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Between-session progressive ratio performance in rats responding for cocaine and water reinforcers

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Abstract

Rationale—A between-session progressive ratio (BtwPR) procedure was tested in rats responding for cocaine and water reinforcers.

Objectives—Experiment 1 evaluated the sensitivity of the BtwPR procedure to the magnitude of cocaine and water reinforcers. Experiment 2 compared BtwPR performance to within-session progressive ratio (WinPR) performance.

Methods—In experiment 1, rats were tested on a BtwPR procedure with three doses of cocaine (0.1, 0.3, and 1.0 mg/kg/inf) or volumes of water (0.01, 0.03, and 0.1 mL/reinforcer). BtwPR test sessions began with a seeking phase, during which the animal is required to complete a fixed ratio in order to initiate a 2-h consumption phase, where the reinforcer was available according to a fixed ratio 1 (FR1) schedule. Failure to complete the seeking ratio, which was increased after each test session, determined the breakpoint (BP). In experiment 2, the same BtwPR procedure was used except that the consumption phase was a WinPR schedule of reinforcement for cocaine (1.0 mg/kg/inf) or water (0.1 mL) reinforcers.

Results and conclusions—BtwPR BPs increased as a function of the magnitude of both cocaine and water reinforcers. The BtwPR produced smaller BPs than the WinPR for cocaine reinforcers. In contrast, the BtwPR produced larger BPs than the WinPR for water reinforcers. One possible explanation is that priming and response activating effects of the cocaine reinforcer increased the WinPR BP. BtwPR and WinPR procedures may measure different aspects of drug-seeking.

Keywords

Cocaine; Drug abuse; Self-administration; Operant conditioning

Introduction

Within-session progressive ratio (WinPR) schedules are often used in animal drug self-administration (SA) procedures to measure the reinforcing effectiveness of drugs (Roberts et al. 1989; Roberts et al. 2007). In this procedure, response requirements are increased within a single session for successive reinforcer presentations (Hodos 1961). Failure to emit the required response ratio within a specified duration terminates the session, and the ratio value which the animal failed to complete is defined as the “breakpoint” (BP). The BP indicates the amount of effort (e.g., responses) the animal will emit for a reinforcer presentation and is considered to be a measure of the reinforcing value of the drug. Increasing doses of drug results in systematic increases in BPs (Depoortere et al. 1993).

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However, BPs obtained when using a WinPR schedule of reinforcement to measure reinforcing effectiveness of a drug occur while the animal is under the influence of the drug and may not reflect the reinforcing effectiveness of the drug when the animal is not in the drug state. For example, cocaine may have priming or psychomotor effects that result in drug-induced increases in subsequent responding that are independent of the drug's reinforcing value (de Wit and Stewart 1981; Witkin and Goldberg 1990).

An alternative approach to measuring the reinforcing effectiveness of drug reinforcers is to measure the amount of work the animal will emit to gain access to a drug consumption binge. Czachowski et al. (2003; 1999) developed a between-session progressive ratio (BtwPR) schedule of reinforcement in which animals complete a fixed ratio at the start of each test session to gain access to a reinforcer that the animal can then consume with minimal restriction. The fixed ratio is increased between each test session in order to determine the BP. As in the WinPR procedure, the BP is determined by failure to complete the required fixed ratio. Because this BP is determined prior to drug consumption, it is not influenced by the possible effects of having the drug on-board. Because the BtwPR BP is determined in a drug abstinent state, it may model a different aspect of drug seeking and/or drug craving than the WinPR procedure.

The results from two experiments using BtwPR procedures are reported. The objective of experiment 1 was to determine the sensitivity of BtwPR BPs across a range of cocaine and water reinforcer magnitudes. The goal of experiment 2 was to directly compare BtwPR and WinPR BPs obtained using cocaine and water reinforcers in order to determine if BtwPRs and WinPR obtained with cocaine and water reinforcers were different.

