F(2,22) = 14.3, p<0.001).

While controls demonstrated a reasonably selective response on the positive contingency lever (Fig. 2, right panels. Contingency: F(1,11) = 6.7, p<0.05; Session: F(1,11) = 5.9, p<0.05; Reinforcer: F(2,22) = 12.9, p<0.001), unlike sensitized animals they failed to develop a robustly selective within-session pattern across the two levers at any time during exposure to the degraded contingency task (Contingency × Session interaction: F(1,11) = 0.2, N.S; Contingency × Reinforcer interaction: F(2,22) = 0.2, N.S.; Contingency × Session × Reinforcer interaction: F(2,22) = 0.5, N.S.).

3.4. Within-chamber locomotor activity

While there was some general decline in activity across the duration of the degraded contingency task (see Fig. 3, left panel. Session F(6,132) = 16.1, p<0.001), overall levels of locomotor activity within experimental chambers did not differ between sensitized and control groups (Group × Session interaction: F(6,132) =0.5, N.S.; Group F(1,22) = 0.3, N.S.). This was also so for activity on the same side of the experimental chamber as the levers and reinforcer alcove (Fig. 3, middle panel. Group F(1,22) = 0.0, N.S.; Session F(6,132) = 17.7, p<0.001; Group × Session interaction: F(6,132) = 1.0, N.S.). However, sensitized animals were clearly more active than controls on the opposite side of experimental chambers, where levels of activity were generally much lower (Fig. 3, right panel. Group F(1,22) = 6.3, p<0.05; Session F(6,132) = 17.1, p<0.001; Group × Session interaction: F(6,132) = 3.5, p<0.01).

3.5. Within-session locomotor activity

Inspection of locomotor activity within sessions on the opposite side of experimental chambers to the levers and alcove showed that sensitized animals tended to be more active than controls early in sessions (see Fig. 4. Group × Reinforcer interaction: F(2,44) = 3.3, p<0.05; Group F(1,22) = 6.8, p<0.05; Session F(1,22) = 7.0, p<0.05; Reinforcer F(2,44) = 45.2, p<0.001). This difference declined across the duration of the degraded contingency task (Sessions 1–9: Group × Reinforcer interaction: F(2,44) = 4.6, p<0.05; Group F(1,22) =8.8, p<0.01; Reinforcer F(2,44) = 39.7, p<0.001. Sessions 10–18: Group × Reinforcer F(2,44) = 1.7, N.S.; Group F(1,22) = 4.2, p = 0.051; Reinforcer F(2,44) = 38.6, p<0.001).

3.6. Reinforcers

The number of reinforcers made available following a lack of response on the levers ('Free' reinforcement, $p = 0.05$/s) increased somewhat across the course of the contingency training task (see Table 2. Session F(5,110) = 15.8, p<0.001). However, this pattern was shown by both groups to a comparable degree (Group F(1,22) = 0.6, N.S.; Group × Session interaction: F(5,110) = 0.8, N.S.). The number of reinforcers earned following a response on the noncontingent lever (Noncontingent reinforcement: $p = 0.05$/s) followed a broadly opposition pattern, in which numbers gradually declined across sessions (Session F(5,110) = 16.2, p<0.001), and to a similar amount in both groups (Group F(1,22) = 1.8, N.S.; Group × Session interaction: F(5,110) = 0.4, N.S.). Levels of contingent reinforcement were relatively stable across sessions (Table 2. Session F(5,110) = 2.2, N.S.) as to be anticipated, given that the appropriate action–outcome relationship was essentially a continuation from training prior to the introduction of the degraded conditioning phase. Sensitization was without effect on levels of contingent reinforcement (Group F(1,22) = 0.8, N.S.; Group × Session interaction: F(5,110) = 0.4, N.S.).

