Psychopharm

Journal of Psychopharmacology
18(4) (2004) 516–526

ISSN 0269-8811
SAGE Publications Ltd, London, Thousand Oaks, CA and New Delhi
10.1177/0269881104047279

Amphetamine decreases the expression and acquisition of appetitive conditioning but increases the acquisition of anticipatory responding over a trace interval

E. Kantini *School of Psychology, University of Nottingham, University Park, Nottingham, UK.*
C. Norman *School of Psychology, University of Nottingham, University Park, Nottingham, UK.*
H. J. Cassaday *School of Psychology, University of Nottingham, University Park, Nottingham, UK.*

Abstract

The effects of amphetamine on selective learning were tested in a trace conditioning procedure, in which the informativeness of the conditioned stimulus (CS) (noise) was manipulated through the introduction of a time interval before the delivery of the unconditioned stimulus (UCS) (food). The results showed that *d*-amphetamine (0.5 and 1.5 mg/kg) impaired both the expression (Experiment 1b) and acquisition (Experiment 2) of appetitive conditioning. This was true for both trace and contiguously conditioned groups. The effects of the 0.5 mg/kg dose of *d*-amphetamine were not attributable to general motor (measured pre-CS) or motivational (measured post-UCS) effects of the drug. Moreover, the same pattern of effects (impaired appetitive conditioning, irrespective of the trace interval between CS and UCS) was confirmed in drug-free extinction tests. By contrast to the general depression in the acquisition and expression of associative learning observed under amphetamine, the 0.5 mg/kg dose promoted the acquisition of anticipatory responses made later in the trace interval (in Experiment 2 but, again, not the expression of previous conditioning in Experiment 1b). This suggests a dissociable effect of low-dose *d*-amphetamine on learning about the temporal relationship between CS and UCS.

Keywords

amphetamine, appetitive conditioning, dopamine, trace conditioning

Introduction

The dopamine hypothesis and related amphetamine model of schizophrenia (Ellison and Eison, 1983) have prompted considerable interest in how amphetamine may affect basic cognitive processes in animal models. In particular, evidence for disturbance of attentional processes in schizophrenics has led to animal models based on dysfunctional associative learning.

In short, amphetamine can increase conditioning to poor predictors of reinforcement in selective learning tasks [e.g. latent inhibition and blocking in which stimuli are first established as irrelevant (Solomon *et al*., 1981; Weiner *et al*., 1981, 1988; Gray *et al*., 1992; Kumari *et al*., 1999) or redundant (Crider *et al*., 1982; Ohad *et al*., 1987; Jones *et al*., 1997)] before later assessing their effects on conditioning. However, in such two-stage procedures, it is not clear whether a treatment such as amphetamine is effective because of an action that somehow reduces the influence of earlier associations.

There already some good general evidence for the role of dopamine in both aversive (Feenstra *et al*., 2001) and appetitive (Harmer and Phillips, 1998; Dalley *et al*., 2002) conditioning, as well as in the association of neutral stimuli before any reinforcement (Young *et al*., 1998). Thus, it is important to distinguish the role of dopamine in simple associative learning from its effects in producing performance deficits when the animal is required to show behavioural flexibility in response to current contingencies. Such an effect could be mediated through generally increased behavioural switching (Weiner and Feldon, 1997; Weiner, 1990, 2003) or, more specifically, because the effects of stored associations on current responding are somehow reduced.

Therefore, in the present series of experiments, we used a simple one-stage procedure to compare drug effects on the acquisition

Corresponding author: H. J. Cassaday, School of Psychology, University of Nottingham, University Park, Nottingham NG7 2RD, UK. *Email*: helen.cassaday@nottingham.ac.uk

and expression of conditioning without invoking the need explicitly to compare competing associative representations. This was an on-the-baseline appetitive task that used stimuli varying in their predictive power. Within experiments, the baseline level of learning was manipulated by the introduction of a time (trace) interval between conditioned stimulus (CS) (noise) and unconditioned stimulus (UCS) (food). The trace CS is a less informative predictor of the UCS than the CS immediately followed by the UCS (Kamin, 1965). Here, the target CS was presented (with or without trace) to allow between subjects' comparison of conditioning to strong and poor predictors. Second, an alternative background stimulus was presented continuously throughout the session. This procedure allowed measurement of conditioning to an experimental context in the same way as to the discrete target CS, in the same apparatus and the same rats (Tanner *et al*., 1987; Tsaltas *et al*., 1989; Rawlins and Tanner, 1998). Because it is continuously present throughout the conditioning session, the background stimulus should constitute a relatively uninformative predictor of the food UCS.

In designs of his kind, where there are two behavioural conditions that require quite large numbers of subjects per experimental group, it is usual to justify testing a couple of doses that are of *a priori* interest. In this case, we tested the effects of the indirect dopamine agonist amphetamine because it can abolish latent inhibition (at 1.5 mg/kg *d*-amphetamine) in a similar appetitive conditioning procedure (Killcross *et al*., 1994). Thus, the doses, isomers and route of administration of systemic amphetamine used in these experiments were chosen for comparison with the latent inhibition literature (Weiner *et al*., 1987, 1988; Killcross *et al*., 1994). Throughout, we used a sensitizing injection to produce the impulse dependent flow of dopamine release found to be necessary for the disruption of latent inhibition (Warburton *et al*., 1996; Gray *et al*., 1997; Joseph *et al*., 2000). Electrophysiological studies have shown that dopamine responses during conditioning are not simply a consequence of the presentation of reward, rather they depend on the ability of an animal to predict the occurrence of reward on the basis of the available stimuli (Waelti *et al*., 2001). Because rewards are in effect most unpredictable early in acquisition, and dopamine neurones respond less as learning approaches asymptote, it follows that dopaminergic treatments should be differentially effective at different stages of acquisition. Accordingly, Experiment 1a examined the distribution of responding during CS and UCS presentations and within the trace (inter-stimulus) interval over the course of acquisition. Subsequently, in Experiment 1b, we examined the effect of amphetamine (0.5 and 1.5 mg/kg) on the expression and further acquisition of conditioned and unconditioned responding. Finally, using the behavioural procedures developed in Experiment 1a, Experiment 2 went on to test the effect of the same amphetamine treatments on the acquisition of responding, in animals without this pre-training.

Materials and methods

Animals

Experiment 1 used 24 naïve male Wistar rats (Charles River, Margate, UK) weighing in the range 248–282 g. Experiment 2 used 48 non-naïve male Wistar rats (Charles Rivers, UK) weighing in the range 366–488 g. All animals were caged in pairs on a 12 : 12 h light/dark cycle (lights on 08.00 h) and handled over 2 weeks before the experiments were started. Then, food in the home cage was restricted to 5 g per 100 g rat body weight and adjusted as necessary to prevent further weight gain in rats weighing over 400 g. Water was available *ad libitum*. In each case, before pre-training began, rats were exposed to sucrose reward pellets in the home cage.

In Experiment 1, rats were randomly assigned to experimental conditions. In Experiment 2, rats were non-randomly allocated to groups, counterbalanced for their previous experimental experience. In both experiments, all training and testing took place during the light phase (between 08.00 h and 14.00 h).

All procedures were carried out in accordance with the United Kingdom Animals Scientific Procedures Act 1986, Project Licence number PPL 40/2019.

Drugs

There were three treatment conditions to test the effects of *d*-amphetamine sulphate (Sigma, Poole, UK) in Experiments 1b and 2: saline, low dose (0.5 mg/kg) and high dose (1.5 mg/kg). These were administered by intraperitoneal injection 1 day before the start of the conditioning tests and thereafter 15 min before each conditioning session. Extinction tests were conducted drug free.