Experiment 1

Methods and materials

Subjects—Sixty-four male Holtzman Sprague Dawley rats were used. Rats weighed approximately 400 g and were housed in pairs in plastic cages (42.5 × 22.5 × 19.25 cm). Following surgery, the rats were singly housed for the duration of the experiment in order to protect the catheter/harness assembly used for SA. Rats in both the cocaine ($n = 40$) and water ($n = 24$) reinforcer conditions described below were fitted with harnesses (although only the cocaine SA rats were implanted with catheters). Lights were on in the colony room from 2000 to 0800 hours. All behavioral testing occurred between 0800 to 1300 hours. Subjects were acclimated to the light cycle for at least 7 days prior to behavioral testing. Food (Harlan Teklad Laboratory Diet #8604, Harlan Inc., Indianapolis, IN, USA) was continuously available. All rats were maintained on a water restriction schedule in which they had free access to water for 20 min following test sessions. This study was conducted in accordance with the guidelines set up by the Institutional Animal Care and Use Committee of The University at Buffalo, The State University of New York.

Self-administration apparatus—Twenty-four experimental chambers were used. These chambers have been described in detail previously (Richards et al. 1997). Briefly, the chambers have stainless steel grid floors, aluminum front and back walls, and Plexiglas sides and top. Three snout poke holes were located on the left, center, and right sides of the test panel. Stimulus lights were located above each of the three snout poke holes. A stimulus light located on the middle of the back wall of the test chamber was used as a house light. Response contingent auditory feedback was produced by a Sonalert device (Mallory, SC628R), which produced a pure tone at 2,900 Hz. Snout pokes and head entries were monitored with infrared detectors. The entire apparatus was computer controlled using a MED Associates interface with MED-PC (version 4). The temporal resolution of the system is 0.01 s. Before each session, Vascular Access harnesses (VAH95AB, Instech Solomon,

Plymouth Meeting, PA) were connected to a flexible polyethylene tubing enclosed in a spring tether (PS95, Instech Solomon, Plymouth Meeting, PA, USA) attached to a swivel (375,22PS Instech, Plymouth Meeting, PA, USA) mounted by a single axis balance arm (CM375BP, Instech Plymouth Meeting, PA, USA) on top of the chamber allowing the animal to move freely around the operant chamber. Water and cocaine reinforcers were delivered using syringe pumps (Model # PHM-100, Med Associates).

Drugs—Cocaine hydrochloride was gifted by NIDA (RIT Log no: 13070-12C, ref # 013277), solutions were made weekly, and cocaine was dissolved in sterile saline. Concentrations of the cocaine solutions for SA were adjusted as 0.5, 1.5, and 5.0 mg/mL according to dose (0.1, 0.3, or 1.0 mg/kg/inf, respectively). Pump duration was adjusted according to body weight in order to deliver the correct dose of the drug. Infusion durations ranged between 1.55 and 2.25 s.

Procedure—The purpose of this experiment was to examine BtwPR performance across a range of water and cocaine reinforcers. There were three groups of rats assigned to self-administer cocaine (0.1, $n = 16$; 0.3, $n = 16$; or 1.0, $n = 8$ mg/kg/inf) and three groups of rats assigned for water reinforcement (0.01, $n = 8$; 0.03, $n = 8$; or 0.1 mL/reinforcer, $n = 8$).

Intravenous catheterization—Rats assigned to cocaine conditions were anesthetized using ketamine/xylazine (60.0 and 5.0 mg/kg, i.p., respectively). The right external jugular vein was carefully isolated through blunt dissection of the surrounding tissue and the catheters were inserted approximately 3 cm into the vein. As a control for possible stress effects due to the harness, rats in the water reinforcer groups were fitted with harnesses and attached to the infusion tether during testing.

The catheters were flushed 6 days a week with 0.2-mL solution of enrofloxacin (4.0 mg/mL) mixed in a heparinized saline solution (50 IU/mL in 0.9% sterile saline) to preserve catheter patency. At the end of behavioral testing, each animal received an i.v. infusion of ketamine hydrochloride (0.5 mg/kg, i.v., in 0.05 mL) and the behavioral response was observed to verify catheter patency. Only rats with patent catheters were used in data analysis. One rat from the 1.0-mg/kg/inf cocaine group was removed from the analysis due to failure of the catheter patency test.

