Original Paper

Psychopharm

Journal of Psychopharmacology
00(0) (2007) 1–11

ISSN 0269-8811
SAGE Publications
Los Angeles, London,
New Delhi and Singapore
10.1177/0269881107083842

Methylphenidate and nicotine focus responding to an informative discrete CS over successive sessions of appetitive conditioning

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Abstract

Methylphenidate (MP) and nicotine would be expected to improve associative learning, though previous evidence suggests that they should reduce the selectivity with which associations are formed. Here we tested their effects on learning the association between a conditioned stimulus (CS) and food (unconditioned stimulus, UCS) in male Wistar rats. The UCS was delivered immediately (0 s) following CS offset or after a 10 s trace. In addition to the measures of discrete CS conditioning, contextual and trace responding was measured in the inter-trial- and the inter-stimulus-interval, respectively. In all cases, conditioning was measured as nose poking for food. Both MP and nicotine improved the acquisition of discrete cue conditioning. Acquisition was accelerated (compared to saline) under 5 but not 1 mg/kg MP and 0.6, but not 0.4 mg/kg nicotine. In each case, this effect was observed in 0 s but not 10 s conditioned groups. For comparison, some earlier published data obtained following the same procedure with D-amphetamine were re-analysed in the same way. Amphetamine similarly improved conditioning in the 0 s group, in this case at 0.5, but not 1.5 mg/kg. Thus three different dopamine agonists increased the ability to focus responding to CS presentations over successive sessions of appetitive acquisition.

Keywords
methylphenidate, nicotine, trace interval, appetitive conditioning, rat

Introduction

The amphetamine model of schizophrenia (Ellison and Eison, 1983) has prompted considerable interest in how dopamine (DA) agonists influence salience processing in animal learning tasks (Gray *et al.*, 1991, 1997; Kapur, 2003, 2004). It is by now very well-established that both amphetamine (Solomon *et al.*, 1981; Weiner *et al.*, 1981, 1988; Gray *et al.*, 1992; Kumari *et al.*, 1999) and nicotine (Joseph *et al.*, 1993; Gray *et al.*, 1994; Young *et al.*, 2005) can increase conditioning to poor predictors of reinforcement in latent inhibition (LI) tasks, in which stimuli are earlier established as irrelevant. Similarly, amphetamine produces 'over-conditioning' to redundant stimuli that should have low salience in the blocking procedure (e.g., Crider *et al.*, 1982; Ohad *et al.*, 1987; Jones *et al.*, 1997). Such aberrant salience processing is likely to contribute to a number of disorders, not just schizophrenia, in which attentional processes are disordered and the brain DA system dysfunctional. The present study extends the study of salience processing in a procedure that similarly presents weakened predictors to examine the effects of nicotine and methylphenidate (MP), which have common actions on the DA system.

The effects of MP and nicotine in animal learning tasks of this kind have been little investigated to date. This is surprising since amphetamine, MP and nicotine share a number of properties: all are stimulants and increase extracellular DA in the nucleus accumbens (n.acc) and striatum, albeit by different mechanisms (Chiueh and Moore, 1975a, b; Hurd and Ungerstedt, 1989; Nissell *et al.*, 1994; Giros *et al.*, 1996; Fu *et al.*, 2000; Kuczenski and Segal, 2001; Balfour, 2004). In the present study, we therefore compared the effects of MP and nicotine in the same associative learning task that we have previously used to examine the effects of DA agonists (Nayak and Cassaday, 2003; Norman and Cassaday, 2003; Kantini *et al.*, 2004), the antagonist haloperidol (Cassaday *et al.*, 2005a), and n.acc lesions (Cassaday *et al.*, 2005b). In this task, the conditioned stimulus (CS) is rendered less salient through the introduction of a trace interval (Kamin, 1965) and we compare learning

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about the trace CS relative to a more salient CS that is immediately followed by the unconditioned stimulus (UCS).

Owing to their common action on the brain DA system, the use of amphetamine and MP for attention deficit hyperactivity disorder (ADHD) is well-established (Gillberg *et al.*, 1997; Solanto, 2000; Fone and Nutt, 2005). MP is increasingly the preferred treatment because of its low abuse potential. For example, MP penetrates the brain more slowly after oral administration and longer-acting formulations of MP are now available to provide slower regulated release during the day (Fone and Nutt, 2005). The reduced abuse potential of MP may also be related to its different profile of action on the DA transporter that results in reduced extracellular availability of DA relative to that typically seen after treatment with amphetamine (see below). Thus the prescription of MP for ADHD (and other disorders) has increased dramatically over recent years (see Biederman and Faraone, 2005). Recently, nicotine has been reported to improve core ADHD symptoms and has been advocated as a potential treatment (Levin *et al.*, 1996; Bekker *et al.*, 2005; Gehricke *et al.*, 2006).

Previously, in an aversive procedure, MP increased conditioning to trace CS, as well as to contextual cues (Horsley and Cassaday, 2007), and this action was similar to that of amphetamine (Norman and Cassaday, 2003). In the case of nicotine, as might be expected given that this drug also stimulates the DA system, there is similarly evidence for increased conditioning over the trace interval in a fear motivated procedure (Gould *et al.*, 2004).

We therefore test the prediction that MP and nicotine should similarly promote conditioning to cues with reduced salience in an appetitive trace conditioning procedure. The appetitive procedure we use enables us to track drug effects on the course of acquisition on-the-baseline and also to measure effects on unconditioned responding for food reward. Owing to the fact that responding to the CS can underestimate conditioning in trace groups, we also examined responding within the inter-stimulus-interval (ISI), that is, during the 10 s trace between CS offset and sucrose delivery, to see whether treatment with MP or nicotine might affect the distribution of anticipatory responding, as was the case under amphetamine (Kantini *et al.*, 2004). More general effects on contextual conditioning can in principle be measured as nose-poke responding in the inter-trial-interval (ITI), though this measure is inevitably confounded with nonspecific effects on response rates.