3.7. Extinction test

Response rates on the lever that previously delivered contingent reinforcement declined a little during the extinction test in both groups, but not to a statistically significant extent (see Fig. 5. Session F(1,22) = 2.1, N.S.; Group F(1,22) = 1.1, N.S.; Contingency F(1,22) = 35.5,

Table 2
Reinforcements available during acquisition of a degraded instrumental contingency task. Subjects were trained to press one lever for a specific reinforcer (food pellet or sucrose solution), and a second lever for the alternative reinforcer. The final probability of reinforcer delivery for a leverpress in any 1 s interval was 0.05 ($p = 0.05$/s). Then, one group was pretreated with *d*-amphetamine (Sensitized; 1 mg/kg/day for 7 consecutive days), and a second group received vehicle (Controls). During the test phase shown above, each reinforcer continued to be delivered following depression of the appropriate lever, but one reinforcer was now also available following the absence of a response on either lever ('Free' reinforcers; $p = 0.05$/s in each case). Thus, while response–outcome contiguities were maintained, response–outcome contingency was maintained at $p = 0.05$/s for one lever (Contingent), but reduced to zero on the alternate lever (Noncontingent). Values are mean (±1SEM) reinforcements per session, in 3-session blocks.

	Reinforcers earned or delivered during acquisition of degraded instrumental contingency task						
	3-session block						
	Reinforcer type	1	2	3	4	5	6
Controls	Nondegraded	17.0 (2.2)	15.2 (2.7)	12.9 (3.2)	13.3 (2.7)	11.9 (2.1)	14.8 (2.1)
	Degraded	19.6 (2.4)	19.5 (2.9)	15.9 (3.9)	12.9 (3.6)	10.3 (3.3)	10.0 (2.9)
	Free	32.0 (1.9)	35.6 (3.5)	40.9 (4.7)	42.4 (4.0)	45.7 (2.8)	45.9 (3.1)
Sensitized	Nondegraded	18.6 (3.2)	18.3 (3.6)	17.7 (3.5)	18.1 (3.6)	15.9 (3.7)	18.0 (3.9)
	Degraded	15.1 (2.1)	13.8 (2.5)	9.9 (2.1)	7.9 (2.2)	7.3 (1.9)	6.8 (2.0)
	Free	36.7 (3.9)	37.8 (4.1)	41.1 (3.9)	43.8 (4.4)	44.9 (4.0)	45.6 (4.2)