Experimental chamber pre-exposure—After 1-week recovery from surgery, animals in both the cocaine and water groups were tethered and placed into the experimental chambers for three 60-min preexposure sessions during which the experimental chambers were dark and snout poke responses had no programmed consequences. The infusion lines were filled with saline during this phase. This phase was conducted in order to habituate the rats to being tethered in the experimental chamber prior to operant training for cocaine or water reinforcers.

BtwPR reinforcement—Following the 3-day preexposure period, rats were exposed to a BtwPR schedule of reinforcement. BtwPR test sessions began with a seeking phase followed by a consumption phase. During the seeking phase, the experimental chambers were dark. The left snout poke hole was designated as active, and snout pokes into this hole resulted in a “click” sound produced by briefly turning on the Sonalert (0.01 s). During the seeking phase, rats were required to complete a fixed ratio in order to initiate the consumption phase. Rats were allowed 1 h to complete the required ratio. Completion of the seeking fixed ratio resulted in illumination of the house light, signaling that the seeking phase had terminated and consumption period had begun. Failure to complete the seeking ratio within the 60 min was determined to be the “between-session breakpoint”. On those occasions when the

animal failed to complete the seeking ratio, the consumption phase was automatically started. The seeking ratio was increased across days using the progression as follows: 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 48, 64, 96, 128, 192, 384, 512, 768, 1,012, 1,536….etc. The PR value was decreased to one fourth of its value after each BP determination. For example, if a rat failed to meet a ratio of 48, the criterion seeking ratio for the next test session was set at 12.

The experimental chamber remained illuminated for the 2-h duration of the consumption phase. Responses to the active alternative during the consumption phase were reinforced on a FR1 schedule of reinforcement. Reinforced responses resulted in illumination of the stimulus light located directly above the active snout poke hole, auditory feedback, and presentation of water into the snout poke hole or an infusion of cocaine. A 30-s time-out period followed each reinforcer presentation during which the reinforcer was unavailable. The light remained on for 30 s and responses that occurred during the 30-s time-out were not followed by auditory feedback. The duration of the consumption phase was 2 h. Maximum session duration was therefore a total of 3 h (1 h seeking and 2 h consumption).

Each rat was trained on this procedure until three BtwPR BPs were obtained. No special training was used to shape initial responding and the rats were not primed at any point with cocaine or water. As is described in the data analysis section, some rats trained with the two low doses of cocaine (0.1 and 0.3 mg/kg/inf) failed to acquire responding and were removed from the study. The criterion for acquisition was to reliably earn greater than 10 water or cocaine reinforcers during the consumption phase. Of the rats that met the criterion for inclusion in the study, the minimum number of days required for a rat to achieve 3 BtwPR BP was 12 days and the maximum number of days was 28. The average number of days to obtain the highest of the largest BtwPR BP was 20.8±0.8.

Data analysis

BtwPR BPs, the cumulative amount of cocaine and water consumed, and the numbers of cocaine/water reinforcers earned during the consumption period were the dependent variables. Three BtwPR BPs were obtained for each animal. The largest BP of the three was transformed using a Log base 10 and was used for statistical analysis (Richardson and Roberts 1996). The average number of reinforcers earned and the average cumulative amount of cocaine or water reinforcement earned in the three sessions prior to the largest BP were used for analysis. Cumulative reinforcement was calculated as: (number of reinforcers earned × dose/volume) during the consumption phase.

Only 6 of the 16 rats tested at the 0.1-mg/kg/inf dose met the criterion for acquisition of cocaine self-administration. Eleven of the 16 rats tested at the 0.3-mg/kg/inf cocaine dose met the acquisition criterion and seven out of eight rats tested at the 1.0-mg/kg/inf cocaine dose were included in the data analysis (one rat removed due to catheter patency). One rat in the 0.01-mL water/reinforcer condition failed to meet the criterion for inclusion and was not used in the data analysis (final $n = 7$). All eight rats in the 0.03 and 0.1 mL water/reinforcer groups acquired water reinforced responding.

The BPs, number of reinforcers earned, and cumulative amount of reinforcement earned during consumption were analyzed for water and cocaine groups separately using a one-way analysis of variance (ANOVA). Post-hoc Tukey HSD tests were conducted to elaborate upon significant F tests. For all statistical tests, an alpha criterion of $p = 0.05$ was used. A Pearson's correlation was determined between BtwPR BP and cumulative amount of reinforcement earned during consumption for both cocaine and water reinforcers.