Appetitive studies are important to establish the generality of observed effects in terms of learning motivated in different ways, because in studies with amphetamine (Norman and Cassaday, 2003; Kantini *et al.*, 2004) and lesions to the brain DA system (Cassaday *et al.,* 2005b), effects in appetitive and aversive procedures have not been equivalent. In part, such differences may arise from the effects of DA treatments on the level of motor responding. For example, we earlier reported that amphetamine not only depressed acquisition, but also the expression of earlier acquired appetitive conditioning (Kantini *et al*., 2004). Therefore, in the present study, we assessed conditioning to the discrete CS as a percentage of responding in the remainder of the session, to allow for any such nonselective effects.

In Experiment 1, we tested two doses of MP: 1 and 5 mg/kg. These were exactly the doses of MP shown to be effective in an aversive variant of the procedure (Horsley and Cassaday, 2007) and based on earlier published findings (Brandon *et al.*, 2001). In our aversive procedure both doses MP (1 and 5 mg/kg sc) increased learning about the trace conditioned CS, as well as the contextual cues. Similar effects have been reported under amphetamine (Norman and Cassaday, 2003) and nicotine (Gould *et al.*, 2004), again in aversive procedures.

In Experiment 2, we tested two doses of nicotine: 0.4 and 0.6 mg/kg. The nicotine doses were based on their actions in aversively motivated LI (Joseph *et al.*, 1993; Gray *et al.*, 1994; Rochford *et al.*, 1996; Gould *et al.*, 2001; Young *et al.*, 2005). In the selective learning task provided by LI, the normal effect of stimulus pre-exposure in reducing later learning is abolished by treatment with amphetamine (Solomon *et al.*, 1981; Weiner *et al.*, 1981, 1988; Gray *et al.*, 1992; Kumari *et al.*, 1999).

In addition to its action on DA, nicotine has other actions too (as do MP and amphetamine, see below) for example, due to its stimulation of acetylcholine receptors (Wonnacott *et al.*, 1989). However, nicotine and MP, like amphetamine, have a shared action on DA function in n.acc. Nicotine increases n.acc DA function via an action at cell bodies in the VTA (Nissell *et al.*, 1994; Balfour 2004; Fu *et al.*, 2000). Consistent with a key role for n.acc DA in mediating its attentional learning effects, the abolition of LI otherwise produced with systemic nicotine at 0.6 mg/kg is reversed by DA antagonists injected directly into n.acc (Young *et al.*, 2005). The lower of the MP doses we used (1 mg/kg) is the minimum effective to increase extracellular DA in n.acc (0.5 mg/kg was below threshold, Kuczenski and Segal, 2001). Our maximum dose of MP (5 mg/kg) was used (in comparison with 1 mg/kg) because doses below 5 mg/kg are considered low and comparable to human clinical doses (Brandon *et al.*, 2001; Gainetdinov *et al.*, 1998; Gerasimov *et al.*, 2000).

Methods

All procedures were carried out in accordance with the UK Animals Scientific Procedures Act 1986, Project Licence number PPL 40/2648.

Animals

All animals were caged in pairs on a 12:12 h light/dark cycle (lights on 08.00 to 20.00 h) and handled during the first two weeks after arrival in the laboratory, in each case for on average 10 min per day, on a total of seven days during the two week settling period. All training and testing took place during the light phase (between 09.00 and 17.00 h). Both experiments used 48 male Wistar rats (Charles Rivers, UK). During this time, water was available *ad lib* and rats were fed a maintenance ration of at least 15–20 g per rat. In line with the requirements of the Home Office Licence, this ration was adjusted as necessary to allow for healthy weight gain and then to stabilize weights in those over 400 g.

Each set of rats had previously participated in an aversive trace conditioning experiment testing effects of the same drugs (MP, nicotine). In each case, there was two a week gap between

the previous experiment and the start of the experiments presented here. This is continuous use to compare the effects in aversive and appetitive procedures, as previously reported (Nayak and Cassaday, 2003; Cassaday *et al.*, 2005b). Allocation to groups was counterbalanced for previous behavioural experience but kept within the same drug condition. The single prior treatment with relatively low dose MP is unlikely to result in sensitization on this schedule (Crawford *et al.*, 1998; McNamara *et al.*, 1993).

Then to motivate appetitive responding, food in the home cage was restricted to 5 g/100 g rat body weight. This basic ration was adjusted (up to a maximum of 20 g per rat per day) to allow further weight gain in rats of below average weight. Water was freely available in the home cage. Weights were in range 314–412 g (Experiment 1) and 308–465 g (Experiment 2) at the start of food deprivation.

Drugs

MP hydrochloride (Sigma Aldrich, Dorset, UK) was dissolved in physiological saline and injected in 1 mL/kg body weight, at doses 1 and 5 mg/kg. Drug treatments were s.c. in for the first five days of Experiment 1. At this point in the experimental schedule there was some skin reaction in rats treated with the higher dose MP. Under veterinary advice, we therefore, switched to the i.p. route of administration.

Nicotine doses were calculated as the free base from approximately 35% of the salt: (−) –nicotine di tartrate (Sigma Aldrich, Dorset). This was dissolved in physiological saline and neutralized to pH 7 with NaOH. Nicotine was then injected in 1 mL/kg body weight, at the following doses expressed as the free base: 0.4 and 0.6 mg/kg.

In both experiments, rats were injected according to the same schedule each day, 15 min prior to each conditioning session.

Apparatus Experimental testing was conducted within a set of six fully automated ventilated conditioning chambers, housed within sound-attenuating cases containing ventilation fan (Cambridge Cognition, Cambridge, UK). 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 (that were not in use) and three stimulus lights. A loudspeaker for the presentation of auditory stimuli was set in the roof. The food magazine (recessed in a side wall of each of the chambers) was constantly illuminated whenever food was available. Access to the magazine was via a magazine flap. Nose pokes were recorded by the breaking of the photo beam within the food magazine. The UCS consisted of two 45 mg sucrose pellets dispensed serially into the magazine (Formula F, Noyes Precision Food, New Hampshire, UK).