Apparatus

Four identical fully automated conditioning chambers, housed within sound-attenuating cases containing ventilation fans (Cambridge Cognition, Cambridge, UK) were used throughout. Each of the inner conditioning chambers consisted of a plain steel box (25 × 25 × 22 cm high) with a Plexiglas door (19 × 27 cm) at the front. The floor was a shock grid with steel bars 1 cm apart and 1 cm above the lip of a 7 cm deep sawdust tray. Mounted in one wall were two retracted levers (not used for these experiments), three stimulus lights and a food magazine where the UCS of two 45 mg precision sucrose pellets (Formula F, Noyes Precision Food, New Hampshire, UK) was delivered.

The food magazine was a metal well with a Plexiglas front flap hinged at the top and was illuminated by a light on the top inside wall of the well during experimental sessions. Food pellets were automatically delivered into the magazine well, as programmed, and the nose pokes were registered by the breaking of a photobeam behind the flap as it was pushed open.

A loudspeaker for the presentation of auditory stimuli was set in the roof. Two stimuli were used in this procedure; a mixed frequency noise set at 70 dB as the target stimulus (i.e. the CS paired with the UCS) and a flashing light as the alternate or background stimulus, provided by the three wall mounted stimulus lights and the house light flashing both on and off for 0.5 s. Stimulus control and data collection was by a RISC personal computer programmed in Basic with additional interfacing using an Arachnid extension (Cambridge Cognition, Cambridge, UK).

Behavioural procedure

The behavioural procedures were identical for both experiments. Experiment 1b followed 24 days after Experiment 1a. In each case, the procedure was identical except that Experiment 1a used a pure tone (set at 2 kHz and at 70 dB including background) and Experiments 1b and 2 used a mixed frequency noise (again set at 70 dB including background).

Pre-experimental On the first day, each rat was placed in its allocated conditioning box with access to food pellets in the magazine and shaped to nose poke. On the second and third day, rats were placed singly in the boxes and allowed to nose poke for 10 unsignalled rewards, delivered on a variable interval schedule over a 10-min session.

Conditioning Rats were conditioned with 10 signalled rewards (UCS) presented on a variable interval over a 30-min session. Conditioning took place over 15 days in Experiment 1a, a further 10 days in Experiment 1b and for 10 days in Experiment 2. The target CS was in each case a 5-s auditory stimulus, set at 70 dB (see above). During this time, a continuous flashing light stimulus was presented in the background. The contiguously conditioned group received rewards at the offset of each CS presentation, whereas the trace group was exposed to a delay of 10 s between CS offset and UCS delivery.

Assessing effects on conditioning could be confounded by the role of the dopamine system in motivational (reward-related) or motor (nose poking) responses. However, drug effects on levels of responding to the CS were compared with responding during the intervals immediately before CS presentation and the equivalent time period after UCS delivery in each case. Specifically, we recorded the number of nose pokes in the following response bins: (i) 'Pre-CS' in the 5 s before CS presentation; (ii) 'CS' in the 5 s of CS presentation; (iii) 'Post-UCS' in the 5 s immediately following UCS delivery; and (iv) 'Trace' during the 10 s inter-stimulus-interval (ISI) between CS and UCS (in the trace conditioned rats). To further examine the pattern of anticipatory responding within the trace interval, responses were collected in five 2-s bins.

Extinction There were two sessions on each of 2 days (one for each stimulus type) to provide drug-free measures of the levels of conditioning in Experiments 1b and 2. Rats were presented with the stimulus, either the noise or the flashing light, in the absence of any UCS deliveries. In either case there were 10 presentations on a variable interval over the 30-min session. Extinction tests were counterbalanced for the order in which conditioning was tested to the noise CS and the flashing light background stimulus. Nose pokes were recorded in the same response bins as for conditioning, except that there was no trace interval in use and, because there were no UCS deliveries, there was no need to consider responding in the post-UCS bin.

Data analyses

All statistical tests used analysis of variance with repeated measures (Days) to check the course of conditioning. Trend analyses were also used to examine conditioned responding in the different response bins over days. Analysis of covariance (ANCOVA) was used to adjust for any significant drug effect on baseline responding, using the Pre-CS as covariate. Separate analyses were conducted for the extinction of responses to the tone CS and light background in Experiments 1b and 2.

In each case, alpha was set at 0.05. Trace had two levels (0- and 10-s conditioned groups) and Drug (in Experiments 1b and 2) had three levels (vehicle, low and high doses of amphetamine).

Before assessing drug effects on responding to the stimuli of interest, analyses were first carried out to check for pre-existing differences between the rats allocated to the different experimental conditions-to-be, both pre-experimentally, on the pre-conditioning days used to establish the baseline response of nose poking, and immediately pre-stimulus on experimental days on which the level of conditioning was assessed.

Results

Experiment 1a: the acquisition of responding over a trace interval

The results detailed below show that, as expected, rats showed increased nose poke responding to the CS over the course of the experiment, especially in the contiguously conditioned group. The trace conditioned groups showed, again as expected, relatively reduced responding to the CS. However, this group did show their anticipation of food deliveries in the ISI, especially towards the end of this interval, as conditioning progressed.

Pre-experimental responding

The groups were well matched for their behavioural condition because there was no effect of Trace, either overall or in interaction with Days (both $F < 1$).

On-the-baseline tests

Mean responding in the various response bins is shown in Table 1.

Pre-CS There was a significant effect of Days [$F(9,206) = 2.01$, $p < 0.05$]. This arose because the number of nosepokes made in the pre-CS was variable over the course of conditioning. However, there was no consistent trend in this variation (means ranged from 2.15 on day 10 to 5.21 on day 4). Moreover, there were no significant effects involving Trace (all $F < 1$). Thus, the subjects were well matched for their baseline response rates before presentation of the CS.

CS Again, there was significant effect of Days [$F(6,137) = 20.59$, $p < 0.001$]. This arose because the level of responding during the CS increased over days, from a mean of 3.83 (day 1) to 20.38 (by day 15), reflecting acquisition of the association between noise and food. As expected, there was both a significant effect of Trace

