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ORIGINAL INVESTIGATION

Enhancement of a visual reinforcer by D-amphetamine and nicotine in adult rats: relation to habituation and food restriction

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Abstract

Rationale and objectives Nicotine and D-amphetamine can strengthen reinforcing effects of unconditioned visual stimuli. We investigated whether these reinforcement-enhancing effects reflect a slowing of stimulus habituation and depend on food restriction.

Methods Adult male rats pressed an *active* lever to illuminate a cue light during daily 60-min sessions. Depending on the experiment, rats were challenged with fixed or varying doses of D-amphetamine (0.25–2 mg/kg IP) and nicotine (0.025–0.2 mg/kg SC) or with the tobacco constituent norharman (0.03–10 μg/kg IV). Experiment 1 tested for possible reinforcement-enhancing effects of D-amphetamine and norharman. Experiment 2 investigated whether nicotine and amphetamine inhibited the spontaneous within-session decline in lever pressing. Experiment 3 assessed the effects of food restriction.

Results Amphetamine (0.25–1 mg/kg) and nicotine (0.1 mg/kg) increased active lever pressing specifically (two- to threefold increase). The highest doses of nicotine and amphetamine also affected inactive lever responding (increase and decrease, respectively). With the visual reinforcer omitted, responding was largely extinguished. Neither drug appeared to slow habituation, as assessed by the within-session decline in lever pressing, and reinforcement-enhancing effects still occurred if the drugs were given after this decline had occurred. Food restriction enhanced the reinforcement-enhancing effect of amphetamine but not that of nicotine.

Conclusions Responding remained goal-directed after several weeks of testing. Low doses of D-amphetamine and nicotine produced reinforcement enhancement even in free-feeding subjects, independent of the spontaneous within-session decline in responding. Reinforcement enhancement by amphetamine, but not nicotine, was enhanced by concurrent subchronic food restriction.

Keywords Nicotine · Amphetamine · Norharman · Reinforcement enhancement · Habituation · Food restriction

Introduction

Both D-amphetamine and nicotine have been reported to enhance the reinforcing effects of diverse primary and conditioned reinforcers in adult rats (Kiernan 1965; Liebman and Butcher 1974; Phillips and Fibiger 1990; Robbins et al. 1983; Rupprecht et al. 2015; Shin et al. 2010; Winterbauer and Balleine 2007). Such effects, often referred to as reinforcement enhancement (Rupprecht et al. 2015), can promote drug self-administration behavior in animals (Caggiula et al. 2002; Collins and Woods 2009; Rupprecht et al. 2015; Shin et al. 2010) and also appear to maintain drug-taking in human subjects (Perkins et al. 2017; Rupprecht et al. 2015). The present study specifically concerns the effects of non-contingent, systemic administration of amphetamine and nicotine on responding for a *sensory* stimulus (i.e., a cue light) which served as a primary reinforcer (Berlyne et al. 1964; Stewart 1960). As primary reinforcers, visual stimuli offer several advantages (Keller et al. 2014): in particular, they sustain stable and low rates of responding for many weeks, and they permit the study of motivational processes independent of homeostatic mechanisms.

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Isolating the true reinforcement-enhancing effects from the motor-stimulant effects of amphetamine and nicotine is a significant experimental challenge (Clarke 1987; Grilly and Loveland 2001). Thus, the first demonstrations of reinforcement enhancement by amphetamine and nicotine were based on measures of intracranial electrical self-administration that were designed to be insensitive to any generalized drug effects on operant responding (Clarke and Kumar 1984; Esposito et al. 1980; Liebman and Butcher 1974). In the case of sensory reinforcers, drug-induced reinforcement enhancement is distinguished from drug-induced motor-stimulant responses by comparing the rates of active vs. inactive lever pressing. In this regard, amphetamine and nicotine inconsistently exhibit a reinforcement-enhancement effect. Thus, nicotine, which has been investigated extensively, specifically enhanced active lever pressing in only a subset of reports (Constantin and Clarke 2017, and references therein), and amphetamine, when tested at moderate doses, produced either a selective increase in active lever responding (Keller et al. 2014; Shin et al. 2010; Winterbauer and Balleine 2007) or else a generalized stimulant effect (Kiernan 1965) as also reported with methamphetamine (Lloyd et al. 2012b).

In experiment 1 of the present study, we revisited the question of behavioral selectivity, using a test procedure in which rats were permitted to press one of two levers to obtain a brief light cue serving as a primary visual reinforcer. Here, drug injections were given immediately before the session, and a range of amphetamine doses was tested, with nicotine serving as the main point of comparison. In this experiment, nicotine was tested at a single dose, since its dose-response relationship has been documented elsewhere (Constantin and Clarke 2017). We also investigated the tobacco constituent norharman (Rommelspacher et al. 2002), which was of interest as it appears to weakly sustain intravenous self-administration in rats (R.E. Sorge and P.B.S. Clarke, unpublished). Therefore, in experiment 1, norharman was administered intravenously, with intravenous nicotine serving as a positive control. This experiment concluded with an extinction phase to evaluate whether responding remained goal-directed.

In this first experiment, we found that amphetamine, like nicotine, selectively increased active lever pressing. These drug effects tended to grow across the session, at a time when response rates were declining in the control (saline) condition. This was of interest because both amphetamine and nicotine have been reported to delay habituation to sensory stimuli in other test procedures (Dieu et al. 2005; File 1975; Lloyd et al. 2014; Veltri et al. 2017). Accordingly, we hypothesized that, pharmacokinetic factors apart, the appearance of reinforcement-enhancing effects reflects a drug-induced slowing of the natural within-session decline in responding. In experiment 2, we addressed this issue using two approaches. In the first approach, amphetamine and nicotine were administered well in advance of test sessions to eliminate delays due to drug absorption. In the second approach, the drugs were given after response rates had substantially declined, i.e., 30 min after the start of the test sessions. In experiment 2, amphetamine was tested at a single dose, whereas nicotine was tested across a range of doses in order to straddle the smoking-relevant range (see Constantin and Clarke 2017).

The first two experiments revealed clear reinforcer-enhancing effects of both amphetamine and nicotine in free-feeding animals. However, in a recent amphetamine study, reinforcement enhancement was found to be larger and more consistent when rats were chronically food-restricted (Keller et al. 2014). Food restriction also strengthens some other effects of amphetamine, notably locomotor stimulation and enhancement of brain stimulation reward, while leaving analogous effects of nicotine unchanged (Cabeza de Vaca and Carr 1998; Cadoni et al. 2003). Therefore, in experiment 3, we asked whether subchronic food restriction would amplify the reinforcement-enhancing effects of amphetamine but not nicotine.