Results

BtwPR BP

Cocaine—A one-way ANOVA of the cocaine BPs (Fig. 1a) produced a main effect of dose [$F(2,23) = 4.121$, $p<0.05$]. Post-hoc Tukey tests revealed rats responding to gain access to 1.0 mg/kg/inf had significantly higher BPs than rats responding to gain access to 0.1 mg/kg/inf. There were no significant differences in BPs between rats responding for access to 0.1 and 0.3 mg/kg/inf. These data indicate that the reinforcing value of cocaine increases as a function of dose of cocaine.

Water—A one-way ANOVA of the water BPs (Fig. 1b) produced a main effect of water volume [$F(2,22) = 7.397$, $p<0.05$]. Post-hoc Tukey tests revealed rats responding to gain access to 0.1 mL of water/reinforcer had significantly higher BPs than rats responding for 0.01 and 0.03 mL/reinforcer. There were no significant differences in BPs between rats responding for access to 0.01 and 0.03 mL/reinforcer. These data indicate that the reinforcing value of water increased as a function of the volume of water. In general, rats in the water reinforced group had greater BtwPR BPs than rats in the cocaine reinforced group across the range of doses and water amounts tested.

Cumulative magnitude of reinforcement

Cocaine—There was a main effect of dose of cocaine on cumulative reinforcement during the consumption period [$F(2,23) = 17.314$, $p<0.05$]. Post-hoc Tukey tests revealed that rats self-administering 1.0 mg/kg/inf earned a significantly larger cumulative dose across the consumption period than rats self-administering 0.1 and 0.3 mg/kg/inf. Rats responding for 0.3 mg/kg/inf did not significantly differ in the cumulative dose of cocaine earned during the consumption period compared to rats responding for 0.1 mg/kg/inf. These data indicate that cumulative dose of cocaine earned during the consumption period increases as a function of dose of cocaine infused (Fig. 2a).

Water—There was a main effect of volume of water on cumulative reinforcement earned during the consumption period [$F(2,22) = 176.963$, $p<0.05$]. Post-hoc Tukey tests revealed that rats responding for 0.1 mL/reinforcer earned a significantly greater volume water across the consumption period than rats responding for 0.01 and 0.03 mL/reinforcer. Furthermore, rats responding for 0.03 mL/reinforcer earned a significantly greater volume of water than rats responding for 0.01 mL/reinforcer. These data indicate that cumulative volume of water earned during the consumption period increases as a function of volume of water per reinforcer presentation (Fig. 2b).

Number of reinforcers

Cocaine—There was a main effect of dose of cocaine on number of reinforcers earned during the consumption period [$F(2,23) = 3.508$, $p<0.05$]. Post-hoc Tukey tests revealed that rats self-administering 1.0 mg/kg/inf earned significantly fewer infusions across the consumption period than rats self-administering 0.1 mg/kg/inf. There were no significant differences in the number of reinforcers earned between rats self-administering 1.0 and 0.3 mg/kg/inf. Nor were there significant differences in the number of reinforcers earned between rats self-administering 0.1 and 0.3 mg/kg/inf. These data indicate that the number of reinforcers earned during the consumption period decreased as a function of dose of cocaine infused (Fig. 2c).

Water—There was a main effect of volume of water on the number of reinforcers earned during the consumption period [$F(2,22) = 7.158$, $p<0.05$]. Post-hoc Tukey tests revealed that

rats responding for 0.03 mL/reinforcer earned a significantly larger number of reinforcers across the consumption period than rats responding for 0.01 and 0.1 mL/reinforcer. No other significant differences were observed. These data indicate that the function describing the relationship between the number of water reinforcers earned and the volume of water earned per reinforcer was an inverted "U" shaped function (Fig. 2d).