In both experiments, two stimuli were available as potential predictors of food delivery. The target stimulus was in each case a noise CS (mixed frequency), presented via a loudspeaker inset on the roof of the chamber, set at 75 dB including background noise (e.g., from ventilating fans) and of 5 s duration. The experimental background stimulus was provided by three wall mounted stimulus lights and the house light flashing on (0.5 s) and off (0.5 s), continuously throughout the conditioning session.

Procedures Allocation to conditioning groups was counterbalanced across the six conditioning chambers. Acquisition was then conducted over 10 days. On each day there were 10 pairings of noise CS and food presented at 10 or 0 s trace.

Pre-conditioning

There were three days shaping to accustom rats to eating from the magazine. These gave access to a preload of 10 reward pellets. The tray flap door was wedged open with reward pellets on day 1, with an additional 5 rewards delivered over 5 min, to familiarize rats with the food deliveries. Rats that did not initially eat on day 1 were given additional shaping at the end of the session. On each of days 2 and 3, there were 10 unsignalled rewards in 10 min, delivered on a variable interval around 3 min. The tray flaps were closed on days 2 and 3 so the rats were required to nose poke the door open to collect food. The total number of nose pokes was recorded and the average number of nose pokes on days 2 and 3 was analysed to check for pre-existing differences in response rates. No experimental stimuli were presented in this phase.

Conditioning

Conditioning consisted of 10 signalled rewards presented over 30 min. Depending on the experimental group, the reward (UCS) was delivered immediately after CS offset (in the 0 s group) or 10 s after CS offset (in the trace group). The UCS deliveries were programmed to occur independently of any nose poke conditioned response (CR). Conditioning trials were presented throughout the 30 min session, on a variable interval, with the constraint that the ITI in both 0 and 10 s conditioned groups was at least 1.5 times longer than the ISI length. The ISI added 100 s to the overall duration of the session for 10 s trace conditioned groups. Thus the minimum ITI was 15 s and the average ITI was 150 s, for both sorts of conditioning. Throughout the 30 min of acquisition, the background stimulus (flashing lights) was presented continuously. This continuous presentation also encompassed the 10 s ISI, where applicable.

The dependent variables were the number of nose pokes in the following response bins: 5 s prior to the CS (pre-CS responding); during the 5 s of the CS (CS responding); during the 10 s trace interval between CS and UCS, where applicable (ISI responding); 5 s after the delivery of the UCS in acquisition (UCS responding); and in the remainder of the session not included in the aforementioned response bins (ITI responding). The measure of ITI responding excluded responses made in the ISI in trace-conditioned groups.

Design and analysis In both experiments, there were six experimental groups run in a 3 × 2 factorial design. The between subject factors were Drug (at levels saline, 1 and 5 mg/kg MP) and Trace (at levels 0 and 10 s), and to assess effects over the course of acquisition, there was a repeated measures factor of Days. For Experiment 1, there was also a Replication factor because of the change in injection route required after day 5. To anticipate, the change in

injection route produced an unexpected shift in responding in a number of response bins, as well as in the selective learning measure. All subsequent analyses of Experiment 1 were therefore, restricted to the first five days of acquisition. Experiment 1 analyses exclude 1 rat from the 5 mg/kg MP (0 s conditioning) group, which did not respond at all during the first conditioning session, did not respond to collect reward for the first two days, and subsequently conditioned very poorly. In Experiment 2, there was no Replication factor to consider and analyses are based on the full 10 days of conditioning.

The dependent variable for pre-CS, CS, UCS and ITI responding was in each case the number of nose pokes into the food magazine. The dependent variable to show selective conditioning to the CS over and above that seen in the remainder of the session was CS responding expressed as a percentage of responding seen overall in the experimental session, excluding the ISI where applicable. This was important to correct for day-by-day fluctuation in overall responding, particularly in Experiment 2.

To anticipate, the results of both experiments showed that the three-way interaction between Drug, Trace and Days for the dependent variable of interest, percentage CS responding, was significant in the linear trend. We therefore followed up with contrast analyses to compare the differential rates of linear increase in learning over trials in different drug conditions in the 0 and 10 s groups in each experiment (Abelson and Prentice, 1997). Figures 1, 2 and 4 show some departure from linearity in the acquisition function under nicotine and amphetamine, but differential curvilinear trends would have to be estimated separately for each experiment. Given the moderate deviations from linearity observed here and the moderately large standard errors about the mean, we have applied the same linear contrasts in each case (Abelson and Prentice, 1997).

In the trace group, the responding of the animals during the 10 s trace between CS offset and sucrose delivery was also tested for any effects of drug treatments. The response period was broken down into two second bins of time and analysed using a $3 \times 5 \times 5$ (Experiment 1) or a $3 \times 5 \times 10$ (Experiment 2) repeated measures ANOVA, with Bins (5) and Days (5 or 10, respectively), as repeated measures factors.

Results

Experiment 1: the effects of MP on appetitive trace conditioning

Effect of replication The need to change the route of drug administration on the 6th day disrupted the course of acquisition. There were significant interactions between Replication and Days on all the dependent variables: pre-CS, CS, UCS, ITI responding and percentage CS responding [minimum F (4,164) = 3.93, $P < 0.005$]. In addition, there were significant three-way interactions between Replication, Days and Trace, both on CS and UCS responding, as well as percentage CS responding [minimum F (4,164) = 2.90, $P < 0.05$]. The numerous interactions with Replication are consistent with a generally disruptive effect of changing the route of administration, perhaps, related with the differences in the bioavailability of i.p. versus s.c. MP in rats (Gerasimov *et al.*, 2000).