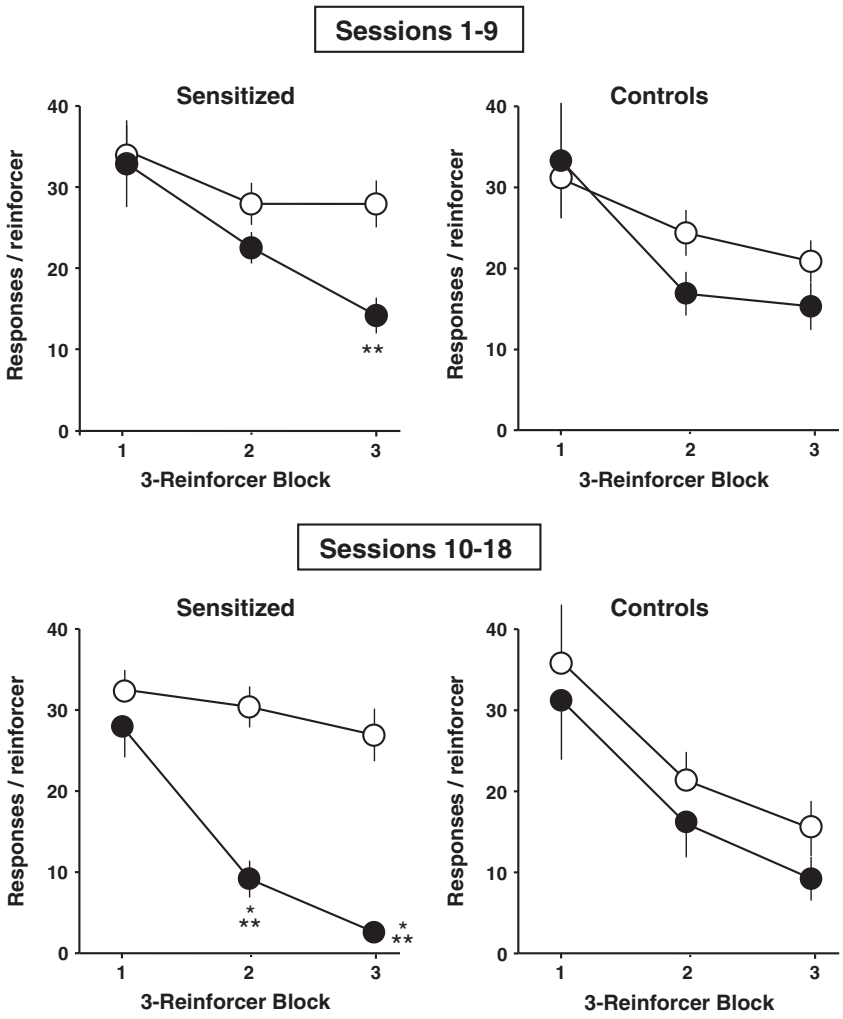


Fig. 2. Effects of sensitization on within-session response rates during acquisition of a degraded instrumental contingency task. Values plotted are mean (±1SEM) leverpresses during the first nine reinforcements earned each session, in 3-reinforcer blocks. Sessions 1–9, first nine sessions of differential contingency task; Sessions 10–18, final nine sessions. For outline of differential contingency task, see Table 1. In brief, following initial training, one group was pretreated with *d*-amphetamine (Sensitized; 1 mg/kg/day for 7 consecutive days), and a second group received vehicle (Controls). Instrumental contingency was maintained at baseline ('B') levels of $p = 0.05$/s on one lever (Open circles), but reduced to zero on the alternate lever (Filled circles). Response–outcome contiguity was maintained at all times. Stars indicate statistically significant comparisons with the appropriate nondegraded performance, $^{**}P<0.01$, $^{***}P<0.001$.