Methods

Animals

Male Long-Evans rats (Charles River, Saint-Constant, QC, Canada) initially weighed 239–309, 252–290, and 248–297 g (experiments 1–3, respectively). They were housed two to three per cage in a temperature- and humidity-controlled animal colony maintained on a reverse 12:12-h light/dark cycle, with lights off at 0700 hours. All behavioral testing took place during the dark phase of the cycle, between 0800 and 1700 hours. Food and water were available ad libitum in the home cage, except where noted in experiment 3. Rats were handled for 3–4 days before testing. All experimental protocols were approved by the McGill Medical Faculty Animal Care Committee, in accordance with the Canadian Council on Animal Care guidelines, in order to minimize pain and discomfort.

Drugs

Drugs and suppliers were as follows: (−)-nicotine hydrogen tartrate salt, norharman (Sigma-Aldrich, Oakville, ON), D-amphetamine sulfate (Sigma-Aldrich, Poole, UK), ketamine HCl (Vetalar™, Vetrepharm, London, ON), xylazine HCl (AnaSed™, Novopharm, Toronto, ON), and also carprofen (Rimadyl™), enrofloxacin (Baytril™), and propofol (1% injectable solution, Diprivan™), all from CDMV, Saint-Hyacinthe, Québec. Drugs were dissolved in sterile 0.9% saline as needed. Doses of all drugs are expressed as the base, except amphetamine (expressed as salt). Nicotine solutions

were adjusted to pH 7.1–7.3 with NaOH. Drug solutions were aliquoted and stored at −20 °C until the day of use. Routes of administration are stated in Table 1. Subcutaneous (SC) and intraperitoneal (IP) injections were given in a volume of 1 ml/kg. Intravenous (IV) infusions were made with a constant rate (1.32 ml per 60-min session). Control injections were of saline, given by the same route.

Intravenous catheterization surgery and drug delivery

The IV route of administration was used only for comparing possible effects of norharman with nicotine (experiment 1, days 13–22; Table 1). To this end, rats were first implanted with IV Silastic catheters (ID 0.51 mm, OD 0.94 mm; Fisher Scientific, Montreal, QC) in the right jugular vein, under general anesthesia (ketamine 80 mg/kg IP and xylazine 16 mg/kg IP). The catheter was secured to the vein with silk sutures and was passed subcutaneously to the top of the skull where it was connected to a modified cannula (C313G-5UP; Plastics One, Roanoke, VA) mounted to the skull with jeweler's screws and dental cement. The analgesic carprofen (5 mg/kg SC) was administered during surgery to alleviate post-surgical pain. Immediately after surgery, catheters were flushed with 0.1 ml of a sterile solution of heparin (0.2 mg/ml), the antibiotic enrofloxacin (15 mg/kg, Baytril™), and saline. The cannula was occluded with a plastic stopper (Tygon tubing; Fisher Scientific, Montreal, QC) and shielded with an aluminum cap when not in use. Catheters remained unopened during the 8-day post-surgery recovery period.

From the start of behavioral testing, catheters were flushed on alternating days with 0.1 ml of sterile saline or a solution of heparin (0.2 mg/ml), enrofloxacin (15 mg/kg, Baytril™), and saline. In addition, catheter patency was occasionally assessed, where needed, by rapid (3–4 s) IV injection of the general anesthetic propofol (7 mg/kg, i.e., approx. 0.3 ml of a 1% solution). This dose produces an immediate loss of righting reflex followed by recovery within 2–3 min. During test sessions, drug solutions were delivered at a constant rate via a liquid swivel (rodent swivel model RSP1; Lomir, Notre-Dame-de-l'Île Perrot, QC), connected to a 3-ml plastic syringe mounted in an infusion pump (Med Associates PHM-107) that was set to deliver 1.32 ml in 60 min.

Behavioral apparatus and testing procedure

Subjects were tested in operant conditioning chambers (ENV-008CT; Med Associates, Lafayette, IN) housed within melamine cubicles. Each box was equipped with two retractable levers (ENV-112CM) located 10 cm apart and 8 cm above the stainless steel bar floor. A white cue light (2.5 cm diameter, 28 V, 100 mA, ENV-221M) was situated 3 cm above each of the two levers. A white house light (28 V, 100 mA, ENV-215M) was located on the opposite wall but was not used. All visual stimuli were controlled by Med Associates software. For each rat, one lever was designated "active" and the other "inactive." The left-right positions of the active and inactive levers were counterbalanced within each group of subjects. An FR1 schedule of reinforcement was used, with a single response on (only) the active lever producing a visual stimulus. The stimulus comprised a 3-s cue light illuminated above the active lever. A response on either lever resulted in the immediate retraction of both levers for a time-out period of 60 s, after which the levers were again extended into the chamber. Hence, rats could obtain almost 60 visual stimuli per 60-min session at maximum.

In most cases, drugs (or saline) were either injected SC or IP immediately before the test session. Exceptions are as follows: in experiment 1 (days 13–22 only), norharman and nicotine were given by continuous IV infusion over the course of the test session. In experiment 2, SC and IP injections occurred 30 min before the session or during the session, as described below.

Experiment 1: nicotine, norharman, amphetamine, and extinction

In this experiment, we tested the reinforcement-enhancement effects of norharman and amphetamine, as well as extinction of responding. The timeline is summarized in Table 1. On four consecutive days before surgery, rats received a home cage injection of nicotine 0.1 mg/kg SC in order to accelerate the emergence of a reinforcement-enhancing effect (Constantin and Clarke 2017), and tests on days 7–12 served to confirm this effect. Within each test block, the order of drug testing was either counterbalanced (days 7–12) or based on incomplete Williams square designs (days 13–22 and 23–29). Next, we ranked the rats by level of active responding (averaged across days 23–29). The rats within each matched pair were then randomly allocated to a control and extinction group, respectively. From days 30–39, testing in the control group continued as previously described and the extinction group was tested in the absence of the cue light.

Experiment 2: nicotine and amphetamine: habituation

Here, we investigated the gradual emergence of reinforcement enhancement within individual test sessions (see "Introduction"). Accordingly, rats were first tested repeatedly with nicotine and saline, to establish a reinforcement-enhancing effect, and were subsequently subjected to two types of testing procedure, as described below and summarized in Table 1.