Table 1 Acquisition phase of Experiment 1a

Days	Pre-CS (mean ± SEM)	CS (mean ± SEM)	Post-UCS (mean ± SEM)
Contiguous (0-s) conditioned groups			
1	3.3 ± 1.1	3.1 ± 1.3	6.7 ± 1.5
2	4.5 ± 0.9	9.3 ± 1.6	11.7 ± 2.5
3	4.5 ± 1.1	10.8 ± 1.8	13.3 ± 1.5
4	5.5 ± 1.8	14.8 ± 1.8	16.0 ± 2.3
5	2.5 ± 0.7	13.9 ± 2.6	15.6 ± 2.0
6	2.8 ± 0.5	21.2 ± 2.3	16.7 ± 2.5
7	2.9 ± 0.8	27.2 ± 3.4	17.0 ± 2.3
8	2.5 ± 0.7	25.8 ± 3.7	17.1 ± 2.3
9	2.7 ± 0.9	27.5 ± 3.2	15.3 ± 2.0
10	2.1 ± 0.9	29.1 ± 3.3	14.4 ± 1.8
11	2.9 ± 1.0	29.6 ± 3.3	15.1 ± 2.5
12	3.7 ± 1.1	29.4 ± 3.3	13.9 ± 2.5
13	2.8 ± 0.9	29.7 ± 3.7	13.8 ± 1.2
14	3.2 ± 1.3	28.8 ± 4.5	14.0 ± 1.9
15	3.5 ± 1.0	29.6 ± 4.3	12.4 ± 1.4
Trace (10-s) conditioned groups			
1	4.3 ± 1.1	4.6 ± 1.4	7.9 ± 1.4
2	3.1 ± 0.6	4.8 ± 1.0	13.1 ± 1.1
3	5.2 ± 1.5	6.1 ± 1.1	15.6 ± 1.4
4	4.9 ± 1.5	9.7 ± 2.5	15.6 ± 1.2
5	2.8 ± 0.9	8.7 ± 2.2	12.5 ± 2.2
6	3.3 ± 0.8	6.1 ± 1.2	16.5 ± 2.1
7	3.0 ± 0.8	6.3 ± 1.6	17.0 ± 2.1
8	4.7 ± 0.9	6.9 ± 1.1	17.5 ± 1.8
9	3.0 ± 0.8	7.7 ± 1.4	16.1 ± 1.9
10	2.2 ± 0.9	8.3 ± 1.9	15.7 ± 1.8
11	1.8 ± 0.5	6.8 ± 1.7	17.4 ± 2.5
12	3.3 ± 0.8	8.0 ± 1.5	15.3 ± 1.8
13	3.8 ± 0.7	10.5 ± 2.3	17.3 ± 1.3
14	5.7 ± 1.2	14.3 ± 1.7	19.6 ± 1.9
15	3.8 ± 0.9	11.2 ± 2.2	19.4 ± 1.8

Mean ± SEM nose poke responding in the different response bins (pre-CS, CS and post-UCS).

overall [F(1,22) = 27.73, $p < 0.001$] and an interaction between Trace and Days [F(6,137) = 11.63, $p < 0.001$].

The effects of Trace arose because the presentation of food immediately after the CS resulted in more effective conditioning to that stimulus overall (mean = 21.98) compared to that seen in the trace condition (mean = 7.98).

This difference was not significant on conditioning days 1 and 5 [maximum $t(21) = 1.52$]. On all other days of acquisition, contiguously conditioned responded significantly more compared to trace conditioned rats [minimum $t(18) = 2.20$, $p < 0.05$].

Post-UCS Again, there was a significant effect of Days [$F(7,159) = 6.47$, $p < 0.001$]. As would be expected, responding to collect food increased over time and then stabilized, from a mean of 7.29 on day 1 to 15.92 on day 15.

However, there was no significant effect of Trace either overall or in interaction with Days [maximum $F(7,159) = 1.57$]. Thus, both contiguous and trace conditioned subjects collected the reward readily, irrespective of the level of conditioning to the CS and the presence or absence of the trace interval.

Trace bins The pattern of responding within the trace interval over the course of conditioning was analysed with respect to five response bins (obtained by collecting responses in 2-s intervals within the 10 s trace used for the trace conditioned group). There was an overall effect of Days [$F(14,154) = 13.70$, $p < 0.001$]. This arose because, as expected when rats learn to anticipate reward, responding in the trace interval increased over days. The effect of Bins was marginal as a quadratic trend [$F(1,11) = 4.82$, $p = 0.05$]. Trend analyses also showed a higher order interaction between Days and Bins [$F(1,11) = 12.78$, $p < 0.005$], and we conducted some additional analyses by week (of 5 experimental days) to examine how the pattern of responding within the trace changed over the course of conditioning (Table 2).

The restricted analysis showed a significant effect of Bins in week 1 [$F(4,44) = 2.80$, $p < 0.05$]. This arose because trace conditioned rats responded significantly more [minimum $t(11) = 2.93$, $p < 0.01$] in bins 1 (mean = 2.6) and three (mean = 2.5) compared to bin 5 (mean = 1.77). Thus early in conditioning, the trace group responded relatively more at the start compared to later in the trace interval. However, although there was a tendency later (by week 3) to show relatively increased responding in bin 5 relative to bin 1 (Table 2), there was no significant effect of Bins in weeks 2 and 3 [maximum $F(4,44) = 2.19$].

Experiment 1b: effect of d-amphetamine on the expression of appetitive conditioning

Rats continued to respond more in contiguous than in trace conditioned groups. In both groups, amphetamine depressed responding

Table 2 Responding in the trace interval shown by week of acquisition in Experiment 1a

Bins	Week 1 (mean ± SEM)	Week 2 (mean ± SEM)	Week 3 (mean ± SEM)	Total (mean ± SEM)
1	2.60 ± 0.38	3.50 ± 0.61	5.43 ± 0.81	4.80 ± 0.80
2	2.20 ± 0.31	3.65 ± 0.55	5.88 ± 0.84	3.91 ± 0.52
3	2.50 ± 0.36	4.18 ± 0.74	6.47 ± 0.93	4.33 ± 0.58
4	2.23 ± 0.42	3.68 ± 0.60	6.32 ± 1.19	4.05 ± 0.64
5	1.77 ± 0.31	3.85 ± 0.67	6.23 ± 0.99	3.88 ± 0.57

Mean ± SEM nose poke responding over five 2-s bins of the 10-s trace.

to the CS but there was no consistent effect of drug on collecting reward. All rats continued to respond later in the trace interval and treatment with amphetamine did not affect this distribution of responding in the trace interval, there was just a marginal depression of overall responding (at the higher dose).

Pre-experimental responding

There were no overall effects of Trace, Drug condition-to-be, or Trace by Drug condition-to-be (all $F < 1$). Similarly, there were no significant interactions between treatments-to-be and Days [maximum $F(1,18) = 3.01$]. This confirmed that the experimental groups were well matched in terms of baseline responding before any further conditioning.

On-the-baseline tests

Pre-CS There were no significant effects of Days, Trace or Drug, either overall or in interaction [maximum $F(2,39) = 1.87$]. This confirms that rats in the different treatment groups were responding very similarly in the equivalent time periods before the CS presentations.

CS There was an overall effect of Trace [$F(1,18) = 79.85$, $p < 0.001$]. This arose because, as expected, the contiguous group produced a greater number of responses (mean = 25.78) compared to the trace group (mean = 5.76). There was also an overall effect of Drug [$F(2,18) = 12.18$, $p < 0.001$]. This arose because saline-treated rats produced significantly [$t(11) = 2.36$, $p < 0.05$] more nose pokes (mean = 22.99) compared to those in the 1.5 mg/kg *d*-amphetamine group (mean = 9.56). No other differences between drug groups were significant [maximum $t(14) = 1.22$]. As might be expected given that the rats had already been conditioned, there were no interactions between Trace or Drug and Day (both $F < 1$), so the reduction in responding under amphetamine did not depend on whether the rats were trace conditioned or not and this effect was stable over time (the overall means are shown in Fig. 1).