Critically, in terms of a disruptive effect on selective learning, there were significant interactions between Replication, Days, Trace and Drug [minimum F (8,164) = 2.18, $P < 0.05$] on both

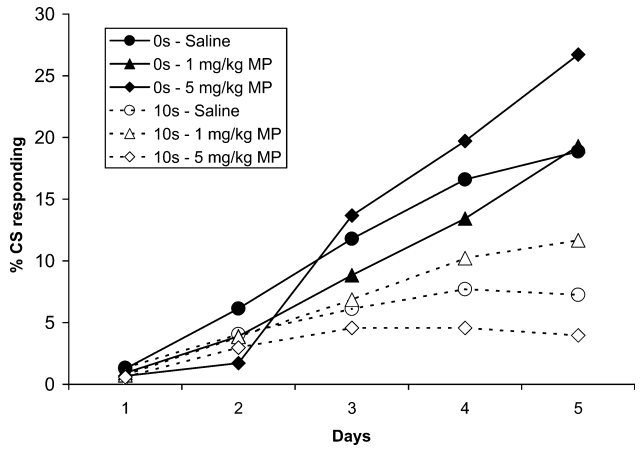

Figure 1 Experiment 1 CS acquisition under MP, measured as magazine entries during CS presentations and expressed as a percentage of responding seen in the remainder of the session. CS previously paired with food deliveries either at 0 s (solid lines) or at a 10 s trace (broken lines). Key gives symbols that denote each drug condition: saline, 1 mg/kg and 5 mg/kg MP. Error bars show two standard errors of the mean for approximate between groups comparisons.

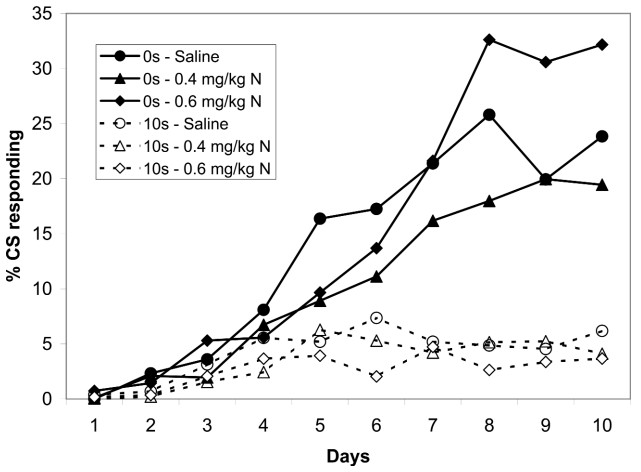

Figure 2 Experiment 2 CS acquisition under nicotine, measured as magazine entries during CS presentations and expressed as a percentage of responding seen in the remainder of the session. CS previously paired with food deliveries either at 0 s (solid lines) or at a 10 s trace (broken lines). Key gives symbols that denote each drug condition: saline, 0.4 mg/kg and 0.6 mg/kg nicotine. Error bars show two standard errors of the mean for approximate between groups comparisons.

UCS and percentage CS responding. This means that the effects of MP on the course of acquisition, and how these effects differed in trace and 0 s conditioned-groups, were altered by the necessary change to the route of drug administration. Accordingly, as acquisition was relatively rapid in this experiment, all subsequent analyses are restricted to the first five days of conditioning.

Mean responding in pre-CS and UCS bins, as well as in the ITI, for the first five days of acquisition are shown in Table 1.

Pre-CS There was only a significant effect of Days [F (4,164) = 4.92, p = 0.001], arising because of non-systematic fluctuation in responding from one day to the next (Table 1a). There were no other main effects or interactions [maximum F (8,164) = 1.63].

UCS Responding in the UCS period increased over the course of acquisition (Table 1b), so again there was a main effect of Days [F (4,164) = 34.27, $P < 0.001$]. No other effects or interactions were significant [maximum F (4,164) = 1.99].

ITI In contrast, responding in the remainder of the session generally reduced (Table 1c), shown statistically as a main effect of Days [F (4,164) = 11.53, $P < 0.001$]. No other effects or interactions were significant [maximum F (1,41) = 2.02].

Table 1 Mean nose poking over five days of conditioning in the 5 s before CS presentations (pre-CS, 1a) in the 5 s after food deliveries (UCS, 1b) and in the variable inter-trial-interval (ITI, 1c) shown after treatment with saline or methylphenidate (MP) and by trace condition (0 or 10 s)

Trace	0 s			10 s		
Drug	Saline	1 mg/kg MP	5 mg/kg MP	Saline	1 mg/kg MP	5 mg/kg MP
a: Pre-CS days						
1	3.13	1.63	4.00	2.88	3.63	4.13
2	3.63	0.75	2.57	2.75	3.25	5.00
3	2.75	2.00	0.71	1.50	2.38	2.88
4	4.00	1.50	1.00	2.00	1.75	2.38
5	1.13	1.25	1.14	3.00	2.50	1.13
b: UCS days						
1	5.63	4.13	7.57	10.38	9.13	7.00
2	13.50	9.50	13.14	16.75	16.50	13.00
3	16.38	15.50	15.00	18.88	17.75	13.75
4	16.88	18.38	17.57	16.50	15.88	16.50
5	13.63	16.75	15.43	19.13	18.00	17.25
c: ITI days						
1	108.00	68.50	144.29	112.50	139.63	144.75
2	116.25	53.88	106.00	115.88	114.75	147.25
3	81.00	70.00	52.86	86.25	94.88	100.38
4	90.75	51.50	47.43	68.38	87.13	100.38
5	70.25	52.25	47.00	73.13	83.88	71.75

Percentage CS responding In addition to the clear effects of Days and Days by Trace interaction that show overall acquisition and the effectiveness of the ISI in reducing conditioning [Fs (4,164) = 72.69 and 19.97, respectively, both $P < 0.001$], there was a Trace by Drug interaction, both overall [F (2,41) = 3.16, $P = 0.05$] and in interaction with Days [F (8,164) = 2.71, $P < 0.01$]. Figure 1 suggests that the difference between trace and 0 s conditioned groups was accentuated by MP at 5 mg/kg. In fact, on t-test analysis, in neither 0 s nor trace-conditioned rats was there any significant difference in responding on any day under 5 mg/kg MP relative to the corresponding saline groups [maximum t(14) = 1.89]. Nevertheless, the fact that the three-way interaction (Drug by Trace by Days) was also significant in the linear trend [F (2,41) = 4.97, $P < 0.05$] means that MP affected the course of appetitive acquisition differently in trace and 0 s conditioned rats. Contrast analyses of drug effects on acquisition curves were conducted within each behavioural (i.e., 0 s versus trace group). In the 0 s group, the rate of acquisition under 5 mg/kg MP was significantly different from that seen under saline [F (1,150) = 7.49, $P < 0.01$]. No other comparisons in the 0 or 10 s groups were significant [maximum F = 2.18].