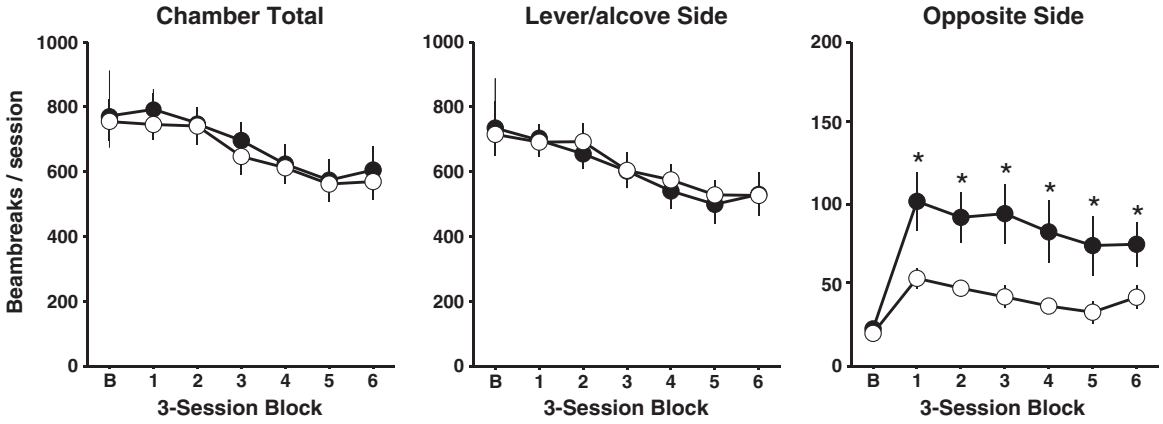


Fig. 3. Effects of sensitization on locomotor activity within experimental chambers during acquisition of a degraded instrumental contingency task. Values plotted are mean (±1SEM) beam breaks per session for final baseline before introduction of differential contingency ('B' on horizontal axes) and subsequent 3-session blocks. For outline of differential contingency task, see Table 1. In brief, following initial training, one group was pretreated with *d*-amphetamine (Filled circles; 1 mg/kg/day for 7 consecutive days), and a second group received vehicle (Open circles). Instrumental contingency was maintained at baseline levels of $p = 0.05$/s on one lever, but reduced to zero on the alternate lever. Response–outcome contiguity was maintained at all times. Four equally spaced photobeams were positioned 4 cm above the grid floor and aligned from front to back. Shown above are total beam breaks per session (Chamber total), breaks of the two photobeams on the same side of the experimental chamber as the levers and alcove (Lever/alcove Side), and breaks of the two photobeams on the opposite side to the levers and alcove (Opposite side). Stars indicate statistically significant comparisons with the appropriate vehicle performance, $^{*}P<0.05$.

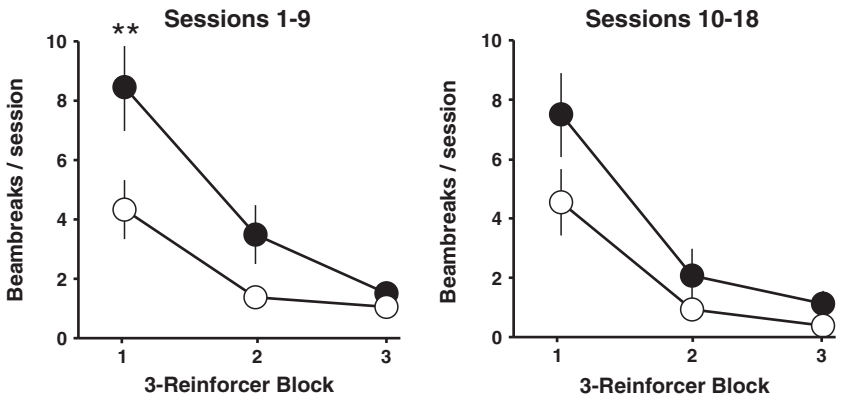


Fig. 4. Effects of sensitization on within-session beam breaks in the experimental chamber during acquisition of a degraded instrumental contingency task. Values plotted are mean (±1SEM) beam breaks on the side of the experimental chamber opposite to the levers and alcove during the first nine reinforcements earned each session, in 3-reinforcer blocks. Sessions 1–9, first nine sessions of adjustment to contingency elimination; Sessions 10–18, final nine sessions of adjustment to contingency elimination. For details of differential contingency procedure, see Table 1. One group was pretreated with *d*-amphetamine (Sensitized: filled circles; 1 mg/kg/day for 7 consecutive days), and a second group received vehicle (Controls: open circles). Stars indicate statistically significant comparisons with the appropriate vehicle performance, $^{**}P<0.01$.

$p<0.001$; largest interaction: Group x Contingency $F(1,22)=3.6$, N.S.). However, responding on the lever previously designated as noncontingent was clearly unchanged by the extinction test (see Fig. 5).

4. Discussion

While the broad effects of sensitization on a range of behaviors are well documented, the precise underlying mechanisms have received less attention. Here, a stringent form of contingency degradation procedure assessed the effects of sensitization on the ability to monitor the relationship between an action, and an outcome. Effects of sensitization took on two main forms. Firstly, sensitized animals were more active, and this heightened activation preceded the development of a more specific response to contingency degradation. Enhanced locomotor activity was most evident on the side of the chamber opposite to the most salient stimuli. Secondly, sensitization did not affect the rate of adjustment to contingency degradation, which was comparable with controls. However, controls showed significant generalization to the nondegraded action–outcome alternative and so reduced responding equally on both levers for many sessions before increasing responding selectively on the nondegraded task late in training. By contrast, sensitized animals maintained a high level of responding on the nondegraded action–outcome task throughout the degradation phase. Both groups reduced responding on the nondegraded action–outcome task to a small extent during a subsequent extinction test, while low rates of responding established on the degraded action–outcome alternative were unaffected.