Association between seeking breakpoint and cumulative magnitude of reinforcement—There was a significant positive association between seeking BP and cumulative dose of cocaine earned during the consumption period [$r = 0.48$, $p<0.05$] and a similar significant association between seeking BP and cumulative volume of water earned during the consumption period [$r = 0.76$, $p<0.001$]. The relationship between the seeking BP and cumulative consumption of cocaine and water are illustrated in Fig. 3a, b, respectively. These figures graphically show that increasing BtwPR BPs (or seeking) corresponded to increases in the cumulative amount of the water and cocaine reinforcers consumed.

Experiment 2

Methods and materials

Subjects—Sixteen male Holtzman Sprague Dawley rats were used in this experiment. The rats were housed and water restricted as described in "Experiment 1". Rats were assigned to either cocaine (1.0 mg/kg/inf, $n = 8$) or water (0.1 mL/reinforcer, $n = 8$) conditions. One rat failed to acquire SA and was therefore excluded from analysis. Therefore, the final sample size in the cocaine condition was a total of seven rats.

Drugs—Cocaine hydrochloride was prepared and delivered as described in "Experiment 1". Rats in the cocaine group were trained with a dose of 1.0 mg/kg/inf.

Intravenous catheterization—Rats in the cocaine group were implanted with catheters as described above in "Experiment 1".

Self-administration preexposure—After 1-week recovery from surgery, animals in both the cocaine and water groups were tethered and placed into the operant chambers for three 60-min preexposure sessions during which the operant chambers were dark and snout poke responses had no programmed consequences.

BtwPR with a WinPR as the consumption component—Following the 3-day preexposure period, rats were exposed to a BtwPR schedule of reinforcement. The seeking phase was identical to that described in "Experiment 1"; however, the consumption component was different from that described in "Experiment 1." In the consumption component of Experiment 2, rats were exposed to a within-session PR schedule of reinforcement. Rats earned reinforcers according to a WinPR schedule of reinforcement in which the fixed ratio was progressively incremented according to the same progression as that used for the BtwPR: 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 48, 64, 96, 128, 192, 384, 512, 768, 1,012, 1,536….etc. Maximum session duration was 6 h. Rats were given 1 h to complete the BtwPR seeking ratio followed by a consumption phase during which cocaine or water reinforcers were available according to the WinPR schedule of reinforcement. The consumption phase lasted a maximum of 5 h. Failure to complete the WinPR requirement in 1 h determined the WinPR BP and resulted in termination of the test session.

Data analysis

BtwPR BPs (obtained during the seeking component) and WinPR BPs (obtained during the consumption component) were the dependent variables. Three BtwPR BPs were obtained

for each animal. The largest BtwPR BP of the three was used for analysis. The highest WinPR BP for the three test sessions prior to the test session in which the largest BtwPR BP was obtained was used for analysis. BtwPR and WinPR BPs were transformed using log base 10 and compared for cocaine and water reinforcers separately using within-subject *t* tests.

Results

Cocaine BPs—Rats in the cocaine group had significantly higher within-session BPs compared to between-session BPs [$t(6) = -3.486$, $p<0.05$]. These data indicate that cocaine rats emitted a greater amount of effort to obtain one cocaine infusion in the WinPR BP procedure than in the BtwPR BP procedure which produced access to multiple infusions in a cocaine binge (Fig. 4).

Water BPs—The opposite pattern of results emerged for rats responding for water reinforcement. Rats in the water group had significantly higher between-session BPs compared to within-session BPs [$t(7) = -4.335$, $p<0.05$]. These data indicate rats emitted a greater amount of effort in the BtwPR BP procedure to gain access to a period of water consumption during which they received multiple reinforcers than in a WinPR BP procedure that produced a single presentation of 0.10 mL water (Fig. 4).

Discussion

BtwPR BPs increased as a function of increasing volumes of water. Similarly, the BtwPR BPs for rats responding to gain access to a period of cocaine reinforcement increased as a function of increasing cocaine doses. The increasing BPs reflected increases in the cumulative amount of reinforcer earned during the consumption period. These results indicate that increasing reinforcer magnitude (dose of cocaine or volume of water) results in a greater amount of effort (seeking) to gain access to a period of reinforcer consumption. This pattern of results indicates that a BtwPR is a practical procedure for measuring the reinforcing effectiveness of natural and drug reinforcers.