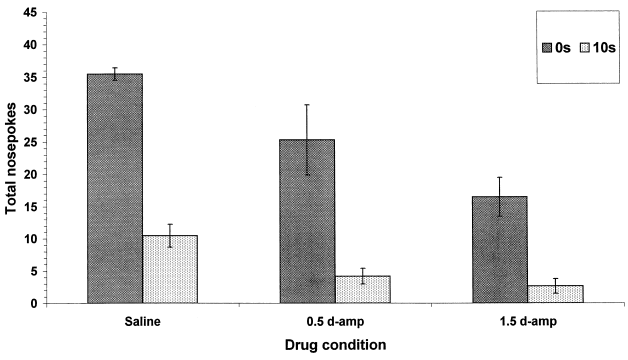

Figure 1 Mean overall nose pokes for conditioned stimulus acquisition in Experiment 1b. 0 s = contiguously conditioned groups; 10 s = trace conditioned groups; 0.5 *d*-amp = groups treated with 0.5 mg/kg *d*-amphetamine; 1.5 *d*-amp = groups treated with 1.5 mg/kg *d*-amphetamine. Bars show 2 SEMs for approximate between-groups comparisons

Post-UCS There was no overall effect of Trace or Drug, nor any Trace–Drug interaction [maximum $F(2,18) = 1.89$], nor were there any interactions over Days involving Trace [maximum $F(8,144) = 1.89$]. Thus delay of delivery after CS offset did not affect reward collection over the duration of conditioning. Although there was a significant Days by Drug interaction [$F(16,144) = 2.66$, $p < 0.005$], this was not due to significant differences on any particular day. The interaction most probably arose because of a general tendency for post-UCS responding in the high-dose *d*-amphetamine group to increase over days (from 14.63 ± 2.49 on day 1 to 23.38 ± 4.32 on day 10, presumably reflecting tolerance to the effects of the drug), whereas responding in the saline group fell off (from 16.75 ± 2.91 on day 1 to 13.00 ± 2.06 on day 10, presumably reflecting increased efficiency in collecting reward with prolonged testing, as there were only 10 deliveries to collect).

Trace bins There was an overall effect of Bins [$F(4,36) = 3.75$, $p < 0.05$]. Post-hoc analysis revealed significant differences in responding between bins 1 and 2 [$t(11) = 3.65$, $p < 0.005$] and bins 1 and 4 [$t(11) = 3.13$, $p < 0.01$]. These differences took the direction that (at this stage of acquisition) rats responded more in bin 2 (mean = 4.86) and four (mean = 5.31) compared to bin 1 (mean = 4.03). None of the other pairwise comparisons was significant [maximum $t(11) = 2.00$]. There was only a marginal effect of Drug [$F(2,9) = 3.97$, $p = 0.058$]. This arose because treatment with high-dose *d*-amphetamine tended to depress nosepoke responding [$t(6) = 2.60$, $p < 0.05$].

Again, probably because of the earlier acquisition, there was no effect of Days and there were no interactions involving Days [maximum $F(3,33) = 1.42$]. Although there was a marginal main effect of Drug, there were no significant interactions involving Drug [maximum $F(8,36) = 1.38$]. Thus, there was no evidence that the distribution of responding within the trace interval was affected by treatment with *d*-amphetamine.

Drug-free extinction tests

Again, there was relatively greater responding in contiguous compared to trace conditioned groups reflecting their stronger association between CS and UCS. The reduced responding seen during acquisition under *d*-amphetamine was confirmed in the drug-free extinction tests.

Tone CS

Pre-CS There was no effect of Trace, Drug, nor any Trace by Drug interaction [maximum $F(2,18) = 1.35$]. This confirms that baseline response rates were equivalent across the groups before the presentation of the CS.

CS Again, there was a main effect of Trace [$F(1,18) = 26.90$, $p < 0.001$] because the contiguously conditioned responded overall more (mean = 10.00) compared to the trace conditioned groups (mean = 2.00). Confirming the effect seen in acquisition, there was also an effect of (prior) Drug [$F(2,18) = 11.06$, $p < 0.002$]. Post-hoc tests confirmed that the saline-treated rats' responding (mean

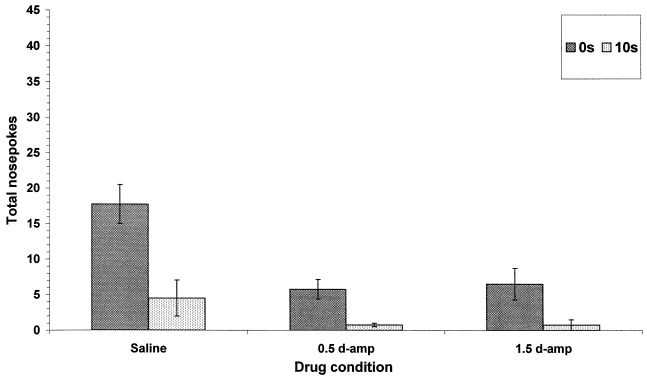

Figure 2 Mean overall nose pokes for conditioned stimulus extinction in Experiment 1b. 0 s = contiguously conditioned groups; 10 s = trace conditioned groups; 0.5 *d*-amp = groups previously treated with 0.5 mg/kg *d*-amphetamine; 1.5 *d*-amp = groups previously treated with 1.5 mg/kg *d*-amphetamine. Bars show 2 SEMs for approximate between-groups comparisons

= 11.13) was significantly greater [$t(14) = 2.20$, $p < 0.05$] compared to the high-dose *d*-amphetamine rats (mean = 3.63). The saline-treated rats also responded significantly more [$t(8) = 2.42$, $p < 0.05$] compared to the low-dose groups (mean = 3.25). There was no significant difference between the responses of the low-dose and those of the high-dose *d*-amphetamine-treated rats ($t < 1$).

However, there was no significant Trace by Drug interaction [$F(2,18) = 2.95$], and the reduction in responding produced under amphetamine did not depend on whether the rats were trace conditioned or not (Fig. 2).

Light background

Pre-background There was no effect of Drug or Trace–Drug interaction (both $F < 1$).

Background There was no effect of Drug or Trace–Drug interaction [maximum $F(2,18) = 1.62$]. However, throughout the background tests, the number of responses produced by the subjects was low (in fact close to zero), and there was probably a floor effect (the mean number of nose pokes in background extinction was 1.5, 0.125 and 0.75 in the in the groups previously treated with saline, low and high drug dose, respectively).

Experiment 2: effect of d*-amphetamine on the acquisition of conditioning*

Again, rats responded more to the CS in contiguous compared to trace conditioned groups and there was evidence that treatment with the higher dose of amphetamine reduced conditioning (taking drug effects on baseline responding into account). However, there was no detectable effect of amphetamine on reward collection. By contrast to the generally reduced responding that reflected impaired associative learning to the CS (and to the cues provided by the experimental chambers), in the ISI, low-dose amphetamine significantly increased the proportion of responses seen later in the trace interval.

Pre-experimental responding

There was no significant effect of Trace, Drug, or the interaction [maximum $F(2,39) = 1.64$]. Nor did any of these effects interact with Days [maximum $F(1,39) = 3.00$]. Thus, the groups were well-matched prior to conditioning.

On-the-baseline tests

Pre-CS There was no effect of Trace on responding immediately prior to CS presentations ($F < 1$) but there was some effect of Drug [$F(2,39) = 3.81$, $p < 0.04$]. This arose because the saline subjects (mean = 3.21) produced a significantly greater number of responses [$t(27) = 2.71$, $p < 0.02$] compared to the high-dose subjects (mean = 1.65). There were no significant differences between the other drug groups [maximum $t(30) = 1.66$]. There was no interaction between Drug and Trace [$F(2,39) = 2.59$]. There was a significant effect of Days [$F(7,287) = 4.02$, $p < 0.001$] but there was no consistency to the variation in responding over time and none of the interactions involving Days were significant [maximum $F(7,287) = 1.07$]. Thus, with the exception of the generally depressant effect of treatment with high-dose *d*-amphetamine, baseline level of responding between groups was similar prior to the presentation of the CS.