ISI 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). Given the disruption caused by the change in injection route it was only appropriate to examine the first five days. There was a significant main effect of Days [F (4,336) = 9.84, $P < 0.001$]. However, at this stage of acquisition, there were no effects involving Bins (reflecting the distribution of responding within the trace interval) or of Drug thereon [maximum F (8,336) = 1.49].

Experiment 2: the effects of nicotine on appetitive trace conditioning

Mean responding in pre-CS and UCS bins, as well as in the ITI, over the course of acquisition are shown in Table 2.

Pre-CS There was an effect of Days [F (9,369) = 3.70, $P < 0.001$], as well as a significant Days by Drug interaction [F (18,369) = 1.93, $P < 0.05$], reflecting nonsystematic fluctuation in baseline responding (Table 2a). No other effects or interactions were significant [all Fs < 1].

UCS There was an effect of Days [F (9,369) = 40.42, $P < 0.001$] as UCS responding generally increased over days (Table 2b). No other effects or interactions were significant [maximum F (2,41) = 2.15].

ITI Again there was an effect of Days [F (9,369) = 11.57, $P < 0.001$], as well as a significant Days by Drug interaction [F (18,369) = 2.05, $P < 0.01$], due to nonsystematic fluctuation in baseline responding (Table 2c). No other effects or interactions were found [maximum F (2,41) = 1.52].

Table 2 Mean nose poking over 10 days of conditioning in the 5 s before CS presentations (pre-CS, a) in the 5 s after food deliveries (UCS, b) and in the variable inter-trial-interval (ITI, c) shown after treatment with saline or nicotine (N) and by trace condition (0 or 10 s)

Trace	0 s			10 s		
Drug	Saline	0.4 mg/kg N	0.6 mg/kg N	Saline	0.4 mg/kg N	0.6 mg/kg N
a: Pre-Cs days						
1	1.63	1.50	2.38	2.14	0.38	1.38
2	1.50	3.88	3.13	3.14	3.13	3.00
3	1.38	3.63	1.63	3.14	3.50	1.63
4	1.50	3.75	1.50	2.71	4.50	1.50
5	0.38	2.38	2.38	2.43	2.25	2.13
6	0.63	1.88	2.75	2.00	1.13	1.00
7	1.63	1.25	0.38	2.71	1.75	0.75
8	2.00	1.38	0.50	2.43	0.63	1.00
9	3.00	2.13	0.75	1.14	1.00	1.13
10	2.25	3.00	1.50	2.57	2.38	1.88
b: UCS days						
1	2.00	0.75	3.25	3.86	0.13	2.38
2	5.38	4.50	6.13	9.14	3.75	7.13
3	6.63	11.88	11.13	15.29	5.88	10.88
4	10.38	15.50	13.00	15.86	12.50	14.13
5	15.88	15.25	17.88	17.14	13.38	15.13
6	13.13	18.88	20.25	14.43	12.88	16.13
7	10.50	15.75	19.25	15.29	15.50	14.38
8	11.38	15.75	17.63	16.86	16.63	17.38
9	10.25	15.38	16.75	12.71	17.00	13.88
10	9.88	16.25	18.25	14.86	19.63	15.38
c: ITI days						
1	46.13	55.63	59.13	99.57	30.13	47.75
2	67.50	108.25	148.75	95.57	86.38	115.25
3	61.88	108.00	96.00	126.29	87.63	71.75
4	71.75	96.63	82.13	114.14	121.50	72.63
5	46.50	56.75	61.13	90.57	72.00	62.63
6	53.75	70.13	59.25	87.86	56.75	43.00
7	51.25	58.75	38.88	78.86	58.50	35.38
8	49.75	58.13	32.13	80.86	64.00	41.00
9	66.00	62.88	32.13	65.14	55.00	43.50
10	57.75	83.13	34.88	81.57	68.50	63.63

Percentage CS responding There was an effect of Days [F (9,369) = 50.53, $P < 0.001$]. Again the effectiveness of the ISI in reducing conditioning was confirmed by the Days by Trace interaction [F (9,369) = 28.59, $P < 0.001$]. The effect of Trace was also significant overall [F (1,41) = 59.60, $P < 0.001$].

Treatment with nicotine resulted in a marginal Days by Drug interaction [F (18,369) = 1.62, $P = 0.053$]. The Days by Drug by Trace interaction was significant [F (18,369) = 1.93, $P < 0.05$]. Figure 2 suggests that the difference between trace and 0 s conditioned groups was accentuated by nicotine at 0.6 mg/kg. In fact, in neither 0 s nor trace conditioned rats was there any significant difference in responding (on any day) under 0.6 mg/kg nicotine relative to the corresponding saline groups [maximum t(14) = 1.99]. However, the fact that the three-way interaction (Days by Drug by Trace) was also significant in the linear trend [F (2,41) = 3.28, $P < 0.05$] means that nicotine affected the course of appetitive acquisition differently in trace and 0 s conditioned rats. No other effects or interactions were significant [maximum F (2,41) = 1.74]. Contrast analyses of drug effects on acquisition curves were conducted within each behavioural (i.e., 0 s versus trace) group. These showed that within the 0 s group, the rate of acquisition in the 0.6 mg/kg nicotine treated rats was significantly different from the saline group [F (1,198) = 9.24, $P < 0.05$]. No other comparisons in either the 0 or 10 s groups were significant [maximum F = 1.696].