The results of “Experiment 2” indicate that WinPR and BtwnPR procedures provide different estimates of the reinforcing effectiveness of cocaine. In “Experiment 2”, BtwPR and WinPR BPs were obtained for water and cocaine reinforcers within the same animal. The finding that WinPR BPs for cocaine (but not water) reinforcers were greater than BtwPR BPs suggests that cocaine reinforcers may have response enhancing effects that increase BPs obtained using the WinPR procedure.

Cocaine-induced increases in responding—There is evidence that cocaine increases operant responding in rats, even when cocaine is not response contingent. Using rats that have been previously well-trained to self-administer cocaine using a lever press response, Norman and Tsibulsky (2006) reported that lever press responding was maintained even when cocaine was administered non-contingently. Their data indicated that the rate of responding (up to certain point) is an increasing function of estimated circulating cocaine levels. This interpretation of cocaine SA being induced by increasing blood levels of cocaine is compatible with the results we obtained with the WinPR procedure in “Experiment 2.” Further support for the interpretation that having cocaine on-board enhanced responding is provided by Fowler et al. (2007). This study carefully monitored movements that occurred during a cocaine binge through the use of a force plate. They reported that rats self-administering cocaine (0.3 mg/kg/inf) displayed a range of unconditioned responses to cocaine including intense bouts of locomotion and focused stereotypy. However, they were unable to determine if these unconditioned behaviors contributed to, or interfered with, operant responding for cocaine. Taken together with the results of Norman and Tsibulsky

discussed above and the present WinPR results, it seems possible that cocaine-induced activation may result in increased rates of responding—particularly when the response has been well-trained as was the case in the Norman and Tsibulsky study. To summarize, (1) the response-inducing effects reported by Norman and Tsibulsky, (2) behavioral activation effects reported by Fowler et al., and (3) in conjunction with reports of priming (de Wit and Stewart 1981) suggest that cocaine reinforcers may have response enhancing effects in WinPR procedures.

In contrast to the results obtained from the WinPR procedure, the results of the BtwPR paradigm do not support Norman and Tsibulsky's hypothesis that operant responding is a function of elevated cocaine levels. In the BtwPR procedure, operant responding increases across test days in the absence of cocaine. The dose-dependent increases in the BtwPR BPs described in this paper clearly indicate that access to a cocaine binge is reinforcing in the absence of circulating levels of cocaine in the blood. This dose-dependent increase in seeking would not have been predicted by Norman and Tsibulsky because animals are in a drug-free state during this phase (therefore, no change in responding between these groups would be predicted by the Norman and Tsibulsky hypothesis).

Animal models of drug-seeking—Relapse often occurs after periods of abstinence (forced or voluntary) (Miller 1996; Miller et al. 2001). The BtwPR procedure measures drug seeking while the animals are in a drug-free state and may model relapse after abstinence. The BtwPR procedure dissociates drug taking into clearly separable seeking and consumption phases, making it possible to independently evaluate the two phases. Previous researchers have used procedures similar to the BtwPR procedure described in this paper to measure the reinforcing effectiveness of cocaine. Griffiths, et al. (1979) required baboons to complete large fixed ratios for a single infusion of cocaine, followed by long (3 or 12 h) time-out periods. Fixed ratio requirements were increased across days until zero or one self-injection was earned. The authors found that increasing cocaine doses resulting in higher BPs. Ranaldi and Roberts (1996) tested rats using a PR in which the response cost of cocaine was increased across test sessions. Their procedure differed from the current BtwPR paradigm in two ways: (1) animals were housed in the operant chamber, and the lever was introduced to signal drug availability, whereas in the current experiment rats were placed in the operant chambers prior to daily test sessions and (2) the same FR was used in both the seeking and consumption phases, whereas in the current experiment, completion of only one fixed ratio was required prior to access to cocaine or water under an FR1 schedule of reinforcement. Using a comparable cocaine injection dose (approximately 1.8 mg/kg/inf), these authors found BPs (<40 responses) that were somewhat lower than the BPs reported in this paper.