CS As predicted, there was a significant overall effect of Trace [$F(2,39) = 29.24$, $p < 0.001$] because contiguously conditioned rats nose poked more (mean = 13.22) compared to those conditioned over a trace interval (mean = 5.23). In addition, there was an overall effect of Drug [$F(2,39) = 10.84$, $p < 0.001$]. This arose because the high-dose *d*-amphetamine group (mean = 4.65) responded less during the CS presentations compared to the saline (mean = 13.33) and low-dose (mean = 9.44) treatment groups [minimum $t(27) = 2.06$, $p < 0.05$]. There was no significant difference in responding between the saline and the low-dose *d*-amphetamine group [$t(30) = 1.60$]. The depressed level of responding in the high-dose amphetamine treatment subjects would seem most likely to be due to non-specific side-effects of this treatment rather than any conditioning failure because this effect was also seen in the pre-CS. Moreover, there was no indication that this effect depended on the informativeness of the CS as the Trace by Drug interaction was insignificant.

The acquisition of the association between CS and food was shown by a main effect of Days [$F(3,119) = 15.74$, $p < 0.001$] and there was also a significant Days by Trace interaction [$F(3,119) = 11.78$, $p < 0.001$]. The interaction with Days arose because the difference between contiguously and trace conditioned rats was somewhat inconsistent over time. However, this difference was clearly significant from the fifth to the tenth and last day of conditioning [maximum $t(29) = 5.51$, $p < 0.02$]. However, none of the interactions involving Drug was significant [maximum $F(6,119) = 1.14$] and the effect of *d*-amphetamine was not differential by Trace or over time (Fig. 3).

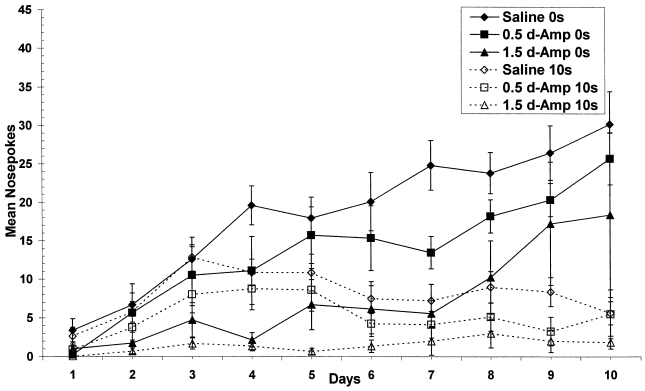

Figure 3 Mean nose pokes for conditioned stimulus acquisition over Days in Experiment 2. 0 s = contiguously conditioned groups; 10 s = trace conditioned groups; 0.5 *d*-amp = groups treated with 0.5 mg/kg *d*-amphetamine; 1.5 *d*-amp = groups treated with 1.5 mg/kg *d*-amphetamine. Bars show two standard errors of the mean for approximate between-groups comparisons

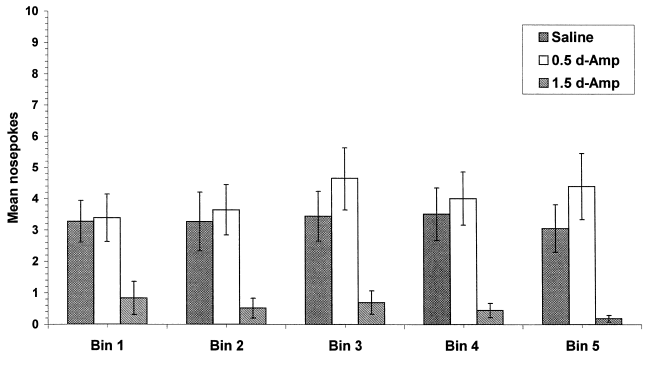

Figure 4 Mean overall nose pokes over five 2-s bins of the 10-s trace interval during the acquisition phase of Experiment 2. 0.5 *d*-amp = groups treated with 0.5 mg/kg *d*-amphetamine; 1.5 *d*-amp = groups treated with 1.5 mg/kg *d*-amphetamine. Bars show 2 SEMs for approximate between-groups comparisons

Although the drug effect on the pre-CS was overall small in magnitude, the above analyses were repeated with the Pre-CS as covariate. This produced the same pattern of results as described above. Overall, there was an effect of Trace [$F(1,38) = 45.13$, $p < 0.001$] and Drug [$F(2,38) = 6.22$, $p = 0.005$]. Again, there was no significant interaction between Trace and Drug [$F(2,38) = 1.74$]. As above, there was a significant main effect of Days [$F(9,342) = 4.44$, $p < 0.001$] and a significant interaction between Trace and Days [$F(9,342) = 11.94$, $p < 0.001$] but none of the interactions involving Drug was significant (both $F < 1$). Thus, the ANCOVA confirms that the effect of *d*-amphetamine was not differential by Trace or over time.

The non-specific effects of the drug treatment were small relative to the decrease in nose poking during the CS and the former provide no obvious account of the latter. This confirms that the depression in responding to the CS finds its most natural account in terms of an effect on associative learning.

Post-UCS There was no effect of Trace or Drug, nor any Trace by Drug interaction [maximum $F(2,39) = 1.87$]. As would be expected, responding during food deliveries did generally increase over time and statistically this was shown as a main effect of Days [$F(7,293) = 7.26$, $p < 0.001$], from day 1 (mean = 9.02) to day 10 (mean = 17.30). Such an effect could be associative, reflecting increased expectation of food, or non-associative, reflecting reduced anxiety in entering the magazine and consuming the sucrose pellet. However, none of the interactions involving Trace was significant [maximum $F(7,293) = 1.78$].

Trace bins There was an effect of Days [$F(3,64) = 4.30$, $p < 0.001$] because, as would be expected, responding within the trace increased over time. The overall effect of Bins was marginal [$F(4,76) = 2.27$, $p < 0.07$] but significant in the quadratic trend [$F(1,19) = 9.8$, $p < 0.01$], and there was an interaction between Days and Bins in the linear trend [$F(1,19) = 8.12$, $p = 0.01$] suggesting that the distribution of responding between the bins changed over the course of acquisition (as had been the case in Experiment 1a).

Trend analyses also showed a higher order interaction between Days, Bins and Drug [$F(2,19) = 4.51$, $p < 0.05$] and we conducted some additional analyses by week (of 5 experimental days) to examine how the pattern of responding within the trace changed over the course of conditioning. As would be expected, the Bins by Weeks interaction was also significant both overall [$F(4,76) = 2.60$, $p < 0.05$], and in the linear trend [$F(1,19) = 12.48$, $p < 0.005$]. This arose because although, in week 1, responding in subsequent bins was in no case significantly greater compared to that seen in bin 1 [maximum $t(21) = 1.41$], by week 2, responding was significantly greater in bins 3–5 [minimum $t(21) = 2.12$]. However, there was no sign of any interaction between Weeks, Bins and Drug, so any effect of the drug was consistent over the duration of testing.

The most important result was the overall effect of Drug [$F(2,19) = 4.73$, $p < 0.05$] and also a clear interaction between Bins and Drug [$F(8,684) = 2.74$, $p = 0.01$]. The main effect of Drug arose because the saline and low-dose-treated groups produced overall more responses than the high-dose-treated groups (Fig. 4). The depression in responding seen at the high-dose most likely arises because of the non-specific effects produced by this treatment, as was also seen in other response bins. Notably, non-specific effects were not an issue at the low dose that tended to increase responding and moreover affected the distribution of anticipatory responses within the trace interval. The interaction between Bins and Drug arose because whereas, in both the saline and high-dose group, responding in later bins was not significantly different from that seen in bin 1 [maximum $t(5) = 1.52$], in the low-dose group, responding was relatively greater in bins 3–5 [minimum $t(7) = 4.31$, $p < 0.05$].