ISI There was a main effect of Bins [F (4,80) = 6.52, $P < 0.001$], so responding was not uniformly distributed within the ISI. The fact that the Bins by Drug interaction was significant means that how responding distributed within the ISI was influenced by treatment with nicotine [F (8,80) = 4.33, $P < 0.001$]. Figure 3 shows these effects averaged over the 10 days' testing.

Planned comparisons were used to test whether nicotine promoted responding later in the ISI (Kantini *et al.*, 2004). This was not the case, in that under both saline and 0.6 mg/kg nicotine (although in the latter case against a lower overall ISI baseline, see below), responding later in the trace was increased relative to bin 1, significantly so in bins 2, 3 and 5 [minimum t (6) = 2.7, $P < 0.05$] and bins 2, 3 and 4 [minimum t (7) = 2.55, $P < 0.05$], respectively; whereas under 0.4 mg/kg nicotine responding dropped significantly in bin 5 relative to bin 1 [t(7) = 2.62, $P < 0.05$].

There was a main effect of Days [F (9,180) = 23.46, $P < 0.001$], because, as in the ITI, response rates fluctuated over the course of acquisition. Moreover, interactions between Days and Bins [F (36,720) = 1.97, $P = 0.001$] and Days, Bins and Drug [F (72,720) = 1.37, $P < 0.05$] mean that the development of nicotine's effects on distribution of responding took some time to develop. Day-by-day analyses confirmed that the pattern seen overall (reflected by the Bins by Drug interaction term) was statistically significant by days 8 and 9 [minimum F (8,80) = 2.59, $P < 0.05$]. The pattern was the same (increased responding later in the trace under saline and 0.6 mg/kg nicotine, decreased responding later in the trace under 0.4 mg/kg nicotine) but statistically the effect was marginal [F (8,80) = 1.94, $P = 0.07$] on day 10.

Finally, there was a main effect of Drug [F (2,20) = 3.71, $P < 0.05$] that appeared to arise from overall reduced responding in the ISI under nicotine. To adjust for any more general reduction in responding under nicotine that could in principle account for any overall shifts in the ISI, we repeated the analyses using ITI responding as a covariate. Importantly, the fact that the main effect of drug in the ISI persisted [F (2,19) = 4.35, $P < 0.05$] when ITI responding was adjusted for in this way means that the general reduction in anticipatory responding within ISI under nicotine can be taken as a real result.

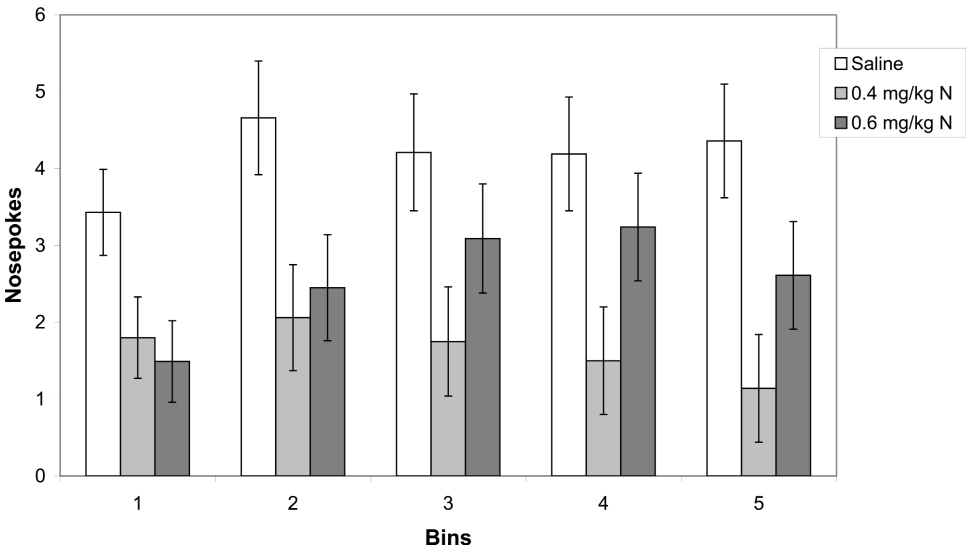

Figure 3 Mean overall nose pokes over five 2 s bins of the 10 s trace interval during the acquisition phase of Experiment 2. Key gives histogram shading that denotes each drug condition: saline, 0.4 mg/kg and 0.6 mg/kg nicotine. Bars show two standard errors of the mean for approximate between-groups comparisons.

Comparison analysis of d- amphetamine data

We have previously published effects of D-amphetamine on acquisition in the same appetitive trace conditioning procedure (Kantini *et al.*, 2004; Experiment 2). For comparison with the present study, these data were reanalysed exactly as above, to examine CS responding as a percentage of the responding seen in the remainder of the session, excluding the trace interval where applicable (and with the same automatic exclusion criterion for rats that failed to respond). There was a main effect of Days [F (9,315) = 24.75, $P < 0.001$]. As would be expected, there was both an overall effect of Trace [F (1,35) = 55.54, $P < 0.001$] and a significant interaction between Trace and Days [F (9,315) = 14.53, $P < 0.001$]. Consistent with the effect found on analysis of CS responding in this experiment (fully reported in Kantini *et al.*, 2004) there was both a main effect of Drug [F (2,35) = 6.36, $P < 0.005$] and an interaction between Drug and Days [F (18,315) = 1.88, $P < 0.05$]. However, when CS responding was expressed as a percentage of responding, it was shown that the effects of drug were different in trace and 0 s conditioned groups. The Trace by Drug interaction was significant [F (2,35) = 5.75, $P < 0.01$]. Figure 4 shows the three-way interaction with Days [F (18,315) = 2.44, $P = 0.001$]. As in Experiments 1 and 2, confirming differential rates of acquisition, the interaction between Trace, Drug and Days was also significant in the linear trend [F (2,35) = 5.81, $P < 0.01$]. Contrast analyses of drug effects on the acquisition curves were conducted within each behavioural (i.e., 0 s versus trace) group. Within the 0 s group, the rate of acquisition under 0.5 mg/kg AMP was significantly different to saline [F (1,253) = 29.96, $P < 0.001$]. No other comparisons in the 0 or 10 s groups were significant [maximum $F = 1.31$].