As before, rats first received four home cage injections of nicotine (0.1 mg/kg SC) before behavioral testing, but now compressed into 2 days (i.e., 0900 and 1530 hours). On days 1–5, all 32 rats received 60-min saline test sessions. On days

Table 1 Timelines for experiments

Days	Drug	Dose (mg/kg) or condition	Route	*n* of rats	Purpose
Experiment 1					
	Nicotine	0.1 (4 times)	SC	21	Home cage injections
1–6	Saline	–	SC	21	Acquisition
7–12	Nicotine	0, 0.1	SC	21	Confirm nicotine effect
13–22	Norharman	0.00003–0.01	IV	16	Norharman dose-response
13–22	Nicotine	0, 0.1	IV	16	Nicotine comparison
23–29	Amphetamine	0, 0.25–2	IP	14	Amphetamine dose-response
23–29	Nicotine	0, 0.1	SC	14	Nicotine comparison
30–39	None	Light cue (un)available		7+7	Extinction test
Experiment 2					
	Nicotine	0.1 (4 times)	SC	32	Home cage injections
1–5	Saline	–		32	Acquisition
6–11	Nicotine	0, 0.1	SC	27	Confirm nicotine effect
12–20	Nicotine	0, 0.025–0.2	SC	27	Test procedures 1 and 2
12–20	Amphetamine	0, 0.5	IP	27	Test procedures 1 and 2
21–29	Nicotine	0, 0.025–0.2	SC	27	Test procedures 1 and 2
21–29	Amphetamine	0, 0.5	IP	27	Test procedures 1 and 2
Experiment 3					
1–12	Nicotine	0, 0.1	SC	32	Acquisition/confirm nicotine effect
13–24	Nicotine	0, 0.1 (AL vs. FR)	SC	32	Stabilize weight loss
25–32	Nicotine	0, 0.1 (AL vs. FR)	SC	14+16	Test effects of food restriction
25–32	Amphetamine	0, 0.1 (AL vs. FR)	IP	14+16	Test effects of food restriction
10 days	–	AL, no testing		30	Recovery before crossover
33–34	Nicotine	0, 0.1	SC	30	Reconfirm nicotine effect
35–44	–	AL vs. FR		16+14	Stabilize weight loss
45–48	Nicotine	0 and 0.1 (AL vs. FR)	SC	16+14	Reconfirm nicotine effect
49–56	Nicotine	0 and 0.1 (AL vs. FR)	SC	16+14	Test effects of food restriction
49–56	Amphetamine	0 and 1 (AL vs. FR)	IP	16+14	Test effects of food restriction

AL ad libitum, *FR* food restriction

6–11, subjects received interleaved saline and nicotine (0.1 mg/kg SC) test sessions to confirm the nicotine effect. At this point, five rats did not prefer the active lever significantly (paired *t*-tests) and were not tested further. The remaining 27 rats were then subjected to a crossover design in which they received two blocks of eight daily tests, i.e., procedure 1 followed by procedure 2, or vice versa.

In procedure 1, drugs were injected 30 min in advance of the normal 60-min test sessions and rats were replaced in their home cages in the interim. In procedure 2, the test session lasted 90 min instead of 60 min, and lever pressing was allowed to decline for 30 min before drugs were injected. These two test blocks occurred respectively on days 12–20 and 21–29. Within each block, rats were tested with nicotine 0 (twice), 0.025, 0.05, 0.1, and 0.2 mg/kg SC and with amphetamine 0 and 0.5 mg/kg IP. Test conditions were ordered according to incomplete Williams square designs.

Experiment 3: nicotine, amphetamine, and food restriction

Rats were first tested repeatedly with nicotine and saline to establish a reinforcement-enhancing effect (Table 1). Next, the effects of food restriction were tested in a crossover design consisting of two blocks of tests (Table 1). Half of the subjects were food-restricted (see below) in the first block and half in the second block. All sessions were of 60-min duration. Tests drugs were administered at constant doses, i.e., nicotine 0.1 mg/kg and amphetamine 1 mg/kg IP. The amphetamine dose was chosen for comparison with a previous study of food restriction (Keller et al. 2014).

On days 1–12, the 32 subjects received daily test sessions, alternately after injection of saline or nicotine. One hour after saline test sessions, rats received nicotine in the home cage in order to accelerate the emergence of reinforcement enhancement across days. Then, on days 13 to 32, half of the animals were food-restricted, as follows. Eight pairs of rats (i.e., 8 out of the 16 home cages) were randomly allocated to food restriction. The aim was to maintain body weight at 85% of rats in the concurrent free-feeding group. The daily food allocation was 15 g/rat on the first 2 days and 15–25 g/rat thereafter, given within 1 h after the session. During this food restriction block, rats initially received alternating tests with saline and nicotine (days 13–24) and subsequently received eight tests (days 25–32), i.e., two tests with each of saline SC, saline IP, nicotine SC, and amphetamine IP. The order of testing was counterbalanced across animals.

After day 32, testing was discontinued for 10 days and all rats had ad libitum access to food. Next, two tests were given, one with saline and one with nicotine (days 33–34), to confirm the nicotine effect was still present. The second period of food restriction followed (days 35 to 56), using the same procedure as in the first period (days 13 to 32). Testing resumed on day 45, after 10 days of food restriction, starting with four alternating saline and nicotine tests (days 45–48). Then, on days 49–56, rats received eight tests with saline, nicotine, and amphetamine (i.e., as on days 25–32).

Data analysis and statistics

As detailed above, subjects were assigned to groups and conditions in a randomized or counterbalanced manner. Experimenters were not blind to drug conditions. Commercial software was used for statistical analyses (SYSTAT, version 11; SPSS, Inc., Chicago, IL, USA). The behavioral variables were the number of active and inactive lever presses in 60 min or per 10-min time bin. The number of reinforcers earned was identical to the number of active presses. Data were subjected to repeated measures analysis of variance (ANOVA) with one or more of the following factors. Within-subject factors were the following: NIC (nicotine vs. saline), AMPH (amphetamine vs. saline), DOSE (doses of nicotine, norharman, or amphetamine), LEVER (active vs. inactive lever), DAY (pairs of sessions in experiments 1 and 3, sessions in experiment 2), and TIME (10-min time bins within session). Between-subject factors were the following: GROUP (two extinction conditions in experiment 1), FOOD (ad libitum vs. food restriction), and ORDER (order of ad libitum and food restriction conditions). For repeated measures ANOVA, the Huynh-Feldt sphericity-corrected p value is reported. Most multiple pairwise comparisons were made using paired t-tests with p values subjected to the Holm-Bonferroni adjustment (Ludbrook 1998), referred to here as "H-B paired t-tests." Active vs. inactive lever preference was assessed in each individual rat using a paired t-test, with session serving as the experimental unit. All p values refer to two-tailed tests, and $p < 0.05$ was considered statistically significant (NS denotes non-significant).