Drug-free extinction tests

These confirmed that the effects on CS responding seen in acquisition

were most likely due to a reduction in associative learning under amphetamine. However, as in Experiment 1, the background tests were uninformative because of low response rates, and they are therefore not reported for Experiment 2.

Tone CS

Pre-CS There was no effect of Trace, Drug, or any Trace by Drug interaction [maximum $F(2,39) = 2.32$]. Thus, the experimental groups were well matched in terms of baseline response rates immediately before CS presentations.

CS There was a significant effect of Trace [$F(1,39) = 8.50$, $p < 0.01$]. This arose because the contiguously conditioned rats still produced a greater number of nose poke responses (mean = 6.17) compared to the trace-conditioned subjects (mean = 2.14). Moreover, the effect of (prior) Drug persisted in extinction [$F(2,39) = 16.07$, $p < 0.001$]. The saline-treated rats (mean = 9.25) produced a greater number of responses compared to the low- (mean = 1.81), or high-dose (mean = 0.92) groups [$t(17) = 3.46$, $p < 0.005$ and $t(16) = 3.96$, $p < 0.002$, respectively]. The number of responses produced by the two drug-treated groups did not differ significantly from each other [$t(25) = 1.21$]. This suggests that doses of *d*-amphetamine that either did (1.5 mg/kg) or did not (0.5 mg/kg) produce non-specific effects had the consistent effect of impairing associative learning (Fig. 5).

In addition, there was a significant Drug by Trace interaction [$F(2,39) = 4.21$, $p < 0.05$]. With respect to the saline and low-dose treatment groups, the contiguously conditioned responded significantly more compared to the trace-conditioned rats [$t(14) = 2.55$, $p < 0.03$ and $t(7) = 3.33$, $p < 0.02$], respectively. Within the high-dose treatment condition, contiguously conditioned were not significantly different from the trace-conditioned rats ($t < 1$). However, this pattern of effects was not of interest in that it was attributable to a 'floor effect' (response rates were just very low after prior treatment with the higher dose, see Fig. 5).

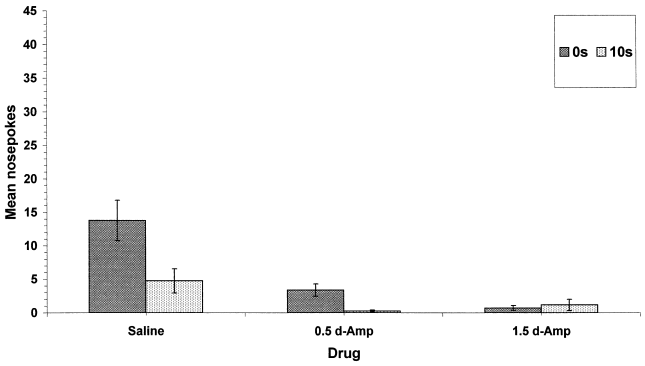

Figure 5 Mean overall nose pokes for conditioned stimulus extinction in Experiment 2. 0 s = contiguously conditioned groups; 10 s = trace conditioned groups; 0.5 *d*-amp = groups previously treated with 0.5 mg/kg *d*-amphetamine; 1.5 *d*-amp = groups previously treated with 1.5 mg/kg *d*-amphetamine. Bars show 2 SEMs for approximate between-groups comparisons

Discussion

Learning that a stimulus (e.g. noise) predicts events such as food is normally reduced when these events are separated in time. This effect was clearly seen here, irrespective of drug treatment. However, treatment with *d*-amphetamine was not simply ineffective in the present study. Irrespective of trace condition, amphetamine impaired both the expression (Experiment 1b) and acquisition (Experiment 2) of appetitive conditioning. By contrast to the general depression in the acquisition and expression of associative learning seen under amphetamine, the 0.5 mg/kg dose promoted the acquisition of anticipatory responses made later in the trace interval (in Experiment 2 but, again, not the expression of previous conditioning in Experiment 1b). This suggests a dissociable effect of this treatment on learning about the temporal relationship between CS and UCS.

Do baseline levels of activity or motivation confound interpretation of the results?

In all three experiments, the pre-conditioning measures demonstrated that groups were matched for baseline levels of nose poking before conditioning procedures. Subsequently, the conditioning procedure in use enabled us to assess the effects of amphetamine on the same baseline nose poke response used to assess the strength of the CS-UCS association. This meant that drug effects on response rates above and beyond those that reflected excitatory conditioning to the CS could be discounted by ANCOVA, where required. As well as this 'on-the baseline' test of associative learning, conditioning was also assessed 'off-the-baseline' in drug free extinction tests (in which drug effects on response rates could not be an issue).

Response rates naturally fell off during extinction, particularly in previously drug-treated groups. As well as providing further evidence of impaired acquisition of the association between CS and UCS, the particular fall off seen in drug-treated groups could (in part) reflect a state dependent effect because extinction tests were drug free. Nevertheless, the extinction test results showed the same pattern of effects, of the (previous) drug treatments, on (the expression of) associative learning.

Moreover, there was no evidence to suggest that floor effects might have masked any drug-induced increase in selective conditioning. The weaker conditioning to the target CS in the trace conditioned group and the weaker conditioning to the alternative background stimulus should have been sensitive to any increase in conditioning produced by amphetamine. Comparing across acquisition (where response rates were relatively high) and extinction (where response rates were naturally lower), we should have been able to detect drug effects in either direction.

Over and above general effects on response rates, it is possible that treatment with amphetamine would have a more specific effect on unconditioned responding to the food UCS (Killcross *et al*., 1994; Falzone *et al*., 2002), the level and nature of secondary reinforcement supported by the food UCS, or some combination of these factors. In extinction, the rats were tested drug-free and there can be no explanation of effects observed here in terms of acute effects of drug, athough, in principle, there could be carry over

effects from prior drug treatment. Moreover, if amphetamine were anorectic or produced a taste aversion to the pellets then the signal for food delivery would be expected to be less effective as an appetitive CS. The question is whether any such action provides the most likely account of effects observed here. Even the lower dose of *d*-amphetamine (0.5 mg/kg) is within the range that can produce conditioned taste aversion (Miller and Miller, 1983) and at the threshold where anorectic effects can be seen. On the other hand, *d*-amphetamine (0.3–1.6 mg/kg) can increase the conditioned reinforcing properties of stimuli associated with (delayed) food reward (Cardinal *et al*., 2000); and doses that increase locomotor behaviour can also increase consummatory behaviour (Grilly and Loveland, 2001).

In the present study, there was no direct evidence that an anorectic or aversive effect confounds interpretation of our results and some evidence that it did not. Drug-induced anorexia or taste aversion would be expected to have a differential (relatively bigger) effect on responding post-UCS than on responding to the CS. In fact, the differential effect that we observed was that amphetamine depressed responding to the CS, in the absence of any consistent depression of responding measured post-UCS in acquisition.

Conditioning to the trace and contiguous CS

There is behavioural evidence to suggest that treatment with *d*-amphetamine should generally enhance associative learning (Harmer and Phillips, 1998, 1999). If amphetamine has the effect of particularly increasing conditioning to less informative stimuli, this should be true regardless of whether they are rendered less informative through stimulus preexposure (in latent inhibition), the introduction of a trace interval or their continuous presence in the background (as was the case in the present study).