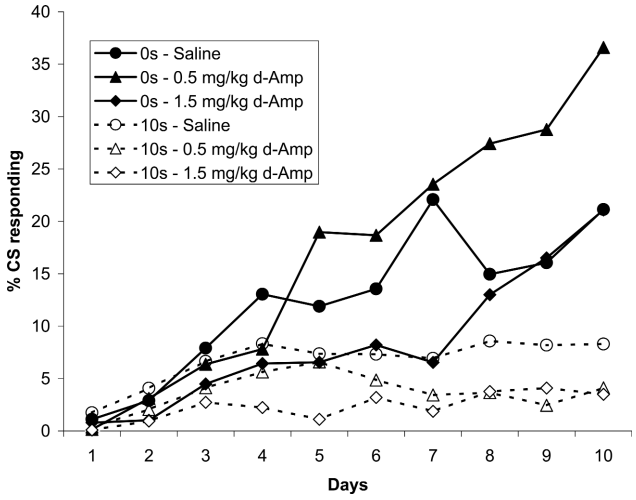

Figure 4 CS acquisition under D-amphetamine (Kantini *et al.*, 2004: Experiment 2), measured as magazine entries during CS presentations and expressed as a percentage of responding seen in the remainder of the session. CS previously paired with food deliveries either at 0 s (solid lines) or at a 10 s trace (broken lines). Key gives symbols that denote each drug condition: saline, 0.5 mg/kg and 1.5 mg/kg D-amphetamine. Error bars show two standard errors of the mean for approximate between groups comparisons.

Discussion

Learning that a CS (e.g., noise) predicts biologically relevant outcomes (UCSs) such as food or footshock is normally reduced when

these events are separated in time. This effect was clearly demonstrated here. Effects of MP and nicotine were seen in the 0 s conditioned groups where (at the higher of the two doses tested) each of these treatments was shown to improve the acquisition of conditioned responding to the CS relative to responding in the remainder of the session. Specifically, this was increased under 5 mg/kg MP and 0.6 mg/kg nicotine. Reanalysis of earlier work (Kantini *et al.*, 2004) using the same percentage CS responding measure showed the same effect under 0.5 mg/kg D-amphetamine. Thus, three different DA agonists effectively improved focus in responding over the course of appetitive acquisition. This result was seen only in the 0 s groups, for which the CS was informative and contrasts with the predicted effect of increased conditioning to less informative (trace conditioned and contextual) stimuli, based on earlier findings in aversive procedures (Norman and Cassaday, 2003; Gould *et al.*, 2004; Horsley and Cassaday, 2007).

Effects of DA drugs such as D-amphetamine can be confounded by nonspecific motor and motivational effects and this may account for differences between measures of associative learning: increased associative learning is not what we earlier reported under amphetamine (Kantini *et al.*, 2004). The analysis of CS responding as a percentage of overall responding in the session automatically adjusts for any effects DA agonists might have on general levels of activity. For example, in Experiment 2, there were some nonsystematic fluctuations in ITI responding by day (probably related to the need to increase the food ration early in conditioning, see Methods). After adjustment for changes in ITI responding, we saw enhanced appetitive acquisition under amphetamine, consistent with earlier reports (Harmer and Phillips, 1998, 1999; but see Dalley *et al.*, 2005).

ISI and ITI responding

In Experiment 1, there was no evidence to suggest that MP affected conditioning to the contextual cues present during conditioning, measured in the ITI, nor was there any effect of MP in the 'mini-context' of the trace interval (ISI). Previously, we have shown that the distribution of responding in the trace can change over time and, moreover, is sensitive to drug effects (e.g., Kantini *et al.*, 2004), but here no such changes were seen. However, it is possible that such changes might have emerged later in acquisition, had this not been disrupted by the necessary change in route of administration of the drug.

In Experiment 2, nicotine generally decreased anticipatory responding in the ISI and this effect persisted when its effects in the ITI were adjusted for statistically. The effect of nicotine in the ITI could reflect a change in the course of contextual conditioning, but this would seem unlikely given that the effect was confined to day 2. In any case there was also some effect on the distribution of responding within the ISI time bins that can find no account in terms of a general response rate shift. While responding under saline and 0.6 mg/kg increased in later bins relative to bin 1, under 0.4 mg/kg nicotine responding was reduced by the end of the session. Any action on timing would be expected to take a number of days to develop and indeed there was a significant three-way interaction between drug, bins and days. Restricted day-by-day analyses showed that the overall effect described above emerged by day 8 of acquisition. This time course supports the interpretation offered above that the absence of any effect of MP on ISI responding during acquisition may well have been due to the fact that the analysis had to be restricted to the first five days.

Clearly, treatment with nicotine did not have the same effect on late trace responding as was seen under amphetamine (Kantini *et al.*, 2004). Neither was the direction of its overall effect – of decreased ISI responding, over and above what would be expected based on changes in the ITI -consistent with the possibility that that in trace-conditioned rats ISI responding was functionally equivalent to CS responding. On the latter measure, there was an increase in responding under 0.6 mg/kg nicotine in the 0 s conditioned group, beyond what would be expected based on changes in the ITI. Thus there was no evidence that nicotine improved conditioning in the trace group, whether measured directly as CS responding or as anticipatory responding in the ISI.