Results

Experiment 1: nicotine, norharman, amphetamine, and extinction

This experiment started with 21 subjects. Rats preferred the active lever from day 1 onwards. However, five subjects were excluded from drug testing from day 13 onwards (four had blocked catheters and another rat died unaccountably). Two additional subjects were excluded from the amphetamine block on days 23–29 (one rat no longer preferred the active lever as assessed by a paired t-test, and the other had a blocked catheter).

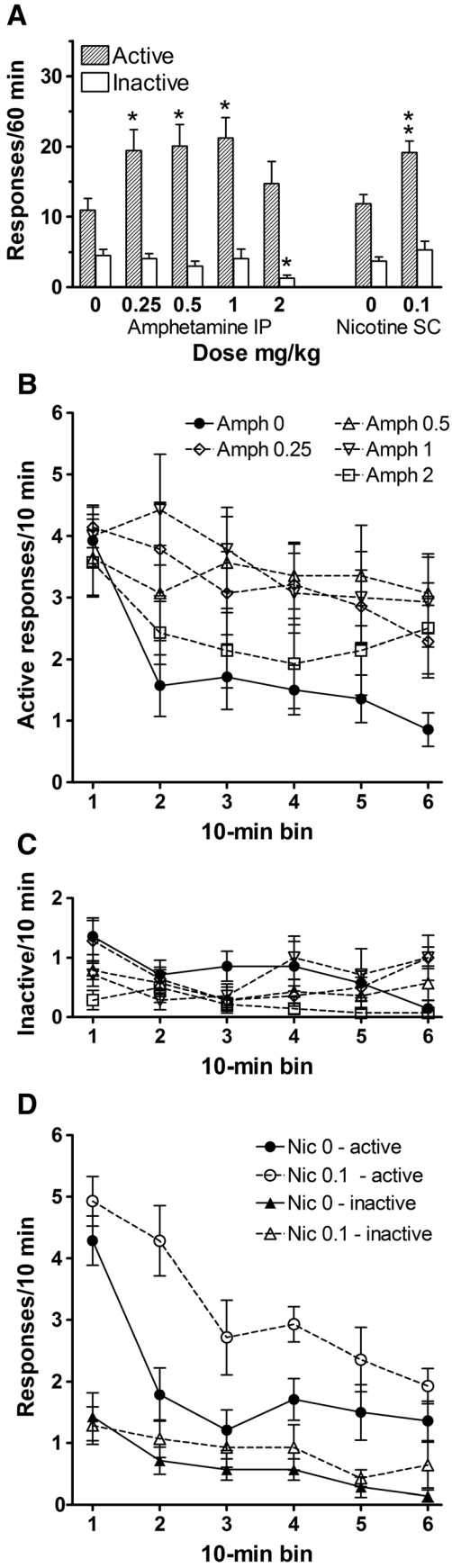
Saline (days 1–6) Pooled across days, all 21 rats pressed preferentially on the active lever. The mean±SEM number of active and inactive lever presses per session was 12.7±0.9 and 6.8±0.5, respectively.

Nicotine/saline (days 7–12) In six interleaved tests with saline and nicotine (0.1 mg/kg SC), the drug significantly increased active lever presses but not inactive lever presses (respectively: $F_{1,\ 20}=28.92$, $p<0.0001$ and NS). Mean±SEM responses per hour under saline vs. nicotine were, respectively, as follows: active presses 8.5±0.8 vs. 13.1±1.0 and inactive presses 2.9±0.3 vs. 4.2±0.7 ($n=21$ rats).

Norharman (days 13–22) Norharman produced no detectable effect (DOSE main effect and DOSE × TIME interaction, both NS). Nicotine (0.1 mg/kg IV), tested in parallel, increased active but not inactive lever presses, as expected (respectively: $F_{1,\ 15}=37.18$, $p<0.001$ and NS). Mean active lever presses per 60 min for the saline, nicotine, and ascending norharman doses were: 9.7, 15.0, 9.8, 11.1, 9.2, 8.9, 9.9, and 9.1 (SEM values range 0.9–1.6). Corresponding values for inactive lever responses were: 3.0, 3.7, 2.4, 3.0, 2.4, 3.2, 3.4, and 3.1 (SEM range 0.3–0.6).

Nicotine (days 23–29) Nicotine (0.1 mg/kg SC), tested in parallel with amphetamine (see below), increased active but not inactive lever presses (H-B paired t-tests: $p<0.01$ and NS, respectively; Fig. 1a). A clear stimulant effect of nicotine only emerged 10 min after injection (Fig. 1d).

Amphetamine (days 23–29) Taking the session as a whole (Fig. 1a), amphetamine increased active lever presses, with significant effects at 0.25, 0.5, and 1 mg/kg, while significantly decreasing inactive lever presses at 2 mg/kg (H-B paired t-tests: $p<0.05$). The stimulation of active lever responding



◀ **Fig. 1** Experiment 1 (days 23–39): effects of amphetamine and nicotine on lever pressing for a light cue. Each rat was tested under all seven drug conditions. **a** Active and inactive lever responses occurring during the whole 60-min session starting immediately after injection. **b**, **c** Time course of active and inactive lever responses for amphetamine tests. **d** same for nicotine. *y*-axes show mean±SEM, $n=14$ rats. *$p<0.05$ and **$p<0.01$, compared to corresponding zero-dose condition (paired *t*-test, Holm-Bonferroni correction)

appeared absent early in the session (Fig. 1b), even though the DOSE × TIME interaction was non-significant ($p>0.2$). *Inactive* lever presses (Fig. 1c) were affected by amphetamine in a time-dependent fashion (DOSE: $p>0.05$; DOSE × TIME: $F_{20,\ 260}=2.03$, $p<0.01$), with a dose-dependent inhibitory effect that was largely confined to the first half of the session (0–30 min, linear DOSE: $F_{1,\ 13}=9.39$, $p<0.01$) and evident even within the first time bin (0–10 min, linear DOSE: $F_{1,\ 13}=16.58$, $p<0.01$).