By contrast, we found that responding to the CS was reduced by amphetamine and furthermore conclude that this effect was associative rather than non-associative (motor or motivational), because the reduced responding in the 5-s CS bin presentation found no parallel immediately before CS presentation or after UCS deliveries. This conclusion derives further support from the fact that there was a comparable depression of responding to the CS in drug-free extinction. We could draw no distinction between the acquisition and extinction of associative learning with respect to the CS because this effect was seen in both Experiment 1b (in which the associations had already been acquired) and Experiment 2 (that tested drug effects on the acquisition of associations in animals that had not already been conditioned in this procedure).

This finding of reduced conditioning contrasts with the heightened conditioning that can be seen to a trace CS in an analogous aversive procedure (Norman and Cassaday, 2003). Appetitive and aversive stimuli interact differently with the dopamine system (Di Chiara *et al*., 1999) and it was difficult to assess the implication of the aversive conditioning results for trace conditioning in an appetitive procedure. However, we were able in this on-the-baseline appetitive procedure to measure (changes in) the distribution of responding over the trace interval between CS and UCS delivery. Thus, we had an additional test of conditioning over the trace interval that enabled us to examine (drug effects on) the animals' expectation of when food would be delivered.

Conditioned responding within the trace interval

Anticipatory responding was also demonstrated in the trace interval between CS and food delivery. In animals already conditioned, amphetamine simply reduced the expression of anticipatory responding in the same way that it did in response to the CS. However, when we examined the effect of amphetamine on the acquisition of anticipatory responding over the trace interval, it was found that this was increased by the low but not the high dose in use, and significantly so in the latter portion of the trace interval. The relative facilitation of later anticipatory responding in the trace interval produced by 0.5 mg/kg accentuates the effect seen to develop week by week and, moreover, contrasts with the general effect of this dose in reducing responding to the CS (whether trace or contiguously conditioned).

The introduction of an ISI in trace conditioning raises the possibility that stimulus offset plus some elapsed time may become an effective CS, hence, the tendency to respond later in the trace interval. However, there were no other indications that treatment with amphetamine could improve associative learning in these procedures.

Accordingly, we need some alternative explanation of the increase in later trace responding under low-dose amphetamine. A general increase in ISI responding could be mediated 'attentionally' through heightened overshadowing of the earlier presented CS by the intervening context in the ISI. However, without some reference to the passage of time, increased overshadowing would not account for the effect of amphetamine on the distribution rather than just the overall level of responding in the ISI. In any case, in other procedures, amphetamine reduces overshadowing (Tuathaigh and Moran, 2002).

We therefore suggest that the increase in responding towards the end of the trace interval reflects the distinction between amphetamine effects on whether and when to respond (Gallistel and Gibbon, 2000). Specifically, this pattern of effects could be produced through an effect on timing in that there is evidence that treatment with amphetamine speeds up the internal 'clock' (Buhusi and Meck, 2002). Such an effect on temporal discrimination is not relevant to the interpretation of amphetamine effects on responding to the CS because these were independent of the presence or absence of a trace interval.

Conditioning to the background stimulus

Animals normally learn relatively little about background stimuli because the general context does not reliably predict food delivery or the onset of foot shock. In Experiment 1b, conditioning to the experimental background stimulus (flashing lights presented for the duration of the session) was unaffected by treatment with amphetamine. However, generally low response rates, which could have been further reduced by state-dependent effect in groups previously treated with amphetamine, precluded further investigation of this effect in Experiment 2.

How best to account for reduced appetitive conditioning under amphetamine?

In appetitive procedures that are conducted over a number of days, rats are necessarily given a series of amphetamine injections. Prior repeated amphetamine injections have been found to enhance the acquisition of both excitatory (Harmer and Phillips, 1998) and inhibitory associations (Harmer and Phillips, 1999). Such carry-over effects raise the possibility that in our 'drug free' extinction test, rats' associative learning would nonetheless be under the influence of their prior drug treatment. However, if the observed effects were due to the cumulative effects of repeated injections and the development of sensitization then there should have been a shift in the effectiveness of the drug treatments over the course of acquisition. Specifically, the effect of amphetamine on associative learning should have depended on how far into the associative learning session the animal was. However, this was not the case in that the clear effects on the expression (Experiment 1b) and acquisition (Experiment 2) of associative learning was seen right from the start (confirmed by the absence of any interaction with Days). Moreover, the reduction in associative learning that we observed was not the predicted direction of effects and contrasts with earlier reports that amphetamine (pre-treatment) enhances associative learning (Harmer and Phillips, 1998, 1999).

The effect of the high dose observed in extinction could in principle have been mediated through a different (state-dependent) mechanism. However, the direction of effects observed was the same as that seen under drug in acquisition (see below).

Implications

In the present study, an uninformative predictor was provided by the trace CS and, on some accounts, such a stimulus would be expected to be functionally similar to that provided by a stimulus rendered uninformative through latent inhibition. Repeated exposure to a CS may result in the latter portions of the CS becoming ineffective and so equivalent to a time interval between CS offset and UCS delivery (DeVietti *et al*., 1987). Consistent with this functional similarity, there is some evidence that trace conditioning and latent inhibition depend on the same limbic structures (Solomon and Schaaf, 1986; Buchel *et al*., 1999). However, in these studies of appetitive conditioning, we found no evidence for heightened conditioning, either to the experimental background stimulus or the discrete CS, irrespective of trace condition. Thus, the uninformativeness of stimuli about subsequent events was neither a necessary nor sufficient condition for observing amphetamine effects on conditioning. Moreover, the observed effects were consistently in the direction of impaired conditioning. Low-dose amphetamine increased the acquisition of later responding within the ISI but, as discussed above, there was no evidence that this had an associative basis.

Specifically, amphetamine here influenced when to respond for food reward (the increased responding towards the end of the trace interval under low-dose amphetamine). There was no evidence for disinhibited responding elsewhere in the session and this effect in the trace was only significant in its latter portion, and probably arose because of an effect on the internal clock (Gallistel and Gibbon, 2000; Buhusi and Meck, 2002). That an effect on timing should be dissociable is consistent with behavioural evidence supporting a model of conditioning in which the associative strength accruing to a CS is orthogonal to the temporal information encoded for that stimulus (Brown *et al*., 1997). In other words, although the trace conditioned CS itself produced little excitatory responding, it nevertheless conveyed information about when food delivery was imminent and this effect (of learning 'when to expect' food) was accentuated under low-dose amphetamine (in Experiment 2).

In terms of the role of dopamine in associative learning (Waelti *et al*., 2001) and its disorder in drug addiction (Di Chiara, 1999), the present study suggests the hypothesis that the appetitive aspects of the UCS provided by drug delivery should enter less readily into association with stimuli provided by the drug-taking environment (compared to the aversive aspects of the UCS provided by drug delivery; Norman and Cassaday, 2003).

Finally, although systemic drug administration is a good initial approach, these findings should ultimately be followed up with studies of the effects of local brain infusions for greater neural and neurochemical precision.

Acknowledgements

These studies were supported by a Wellcome Trust project grant (reference 055330). We thank Andy Smith and Carl Espin for technical support.