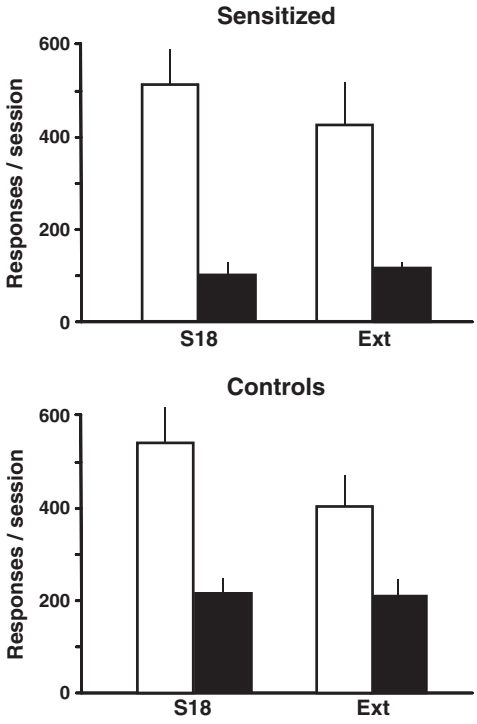


Fig. 5. Effects of sensitization on response to reinforcer removal from degraded instrumental contingency task. Values plotted are mean (±1SEM) responses for the final test session (S18) and subsequent extinction session (Ext). For details of differential contingency procedure, see Table 1. Briefly, following initial training, one group was pretreated with *d*-amphetamine (Sensitized; 1 mg/kg/day for 7 consecutive days), and a second group received vehicle (Controls). During the test phase, the instrumental contingency of $p=0.05$/s was maintained on one lever (Open bars), but reduced to zero on the alternate lever (Filled bars) for 18 sessions. Response–outcome contiguity was maintained at all times.

The degradation procedure carried out here was based closely on the recommendations of Dickinson and Mulatero (1989). Animals first learned that depression of one lever led to the availability of one reinforcer (e.g. food pellet), while depression of a second lever produced the alternative reinforcer (sucrose). The probability that an outcome would follow an action in any 1 s was gradually reduced to 0.05, and then sensitization carried out. The degradation phase then began, in which one contingency was now set to zero by providing the appropriate reinforcer with equal probability for not pressing the relevant lever. There were two particularly stringent features of the current procedure. Firstly, unearned reinforcers were delivered not simply for withholding the designated response ($p=0.05$/s, cf. Colwill and Rescorla, 1986), but were also provided with equal probability following the withholding of the alternative response (see Dickinson and Mulatero, 1989). This was to prevent adventitious pairings of the unearned reinforcer with responses directed at the nondegraded action–outcome relationship, which otherwise might maintain nondegraded responding in part *via* the perceived addition of a second outcome. A second distinguishing feature of the current procedure is that both actions and outcomes were presented concurrently during test sessions (see also Dickinson and Mulatero, 1989). A direct comparison could therefore be made of the perceived relative contingencies associated with the two levers, and the pattern of results seen in which sensitized animals were better able to maintain a selective response on the nondegraded action might very credibly reflect this relatively stringent requirement. Consistent with this, the current study required a relatively high number of sessions for control animals to acquire a selective pattern of responding, which may also reflect related procedural differences. For example, Dickinson and Mulatero (1989) tended not to counterbalance levers and respective

reinforcers within experiments, and Balleine and Dickinson (1998) used relatively distinct manipulanda (levers vs. chains). Similarly, while many of the features of the levers used by Dickinson and Mulatero (1989) and the current study are very comparable (height above floor: 5.5 cm; width: 4.5 cm; distance apart: 11 cm), the thickness of the type of lever used by Dickinson and Mulatero (1989) would typically be a relatively discriminable 1.5 cm, while in the present study the levers were flat and just 2 mm thick at most.