Extinction (days 30–39) During this phase, the light cue was unavailable for one of the two randomly assigned groups (Fig. 2). Over successive sessions, active and inactive lever responding tended to converge in this no-light group (linear DAY × LEVER: $F_{1,\ 6}=9.87$, $p<0.05$) but not in the control group ($p>0.3$). However, extinction was incomplete, since both groups continued to respond preferentially on the active lever even in the final three sessions (no-light and control groups, respectively; LEVER: $F_{1,\ 6}=13.88$, $p<0.01$, and $F_{1,\ 6}=62.5$, $p<0.001$).

Experiment 2: nicotine and amphetamine: habituation

After initial inspection, data from the two SC saline conditions within each drug block were averaged, and data from the two blocks of the crossover design (i.e., days 12–20 and 21–29) were pooled ($n=27$ rats).

Saline (days 1–5) Pooled across days, all but 3 of the 32 rats preferred the active lever (paired *t*-tests). The mean±SEM number of active and inactive lever presses per session was 9.3±0.9 and 5.4±0.4, respectively.

Nicotine/saline (days 6–11) Collapsed across days, nicotine significantly increased active, but not inactive, lever pressing (HB *t*-tests, respectively: $t_{26}=5.63$, $p<0.0001$; $t_{26}=2.37$, $p=0.0512$). Mean±SEM responses per hour under saline vs. nicotine were, respectively, as follows: active presses 8.5 ±0.6 vs. 12.7±1.0 and inactive presses 3.2±0.3 vs. 3.9±0.4 ($n=27$ rats).

Procedure 1 (days 12–29): drug administration 30 min before the start of session Nicotine increased active presses in a dose-dependent manner (DOSE: $F_{4,\ 104}=7.94$, $p<0.0001$; Fig. 3a), with no clear dependence on time within session (DOSE × TIME: $p>0.5$; Fig. 3b). During the first 10-min time bin, the higher doses tended to increase active

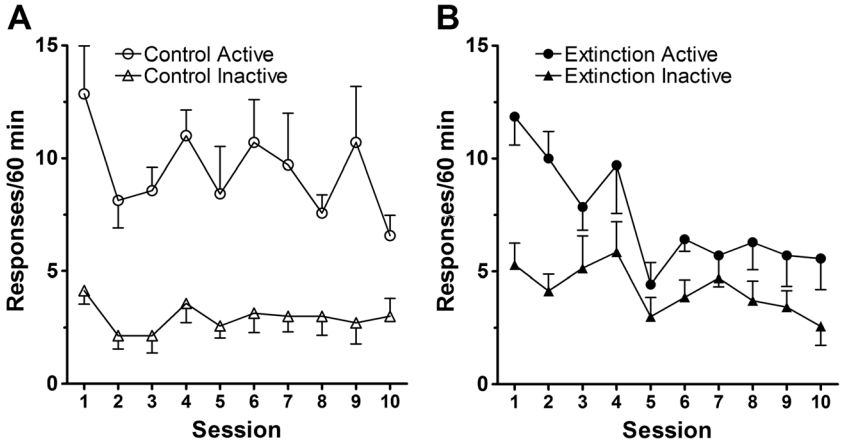


Fig. 2 Experiment 1 (days 30–39): partial extinction of responding upon removal of the light cue. During the 10 daily sessions, responding on the active lever produced the light cue in the control group (**a**) but not the extinction group (**b**). The *y*-axis shows mean±SEM active and inactive lever responses occurring during the whole 60-min session (n=7 rats/group). In the extinction group, active and inactive lever response rates incompletely converged over successive sessions (see text)

responding, but no significant stimulation was detected (linear DOSE: $F_{1,\ 26}$=3.83, p=0.0612; Fig. 3b). Nicotine also increased inactive presses (DOSE: $F_{4,\ 104}$=4.70, p<0.01; DOSE × TIME, NS), with a significant effect only at the highest dose (Fig. 3a, c).

As shown in Fig. 3d, amphetamine (0.5 mg/kg IP) robustly stimulated active presses throughout the session (AMPH: $F_{1,\ 26}$=45.40, p<0.0001; AMPH × TIME, NS), including those in the first 10-min time bin (H-B paired t-test: p<0.001). Amphetamine did not significantly alter inactive presses (main effect and time interaction, NS).

Procedure 2 (days 12–29): drug administration 30 min after the start of session During the 30 min before injection, active and inactive lever presses declined markedly (Fig. 3f–h); brief handing and injection then resulted in a transient increase in responding. Following injection, nicotine (0.025–0.2 mg/kg SC) increased active presses in a dose-dependent manner (DOSE: $F_{4,\ 104}$=25.52, p<0.0001; DOSE × TIME, NS), with significant effects at 0.1 and 0.2 mg/kg (Fig. 3e). This stimulant effect was sustained and was evident even in the first 10 min after injection, i.e., time bin 4 (DOSE: $F_{4,\ 104}$=6.61, p<0.0001; Fig. 3f). Nicotine did not significantly alter inactive presses overall (DOSE, NS), but there was a DOSE × TIME interaction largely driven by the highest dose ($F_{20,\ 520}$=2.47, p<0.05; Fig. 3g).

Amphetamine (0.5 mg/kg IP) significantly increased active presses (AMPH: $F_{1,\ 26}$=9.87, p<0.01; Fig. 3h). However, this effect was time-dependent (AMPH × TIME: $F_{5,\ 130}$=6.73, p<0.0001) and was entirely absent in the first 20 min after injection (Fig. 3h). Amphetamine did not alter inactive presses (AMPH: $F_{1,\ 26}$=0.00; AMPH × TIME, NS; Fig. 3h). In Fig. 3h, the pre-injection difference between the saline and amphetamine conditions (time bin 3) represents random variation.

Experiment 3: nicotine and amphetamine: food restriction

Nicotine (days 1–12) In this period before food restriction, nicotine significantly stimulated active lever pressing from the second test session onwards (HB t-tests: p<0.0436–0.0001). Collapsed across days 1–12, nicotine significantly increased active, but not inactive, lever pressing (HB t-tests, respectively: t_{31}=8.10, p<0.0001 and NS). Mean±SEM responses per hour under saline vs. nicotine were, respectively, as follows: active presses 9.1±0.5 vs. 12.7±0.7 and inactive presses 4.4±0.4 vs. 4.8±0.4 (n=32 rats).