Dopaminergic mediation of effects

Like amphetamine, MP and nicotine are DA agonists, though they have a variety of other actions and promote DA release by different mechanisms. Nicotine stimulates acetylcholine receptors and promotes the release of noradrenaline (NA), serotonin (5-HT) and GABA, as well as DA (Wonnacott *et al.*, 1989). Both amphetamine and MP act on the DA transporter (DAT) but they have different profiles of action in the sense that they have preferential effects in increasing the availability 'newly synthesized' (amphetamine) and 'stored' (MP) pools of DA (Chiuh and Moore, 1975a, b; Hurd and Ungerstedt, 1989; Giros *et al.*, 1996; Volkow *et al.*, 1998). In other words, amphetamine has a preferential effect on DA release and MP has a particular effect on (terminal) reuptake. Although the profiles of action of these drugs are clearly different, their therapeutic properties in ADHD may arise from a common action of increasing extracellular DA availability to postsynaptic receptors.

The higher doses of nicotine (0.6 mg/kg) and MP (5 mg/kg) produced the same pattern of effects as the lower dose of amphetamine (0.5 mg/kg) used in an earlier study (Kantini *et al.*, 2004). The doses of amphetamine were established empirically based on prior studies indicating effects of these doses on the kinds of behaviour (attentional learning) we were interested in, rather than for direct comparison with the doses of MP and nicotine used here. However, increased DA function in n.acc has been demonstrated to mediate effects on LI and is a shared action of MP and amphetamine (Kuczenski, 1983; Kuczenski and Segal, 2001; Rosa-Neto *et al.*, 2005). Similarly, nicotine also has this mechanism of action. Both 0.4 and 0.6 mg/kg doses nicotine have behavioural effects on LI (Joseph *et al.*, 1993; Young *et al.*, 2005) that have been attributed to n.acc selective effects on DA (Nissell *et al.*, 1994; Balfour, 2004; Fu *et al.*, 2000). We therefore, suggest that the common behavioural outcome – increased acquisition in 0 s conditioned groups- observed under the diverse DA agonists used here most likely arises because of shared actions on DA in n.acc.

All of the compounds in use have differential patterns of action on neurotransmitter systems other than DA. Amphetamine increases the availability of NA and 5-HT as well as DA whereas

MP has much less of an effect on NA and 5-HT (Kuczenski *et al.*, 1987, 1995; Kuczenski and Segal, 1997). This means that treatments with equivalent effects on the DA system are highly likely to have differential behavioural effects because of differential effect in non-DA systems. With respect to the present findings, although there is evidence for increased DA function in n.acc at doses of MP as low as 1 mg/kg (Kuczenski and Segal, 2002; Belo and Hajnal, 2006), this dose did not improve discrete cue conditioning. This could be due to competing actions on non-DA systems: For example, low dose (up to 3 mg/kg) MP has been reported to preferentially increase NA function in hippocampus and thus prefrontal cortex rather than DA in n.acc (Kuczenski and Segal, 2002). Conversely, doses of amphetamine that are at threshold to increase locomotor activity act to increase DA function before an effect on NA is shown (Costa *et al.*, 1972). Although they may explain why one dose but not another was effective in the current study, these diverse effects on non-DA systems are an unlikely explanation of the consistent effects of MP, nicotine and amphetamine on attentional learning. This consistency is indicative of a shared action, most likely on DA in n.acc.

Conclusions and implications

Both MP and nicotine produced a relative increase in conditioning to a discrete CS that reliably predicted food using a dependent variable (percentage CS responding) that adjusted for changes in ITI responding. Reanalysis of an earlier study with amphetamine showed the same result. Although none is particularly selective, all of these treatments have been used to treat ADHD. The focus on CS presentations for responding within appetitive conditioning sessions is consistent with improved selectivity in attentional learning, or a reduced 'attentional window' (Shalev and Tsal, 2003).

However, while strikingly consistent across three different indirect DA agonists, these results from appetitive conditioning are clearly discrepant with what has been found in aversive procedures (Norman and Cassaday, 2003; Gould *et al.*, 2004; Horsley and Cassaday, 2007). In aversive procedures, both amphetamine and MP increased conditioning to the trace CS and to the contextual cues, consistent with a widening of the attentional window. There are a number of inevitable differences between appetitive and aversive trace conditioning procedures due to task motivation and related procedural differences, most notably the increased number of conditioning trials in the appetitive procedure may promote responding to the CS over and above (changes in) ITI responding. Appetitive and aversive procedures also require different drug treatment regimes because of the increased number of conditioning trials in the appetitive procedure.

In terms of drug effects thereon, MP, nicotine and amphetamine are likely to have differential motivational effects in appetitive and aversive task variants. In principle, these might relate to their differing profiles of action in DA and non-DA systems, for example, NA and 5-HT. However, the consistency in the effects of diverse DA agonists in appetitive (and aversive) conditioning has still to be explained. The present study is not definitive, but we have argued that this consistency is most likely attributable to a shared action on n.acc DA function. Moreover, the fact that effects are different in aversively and appetitively motivated procedures could be relevant to our understanding of the therapeutic actions of DA agonists in ADHD. In general, task motivation is an important determinant of the deficits displayed in ADHD (Luman *et al.*, 2005; van Meel *et al.*, 2005). In particular, there is evidence to suggest that children with ADHD are less responsive to signals of punishment (Quay, 1997) because of an underactive behavioural inhibition system (Gray, 1982, 1987). Where sensitivity to unfavourable outcomes is reduced (but see van Meel *et al.*, 2005), any widening of the attentional window under DA agonists (Norman and Cassaday, 2003; Gould *et al.*, 2004; Davis *et al.*, 2006; Horsley and Cassaday, 2007) could be of therapeutic benefit. Thus differences in the profile of action of DA agonists between appetitively and aversively motivated tasks could dovetail nicely with differences in baseline task performance when the DA system functions abnormally in ADHD.

Acknowledgements

The experimental work was financed (in part) by a Wellcome Trust project grant (reference 055330). We thank Dr Thom Baguley for statistical advice and help and Professor Mike Joseph for advice on nicotine doses.

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