A lack of effect of sensitization on the primary variable of contingency degradation might appear to contrast with evidence that sensitization rendered animals relatively insensitive to change (Nelson and Killcross, 2006). Broadly converse manipulations such as nigrostriatal (Faure et al., 2005) or dopaminergic lesions of the dorsolateral (but not dorsomedial) striatum (Yin et al., 2004) instead disrupted such habit formation. However, these findings are entirely reconcilable: in general these related studies specifically devalued the outcome while leaving the action–outcome relationship unaltered. By contrast, the current study in a sense 'devalued' the action–outcome relationship through its elimination, but left the value of the outcome itself unchanged. These are very different features of the task, and it should also be noted that Nelson and Killcross (2006) found that the alcove approach response remained sensitive to changes in US value at all times; a finding very consistent with those of this laboratory: indeed, sensitization has been found even to enhance the acquisition of a conditioned inhibition task under the appropriate circumstances (Harmer and Phillips, 1999a).

Given that the number of delivered reinforcers associated with the degraded contingency outmatched the number of earned reinforcers by a ratio of at least 3:1 by the end of the degradation phase, reduced responding on the noncontingent lever conceivably might reflect differential sensory-specific satiety to the unearned reinforcer (Le Magnen, 1956). Indeed, prior selective satiation to one reinforcer preferentially reduces the frequency of the associated action or behavior in subsequent tests with dual action–outcomes (Colwill and Rescorla, 1985b; Corbit et al., 2001; Rescorla, 1978). If sensory-specific satiety were to account for reduced responding on the noncontingent lever, then removal of reinforcement during the extinction test should disinhibit responding on this lever. However, response rates in extinction were unaffected by the removal of the reinforcer, and so sensory-specific satiety to the relative preponderance of unearned reinforcers cannot account for selective reductions in responding directed at the noncontingent action–outcome relationship.

Sensitized animals were more active within experimental chambers, and their more specific response to contingency degradation is conceivably attributable in some measure to these activational differences. In truth, this enhanced activity was not expected, as while sensitization is known to enhance the locomotor stimulant properties of *d*-amphetamine (e.g. Kokkinidis and Zacharko, 1980; Kuczenski and Leith, 1981; Leith and Kuczenski, 1982; Paulson and Robinson, 1991), this laboratory has not found consistent effects on unstimulated activity within an activity or learning-related experimental chamber (Harmer et al., 1997; Harmer and Phillips, 1998, 1999a,b). However, earlier work recorded overall measures of locomotor activity, while the current study found that activity specifically on the opposite side of the chamber was markedly enhanced. As activity levels on the lever side of the chambers were generally far higher than the opposite side, total activity counts were also unaffected by sensitization. Leverpressing behavior, stimulus tracking or alcove approach may have contaminated previous recordings then. However, sensitization is without effect on baseline levels of activity within chambers solely designed to measure locomotion (Harmer et al., 1997; Harmer and Phillips, 1998, 1999a; Phillips et al., 2002), indicating the important role that external stimuli of acquired motivational significance may play in eliciting an enhanced behavioral response in this preparation. There are many stimulus candidates in the current procedure, but all would depend on acquiring some aspect of the unconditioned properties of the pellet and sucrose solution reinforcers. These acquired features might include relatively detailed mental representations of the unconditioned stimuli (Colwill and Rescorla, 1985b), or be confined to a component of the affective state that the unconditioned stimuli engender (Holland and Rescorla, 1975; Rescorla, 1979).