Body weight Food restriction decreased body weight in the first and second drug testing blocks, by an average of 12 and 16%, respectively, compared to the free-feeding control group (t_{28}>8, p<0.001 for both; Supplementary Fig. 1).

Nicotine during initial food restriction (days 13–24) Overall, during this initial 12-day period of food restriction, nicotine significantly increased active, but not inactive, lever pressing (NIC main effects, respectively: $F_{1,\ 30}$=289.7, p<0.0001 and NS). Food restriction had no overall effect and did not alter the nicotine-induced stimulation of active lever pressing (FOOD main effect and interaction: $F_{1,\ 30}$<1.5, p>0.2). Mean±SEM responses per hour under saline vs. nicotine were, respectively, as follows: active presses 7.6±0.5 vs. 11.8±0.7 and inactive presses 2.2±0.2 vs. 2.4±0.3 (n=32 rats).

Nicotine tests (days 33–34 and 45–48) These tests confirmed that the reinforcement-enhancing effect of nicotine was still present (data not shown).

Nicotine (days 25–32 and 49–56) Two rats no longer showed a significant preference for the active lever (paired t-tests) and hence were excluded from the analysis. Nicotine-induced stimulation of active lever pressing was not significantly altered by food restriction

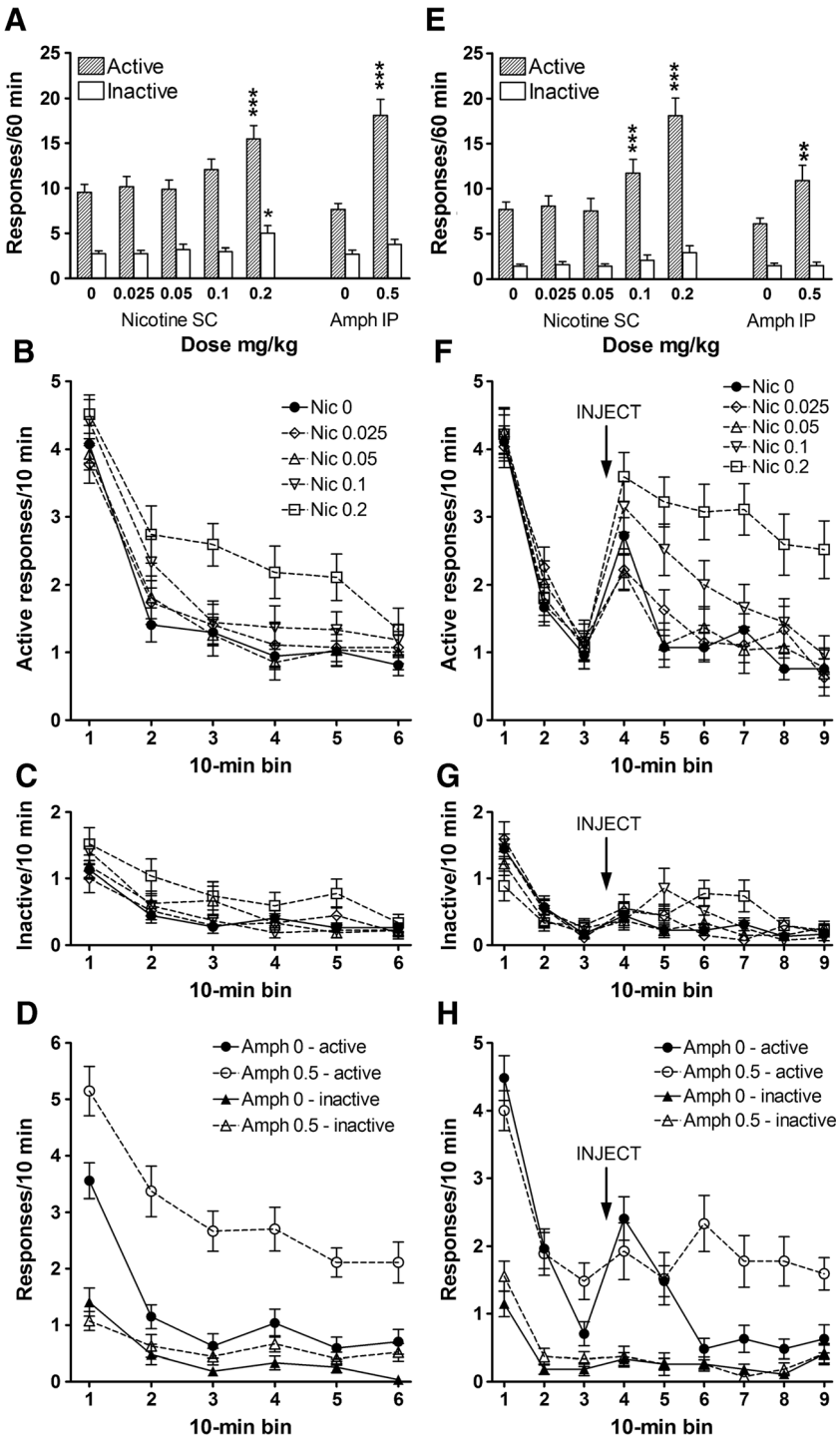


Fig. 3 Experiment 2 (days 12–29): effects of nicotine and amphetamine administered either 30 min *before* the start of 60-min test sessions (i.e., procedure 1, *left panels*) or 30 min *after* the start of 90-min test sessions (i.e., procedure 2, *right panels*). For both procedures 1 and 2, each rat was tested under all seven drug conditions. **a** Active and inactive lever responses summed across the whole 60-min session. **b**, **c** The time course of active and inactive lever responses, respectively, for nicotine sessions. **d** The corresponding time course data for amphetamine. **e**–**h** The corresponding data for procedure 2, except that **e** includes only data corresponding to the 60-min period after injection. *y*-axes show mean±SEM, n=27 rats. *p<0.05, **p<0.01, and ***p<0.001, compared to corresponding zero-dose condition (paired *t*-test, Holm-Bonferroni correction)

(NIC: $F_{1,\ 28}$=41.96, p<0.0001; FOOD × NIC, NS; Fig. 4a). This effect of nicotine did not depend on the order of ad libitum vs. food restriction testing (ORDER × NIC, NS), and there was no significant ORDER × FOOD × NIC interaction. Nicotine did not affect inactive lever pressing (Fig. 4b), regardless of feeding condition (p>0.2 for main effect and interactions).