References

Brown B L, Hemmes N S, Cabeza de Vaca S (1997) Timing of the CS-US interval by pigeons in trace and delay autoshaping. QJEPB *50*: 40–53

Buchel C, Dolan R, Armony J, Friston K (1999) Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event related functional magnetic resonance imaging. J Neurosci *19*: 10869–10876

Buhusi C V, Meck W H (2002) Differential effects of methamphetamine and haloperidol on the control of an internal clock. Behav Neurosci *116*: 291–297

Cardinal R N, Robbins T W, Everitt B J (2000) The effects of d-amphetamine, chlordiazepoxide, α-flupenthixol and behavioural manipulations on choice of signalled and unsignalled delayed reinforcement in rats. Psychopharmacology *152*: 362–375

Crider A, Solomon P R, McMahon M A (1982) Disruption of selective attention in the rat following chronic D-amphetamine administration: relationship to schizophrenic attention disorder. Biol Psychiatry *17*: 351–361

Dalley J W, Chudasama Y, Theobald D E, Pettifer C L, Fletcher C M, Robbins T W (2002) Nucleus accumbens dopamine and discriminated approach learning: interactive effects of 6-hydroxydopamine lesions and systemic apomorphine administration. Psychopharmacology *161*: 425–433

Di Chiara G (1999) Drug addiction as dopamine-dependent associative learning disorder. Eur J Pharmacology *375* (Suppl): 13–30

DeVietti T L, Bauste R L, Nutt G, Barrett O V, Daly K, Petree A D (1987) Latent inhibition: a trace conditioning phenomenon? Learning Motivat *18*: 185–201

Ellison G D, Eison M S (1983) Continuous amphetamine intoxication: an animal model of acute psychotic episode. Psychol Med *13*: 751–761

Falzone T L, Gelman D M, Young J I, Grandy D K, Low M J, Rubinstein M (2002) Absence of dopamine D4 receptors results in enhanced reactivity to unconditioned, but not conditioned, fear. Eur J Neurosci *15*: 158–164

Feenstra M G P, Vogel M, Botterblom M H A, Joosten R N J M A, de Bruin J P C (2001) Dopamine and noradrenaline efflux in the rat prefrontal cortex after classical aversive conditioning to an auditory cue. Eur J Neurosci *13*: 1051–1054

Gallistel C R, Gibbon J (2000) Time, rate, and conditioning. Psychol Rev *107*: 289–344

Gray J A, Moran P M, Grigoryan G, Peters, S L, Young A M J, Joseph M H (1997) Latent inhibition: the nucleus accumbens connection revisited. Behav Brain Res *88*: 27–34

Gray N S, Pickering A D, Hemsley D R, Dawling S, Gray J A (1992) Abolition of latent inhibition by a single 5 mg dose of D-amphetamine in man. Psychopharmacology *107*: 425–430

Grilly D M, Loveland A (2001) What is a 'low dose' of d-amphetamine for inducing behavioural effects in laboratory rats? Psychopharmacology *153*: 155–169

Harmer C J, Phillips G D (1998) Enhanced appetitive conditioning following repeated pre-treatment with d-amphetamine. Behav Pharmacol *9*: 299–308

Harmer C J, Phillips G D (1999) Enhanced conditioned inhibition following repeated pre-treatment with d-amphetamine. Psychopharmacology *142*: 120–131

Jones S H, Hemsley D, Ball S, Serra A (1997) Disruption of the Kamin blocking effect in schizophrenia and in normal subjects following amphetamine. Behav Brain Res *88*: 103–114

Joseph M H, Peters S L, Moran P M, Grigoryan G A, Young A M J, Gray J A (2000) Modulation of latent inhibition in the rat by altered dopamine transmission in the nucleus accumbens at the time of conditioning. Neuroscience *101*: 921–930

Kamin L J (1965) Temporal and intensity characteristics of the conditioned stimulus. In Prokasy W F (ed.), Classical conditioning: a symposium. Appleton-Century-Crofts, New York

Killcross A S, Dickinson A, Robbins T W (1994) Amphetamine-induced disruptions of latent inhibition are reinforcer mediated: implications for animal models of schizophrenic attentional dysfunction. Psychopharmacology *115*: 185–195

Kumari V, Cotter P A, Mulligan O F, Checkley S A, Gray N S, Hemsley D R, Thornton J C, Corr P J, Toone B K, Gray J A (1999) Effects of D-amphetamine and haloperidol on latent inhibition in healthy male volunteers. J Psychopharmacol *13*: 398–405

Miller D B, Miller L L (1983) Bupropion, d-amphetamine, and amitriptyline-induced conditioned taste aversion in rats: dose effects. Pharmacol Biochem Behav *18*: 737–740

Norman C, Cassaday H J (2003) Amphetamine increases aversive conditioning to diffuse contextual stimuli and to a discrete trace stimulus when conditioned at higher footshock intensity. J Psychopharmacol *17*: 67–76

Ohad D, Lubow R E, Weiner I, Feldon J (1987) The effects of amphetamine on blocking. Psychobiology *15*: 137–143

O'Tuathaigh C M P, Moran P (2002). Evidence for dopamine D1 receptor involvement in the stimulus selection task. Overshadowing in the rat. Psychopharmacology *162*: 225–231

Rawlins J N P, Tanner J (1998) The effects of hippocampal aspiration lesions on conditioning to the CS and to a background stimulus in trace conditioned suppression. Behav Brain Res *91*: 61–72

Solomon P, Schaaf E (1986) Hippocampus and trace conditioning of the rabbit's classically conditioned nictating membrane response. Behav Neurosci *100*: 729–744

Solomon P R, Crider A, Winkelman J W, Turi A, Kamer R M, Kaplan L J (1981) Disrupted latent inhibition in the rat with chronic amphetamine or haloperidol-induced supersensitivity: relationship to schizophrenic attention disorder. Biol Psychiatry *17*: 743–756

Tanner J, Rawlins J N P, Mellanby J H (1987) Manipulation of CS-US conditional probability and of the CS-US trace interval on conditioning to the CS and to a background stimulus in a CER situation. Learning Motivat *18*: 371–391

Tsaltas E, Schugens M M, Gray J A (1989) Effects of lesions of the dorsal noradrenergic bundle on conditioned suppression to a CS and to a contextual background stimulus. Behav Brain Res *31*: 243–256

Waelti P, Dickinson A, Schultz W (2001) Dopamine responses comply with basic assumptions of formal learning theory. Nature *412*: 43–48

Warburton E C, Mitchell S N, Joseph M H (1996) Calcium dependent dopamine release in the rat nucleus accumbens following amphetamine challenge: implications for the disruption of latent inhibition. Behav Pharmacol *7*: 119–129

Weiner I (1990) Neural substrates of latent inhibition: the switching model. Psychol Bull *108*: 442–461

Weiner I (2003) The 'two-headed' latent inhibition model of schizophrenia: modeling positive and negative symptoms and their treatment. Psychopharmacology *169*: 257–297

Weiner I, Feldon J (1997) The switching model of latent inhibition: an update of neural substrates. Behav Brain Res *88*: 11–25

Weiner I, Lubow R E, Feldon J (1981) Chronic amphetamine and latent inhibition. Behav Brain Res *2*: 285–286

Weiner I, Israeli-Telerant A, Feldon J (1987) Latent inhibition is not affected by acute or chronic administration of 6 mg/kg dl-amphetamine. Psychopharmacology *91*: 345–351

Weiner I, Lubow R E, Feldon J (1988) Disruption of latent inhibition by acute administration of low doses of amphetamine. Pharmacol Biochem Behav *30*: 871–878

Young A M J, Ahier R G, Upton R L, Joseph M H, Gray J A (1998) Increased extracellular dopamine in the nucleus accumbens of the rat during associative learning of neutral stimuli. Neuroscience *83*: 1175–1183