In any case, enhanced locomotor activity by sensitized animals most likely reflected an exaggerated activational response to conditioned stimuli. This would be consistent with the view that a primary function of mesotelencephalic dopamine is to modulate the vigor or frequency of behavioral activation in a given situation, and that the function of this activation is to enhance behaviors appropriate to the upcoming availability of a reinforcer or goal object (Everitt et al., 2008; Everitt and Robbins, 2005; Robbins and Everitt, 1992, 2002). Direct observations of dopaminergic activity in sensitized animals within the prefrontal cortex (Lin et al., 2007; Peleg-Raibstein and Feldon, 2008), nucleus accumbens (Afanas'ev et al., 2000; Duvauchelle et al., 2000) or amygdala (Harmer and Phillips, 1999b; Phillips et al., 2003c) confirm a greatly elevated and widespread dopaminergic response specifically to stimuli of acquired motivational significance. Alternatively, an additional mechanism termed 'incentive salience' may be necessary fully to account for the role of dopamine in rewarded behaviors (Berridge, 2007; Robinson and Berridge, 2003; 2008; Robinson and Flagel, 2009), and dopaminergic activation is thought to enhance 'wanting' of conditioned stimuli and to govern approach towards such stimuli through facilitating their ability to act as 'motivational magnets' (Berridge, 2001). Evidence cited in favor of this account includes the facilitating effects of sensitization in a Pavlovian-to-instrumental transfer test (Wyvell and Berridge, 2001), and perhaps also conditioned reinforcement (Ranaldi et al., 2009). In any event, while conditions remain unchanged then conditioned stimuli may lose their capacity to elicit an activational or perhaps reinforcing response (Adams and Dickinson, 1981; Bradberry et al., 2000; Dickinson, 1985; Everitt et al., 2008; Everitt and Robbins, 2005; Kalivas and Volkow, 2005; Kelley, 2004; Tolman, 1948; but see Colwill and Rescorla, 1985a; Holland, 1998; Powell, 1999). It should not be surprising then that elevated levels of activity shown by sensitized animals declined as the degraded contingency phase progressed.

Maintained responding by sensitized animals on the nondegraded lever then, relative to controls might be seen as a more robust activational response to relevant Pavlovian stimuli (Bindra, 1974; Hall, 2002; Rescorla and Solomon, 1967). In favor of such a Pavlovian-activational account, behavioral effects of sensitization on the opposite side of experimental chambers to the primary location of discrete stimuli provide clear evidence for an exaggerated, generalized response to detection of conditioned stimuli. Against a purely Pavlovian account though, reduced responding on the degraded lever should then be seen as a form of negative Pavlovian-to-instrumental transfer (Balleine and Killcross, 1994; Colwill and Rescorla, 1988), and the activational effects of sensitization ought to impair the rate of decline on this lever relative to controls. In fact, sensitized animals reduced responding on the degraded lever at the same rate as controls throughout the degradation phase. Secondly, sensitized animals actually reduced responding at a much faster rate than controls in a stringent Pavlovian conditioned inhibition preparation (Harmer and Phillips, 1999a). Finally, both action–outcomes were presented concurrently, and while a specific activational effect of appropriate Pavlovian stimuli cannot be entirely ruled out (Colwill and Motzkin, 1994), the highly selective response by sensitized animals across the two levers weighs against the main effect of sensitization in the contingency degradation task being accountable as an increase in the general activational properties of relevant Pavlovian stimuli.

Consistent with this, while the nucleus accumbens is most closely associated with the activational properties of biologically meaningful stimuli (Mogenson et al., 1980), neither general lesions of the nucleus accumbens as a whole (Balleine and Killcross, 1994) nor specific lesions of shell or core subregions affected in a clearcut manner the

response to degradation of an instrumental contingency (Corbit et al., 2001). Instead, findings reminiscent of those seen in the current study were reported following perikaryal lesions of the prelimbic area of the prefrontal cortex (PL: Balleine and Dickinson, 1998), posterior dorsomedial striatum (see also Shiflett et al., 2010; Yin et al., 2005) or mediodorsal thalamus (Corbit et al., 2003), each closely associated thalamocortical structures (Nauta, 1989). For example, animals with perikaryal lesions of the PL appeared to have difficulty in responding selectively to differential action–outcomes, a deficit that was overcome by providing explicit cues such as outcome-associated Pavlovian stimuli, or even the outcome itself (Corbit and Balleine, 2003). Similarly, PL lesions somewhat reduced the ability of cues associated with competing action–outcome sequences to interfere with performance of an ongoing task, particularly with the introduction of delays between cue and action–outcome presentations (Dwyer et al., 2010). These data suggest that PL or related lesions interfere in some sense with the ability to utilize appropriate action–outcome relationships, and that under these conditions remaining stimulus–response associations may be a predominant force in guiding behavior (see also Killcross and Coutureau, 2003).