Amphetamine (days 25–32 and 49–56) As shown in Fig. 4c, amphetamine (tested here at 1 mg/kg) increased active lever pressing (AMPH: $F_{1,\ 28}$=18.83, p<0.001), and this stimulant effect was enhanced by food restriction (FOOD × AMPH: $F_{1,\ 28}$=6.90, p=0.0138). However, the food/amphetamine interaction was strongly dependent on whether the period of food restriction occurred before or after the crossover (ORDER × FOOD × AMPH: $F_{1,\ 28}$=39.60, p<0.0001).

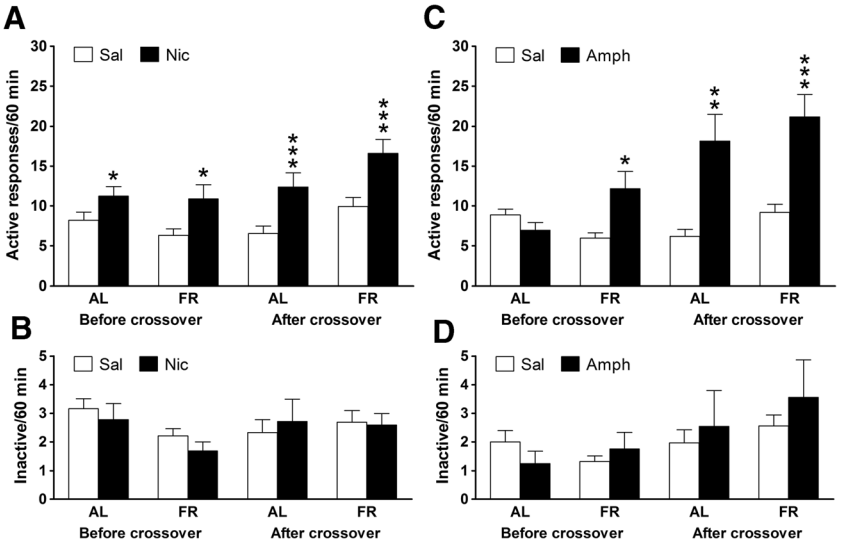


Fig. 4 Experiment 3 (days 25–32 and 49–56): effects of food restriction on the reinforcement-enhancing effects of nicotine (**a**, **b**) and amphetamine (**c**, **d**). Each rat was tested under ad libitum (AL) and food-restricted (FR) conditions, in a crossover design. Results are shown separately for tests occurring before and after crossover, i.e., days 25–32 and 49–56, respectively. *y*-axes show the mean±SEM number of active lever (**a**, **c**) or inactive lever (**b**, **d**) responses per 60-min session (n=14 and 16 rats). *p<0.05, **p<0.01, and ***p<0.001, compared to corresponding saline condition (unprotected paired *t*-tests)

Before the crossover, there was a significant FOOD × AMPH interaction ($F_{1, 28}$=9.87, p<0.01), and amphetamine stimulated active lever pressing responding only in the food-restricted group (unprotected: t_{13}=2.64, p=0.0204). In contrast, after the crossover, amphetamine stimulated responding to a similar extent in both feeding groups (AMPH main effect: $F_{1, 28}$=38.23, p<0.0001; FOOD × AMPH, NS). Amphetamine did not affect inactive lever pressing, regardless of food restriction (p>0.3 for main effects and interaction; Fig. 4d).

Discussion

The main findings are as follows: amphetamine dose-dependently enhanced the impact of a primary sensory reinforcer in free-feeding animals, a result previously seen in some, but not all, studies. The reinforcement-enhancing effects of amphetamine and nicotine were of similar size, and both effects occurred independent of the spontaneous within-session decline in responding. Subchronic food restriction differentially modulated the effects of amphetamine and nicotine; notably, nicotine's effectiveness was not altered by food restriction. Lastly, responding for the light cue remained goal-directed even after weeks of testing.

Behavioral selectivity, dose-response, and extinction in free-feeding subjects

In the present study, with minor exceptions, both amphetamine and nicotine increased responding for a primary visual reinforcer in free-feeding rats, without increasing inactive lever pressing. Nicotine has been shown elsewhere to exert a behaviorally specific effect in the same task (Constantin and Clarke 2017), and as before, the only sign of increased inactive lever pressing by nicotine occurred at the highest dose (0.2 mg/kg). A reinforcement-enhancing effect of amphetamine was seen in all blocks of testing, except in part of experiment 3 (discussed below). Hence, these results are broadly consistent with published findings based on comparable intraperitoneal doses of amphetamine, in which inactive lever pressing appeared completely unaltered (Keller et al. 2014; Shin et al. 2010; Winterbauer and Balleine 2007).

Amphetamine exerted significant reinforcement-enhancing effects at 0.25–1 mg/kg, but not at 2 mg/kg. An inverted-U dose-response relationship has also been noted in previous amphetamine studies using primary visual reinforcers (Keller et al. 2014; Shin et al. 2010). Even our lowest tested dose (0.25 mg/kg) appeared to exert a near-maximal effect. This dose has also been shown to enhance the rewarding effects of electrical brain stimulation (Clarke and Kumar 1984; Esposito et al. 1980; Liebman and Butcher 1974), although it would typically be considered a low dose in behavioral assays (Grilly and Loveland 2001). At moderate doses, amphetamine increased active lever pressing to a similar extent as nicotine, with both drugs tending to produce a two- to threefold increase in the whole-session response rate (Figs. 1a and 3a, e). Our highest amphetamine dose (2 mg/kg) did not appreciably stimulate active lever pressing but *reduced* inactive lever pressing (experiment 1). In previous studies, high doses of amphetamine tended to reduce response rates in free-

feeding subjects, with little or no lever selectivity (Keller et al. 2014; Shin et al. 2010; Vollrath-Smith et al. 2012).

Partial or full extinction of responding for primary visual reinforcers has been reported previously (Barrett and Bevins 2013; Cain et al. 2006; Stewart 1960). Experiment 1 demonstrated that active lever pressing was still largely or completely under control of the visual stimulus, even after 1 month of daily testing. This result was expected, given the fixed ratio nature of the reinforcement schedule (Dickinson et al. 1982) and the fact that the rats collected only about 10 reinforcers per session on average.

Did amphetamine or nicotine increase responding by inhibiting habituation to the visual stimulus?

The reinforcing effectiveness of sensory reinforcers is characterized by rapid within-session habituation (Lloyd et al. 2012a), and amphetamine and nicotine have been reported to delay habituation to various effects of sensory stimuli (Dieu et al. 2005; File 1975; Lloyd et al. 2014; Veltri et al. 2017). Therefore, in experiment 2, we hypothesized that, allowing for pharmacokinetic factors, these drugs would slow the natural within-session decline in responding, by inhibiting a habituation-related process.

In procedure 2 (experiment 2), amphetamine and nicotine were given 30 min into the session, by which time the normal decline in responding had already occurred. Here, both drugs were still able to increase lever pressing, indicating that these drugs could increase responding independent of any potential effect on habituation. In procedure 1 of the same experiment, the drugs were injected 30 min in advance of the session, so that circulating levels would be at or near maximum (Ghosheh et al. 1999; Sood et al. 2009). With this procedure, no DOSE × TIME interaction was detected, suggesting that neither drug slowed the spontaneous within-session decline in lever pressing. Hence, neither drug appeared to inhibit habituation to the visual stimulus.

Reinforcement enhancement by amphetamine was characterized by a gradual onset. Thus, when amphetamine was given immediately before the session, active lever pressing increased from 10 min after injection (Fig. 1b), and when amphetamine was given mid-session, this drug effect emerged 20 min after injection (Fig. 3h). In contrast, when amphetamine was given well in advance of the session, a stimulant effect was seen without delay (i.e., procedure 2, Fig. 3d). These findings suggest that the amphetamine's reinforcement-enhancing effect reflects the rise of plasma and brain amphetamine concentrations after IP administration of a similar dose (Sood et al. 2009). The same considerations also apply to nicotine, which is more rapidly absorbed than amphetamine (Pratt et al. 1983) and tended to produce a more rapid behavioral response (compare Fig. 1b vs. d and Fig. 3f vs. h).

Effects of food restriction

In experiment 3, food restriction initially intensified the reinforcement-enhancing effect of amphetamine, as previously reported (Keller et al. 2014), whereas it had no such effect with respect to nicotine. This differential outcome is reminiscent of findings with locomotor activity and brain stimulation reward (Cabeza de Vaca and Carr 1998; Cadoni et al. 2003).

Our amphetamine findings nevertheless require qualification. In the testing block before the crossover of drug conditions, there was a significant food restriction × amphetamine interaction, and amphetamine did not increase active lever responding in the ad libitum feeding condition. This lack of drug effect is hard to account for, given that amphetamine was otherwise consistently effective in free-feeding subjects, not only after the crossover point (Fig. 4) but also in the earlier experiments (Figs. 1 and 3d, h).

After the crossover, food restriction did not increase the response to amphetamine, even though the degree of weight reduction was slightly greater than it had been before the crossover (i.e., 16 vs. 12%). A tentative explanation is as follows: the food-restricted rats in this later testing block had formerly been tested under ad libitum conditions, so they had not had the opportunity to become *tolerant* to the effects of subchronic food restriction. After the crossover, even the ad libitum control group showed a relatively large reinforcement-enhancing effect of amphetamine. This increased response to amphetamine was probably not due to sensitization to the drug (Keller et al. 2014). Instead, the increased response to amphetamine expressed in these free-feeding animals may have reflected their *history* of being food-restricted (i.e., before the crossover). While several reports indicate that subchronic food restriction can indeed result in enduring effects on behavior and brain biochemistry (e.g., Inoue et al. 2004; Peng et al. 2015), only one study, to our knowledge, has assessed possible carryover effects in the context of reinforcement enhancement (Carr 2002). In the latter study, the ICSS threshold-lowering effect of amphetamine was shown to be augmented by food restriction, and this effect was lost only gradually upon return to ad libitum feeding.

The effects of food restriction seen in the present study were modest compared to the dramatic facilitation of the amphetamine response reported previously (Keller et al. 2014). In addition, unlike in the earlier study, food restriction per se did not increase responding for the visual reinforcer in the absence of drug. Numerous procedural factors may have contributed to these differences, including the strain of rat, the visual stimulus parameters, the reinforcement schedule, and the use of retractable levers (present study only). However, one factor may be particularly relevant here: our food restriction regime was milder than that in the earlier study. Specifically, we maintained body weights at 84–88% of the free-feeding control group, whereas Keller et al. (2014)

maintained weights at 85–90% of the pre-restriction baseline occurring several weeks prior.

Study limitations

First, as indicated above, our food restriction regime was milder than that in the most relevant previous work (Keller et al. 2014). Against this, we achieved a degree of weight loss comparable to that in many other behavioral studies. We also did not try to establish a maximally effective dose of nicotine (i.e., by extending the dose range beyond 0.2 mg/kg), as we wished to avoid exposing rats to plasma levels above the typical smoking range (for details, see Constantin and Clarke 2017). However, higher doses of nicotine would not necessarily have produced larger reinforcement enhancement, based on studies using audiovisual reinforcers (Barrett and Odum 2011) or electrical brain stimulation (Harris et al. 2012; Harrison et al. 2002).

Conclusions

The present findings help to establish that amphetamine, like nicotine, can enhance the reinforcing effects of a visual stimulus, even in free-feeding animals. These drugs exerted a very little effect on inactive lever pressing and produced similar degrees of reinforcement enhancement even though amphetamine is a considerably stronger locomotor stimulant (Clarke 1984; Simola et al. 2014). Hence, our findings add to evidence dissociating reinforcement-enhancing effects from generalized behavioral activation (Keller et al. 2014; Shin et al. 2010).

Reinforcement enhancement has been found to play a critical role in the intravenous self-administration of nicotine (Caggiula et al. 2002; Chaudhri et al. 2005; Rupprecht et al. 2015; Sorge et al. 2009) and also of D2 dopaminergic receptor agonists (Collins and Woods 2009). This phenomenon may also contribute to intravenous amphetamine self-administration, which is typically paired with a light cue (Gancarz et al. 2011) and often studied under conditions of chronic food restriction.

Compliance with ethical standards All experiments comply with the current laws of Canada.

Conflict of interest P.B.S.C. is a member of the Center for Studies in Behavioral Neurobiology at Concordia University, Montreal. The authors have no financial relationship with the organizations that sponsored this research.

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