A specific dopaminergic influence over these regions has received some attention. Although dopamine-specific 6-hydroxydopamine (6-OHDA) lesions of the PL have been reported to be without specific effect on the adaptive response to contingency degradation (Lex and Hauber, 2009), the same manipulation has also been shown to robustly impair this behavior (Naneix et al., 2009), and intra-PL alpha-flupenthixol also impaired adaptation to contingency degradation (Naneix et al., 2009). Similarly, 6-OHDA lesions of the dorsomedial striatum also resulted in a failure to adapt to change in instrumental contingency (Lex and Hauber, 2009), and so it remains a possibility that each region may underpin dissociable aspects of contingency-dependent behavior under the modulatory control of mesocortico-limbic dopamine.

Given the more taxing within-session design of the current study, sensitized animals here performed at levels comparable with controls in Balleine and Dickinson (1998), while the current vehicle group's performance was broadly similar to lesioned animals in the latter study. In essence, both sensitization and lesions of the PL affected the specificity of the response to degradation of one action–outcome relationship, albeit in opposite directions. A subsequent study of the effects of PL lesions on the reaction to contingency degradation did not entirely replicate these findings (Corbit and Balleine, 2003). Interestingly, it was suggested that the earlier study required that a Perspex panel be pushed to gain access to the two reinforcers, and that this common response associated with both outcomes may have given rise to a level of stimulus generalization not seen in the subsequent study. Possibly the most intuitive interpretation of the current findings then would be that sensitized animals were better able to discriminate between the contingent and noncontingent components of the task. This might be due to enhanced discrimination between the reinforcers, the levers or perhaps the action–outcome relationships themselves. Indeed, lesions of the medial prefrontal cortex, which encompass the PL, clearly impair visual discriminative performance (Muir et al., 1996; Passetti et al., 2000).

However, the extent to which these findings reflect a particularly dopaminergic role in discriminative function remains open to debate. Discriminative abilities under particularly taxing conditions are linked squarely with noradrenergic rather than dopaminergic brain function (e.g. Carli et al., 1983; Robbins, 1997; Robbins and Everitt, 1987a), and manipulations of dopamine function within the nucleus accumbens do not affect response accuracy, but instead response likelihood or rate (Cole and Robbins, 1987, 1989). Similarly, while intra-PL infusions of the dopamine D1 receptor antagonist SCH-23390 impaired reversal learning (Ragozzino, 2002; see also Rinaldi et al., 2007), the effects of dopaminergic manipulations of the PL on discriminative function seem relatively inconsistent (Glickstein et al., 2005; Ragozzino, 2002; Rinaldi et al., 2007). Results from dopaminergic manipulations of the dorsomedial striatum are broadly in agreement with these findings: dopaminergic depletion impaired reversal learning (O'Neill and Brown, 2007) yet was generally (Calaminus and Hauber, 2009; O'Neill and Brown, 2007), though not entirely (Darvas and Palmiter, 2010) without effect in discriminative preparations. The extent to which the present findings may be accountable then as a dopamine-dependent facilitation of discriminative features of the leverpressing task remains unclear at the present time.

In sum, sensitization resulted in a general increase in activity, and a specific improvement in adaptation to a contingency degradation test. The facilitatory effects of sensitization on activity occurred relatively early during exposure to the degraded contingency, while adjustment to the new contingency only reached a peak later in training. Enhanced locomotor activity in sensitized animals might well reflect a Pavlovian-activational feature of enhanced mesoaccumbens dopaminergic reactivity, while the more selective response to contingency elimination observed a little later in training may be the outcome either of improved action–outcome utilization or discriminative features of the task.

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