Most of the current procedures used to examine drug-seeking such as: seeking-taking chain schedules (Economidou et al. 2009; Olmstead et al. 2001; Olmstead et al. 2000; Pelloux et al. 2007; Vanderschuren and Everitt 2004), continued responding during periods of extinction (Belin et al. 2008), and demand schedules (Christensen et al. 2009) test animals while under the influence of cocaine. In the seeking-taking chain schedule, animals respond on a seeking lever that provides access to another lever that ultimately results in drug delivery. The time between drug deliveries is usually less than 15 min—not long enough to allow for complete clearance of the drug at the doses tested. With the exception of the first seeking requirement of the test session, all other "seeking" periods occur while the animals are under the influence of the cocaine. Christensen et al. (2009) used a demand schedule to test the elasticity of food and cocaine reinforcers. With this approach, rats were required to emit one fixed ratio per reinforcer delivery, the ratio was increased every third test day, regardless of the rats performance. The results indicated that rats gained similar number of food reinforcers despite increasing ratio requirements. In contrast, the number of cocaine

infusions declined rapidly as fixed ratio requirements increased. This procedure is similar to the seeking–taking chain schedules used in cocaine self-administration, in that with the exception of the first ratio emitted, the animals are responding under the influence of the drug. Perhaps the inelasticity observed for cocaine may have reflected the absence of response facilitating or priming effects of cocaine due to failure to complete the first fixed ratio of the test session. In other paradigms, periods of drug unavailability/availability are alternated within a single test session (Belin et al. 2009; Belin et al. 2008). The period of drug unavailability, during which seeking is measured, is relatively short (15 min), too short in duration to allow for complete clearance of drug.

A disadvantage of the BtwPR procedure pointed out in Roberts et al. (2007) is that it takes multiple test sessions to determine the BP. In contrast, the WinPR procedure provides a BP after every test session. The relationship between BPs obtained with BtwPR and WinPR procedures is not known. For example, do drug treatments affect WinPR and BtwPR BPs similarly? It seems likely that both approaches provide important information about drug-seeking. Choice of which procedure to use is best determined by the hypothesis being tested.

Summary and conclusion—Rats completed a response requirement to gain accesses to a period of cocaine or water consumption. The number of responses the animals completed was found to be a function of increasing amounts of water or cocaine earned during the consumption period. We observed that animals worked harder to gain access to a smaller amount of cocaine (when under the influence of the drug) compared to the amount of work emitted in a drug-free state to gain access to a much larger amount of cocaine. Rats working for a water reinforcer under the same conditions had the opposite pattern of results. The results suggest that having cocaine on-board increases responding on the WinPR procedure, perhaps due to priming and response-inducing effects.

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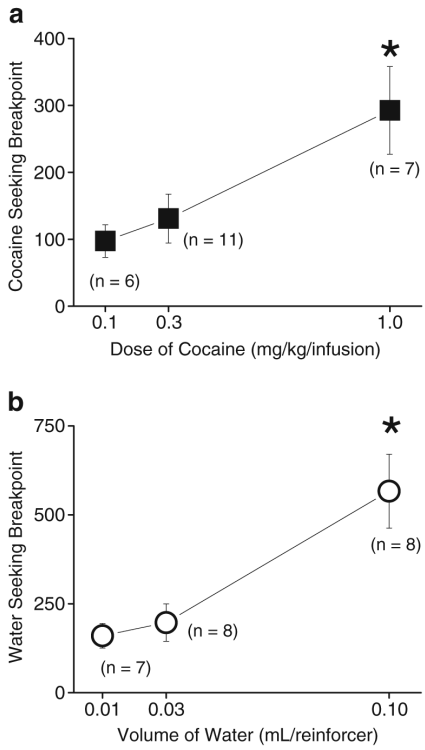

Fig. 1.

These plots indicate BtwPR-seeking BPs for cocaine and water reinforcers as a function of dose of cocaine or amount of water **a** The *top panel* shows BtwPR-seeking BPs as a function of the dose of cocaine available during the consumption phase (0.1, 0.3, and 1.0 mg/kg/inf cocaine). **b** The *bottom panel* shows BtwPR-seeking BPs as a function of the water amount available during the consumption phase (0.01, 0.03, and 0.1 mL/reinforcer). Note that the *Y*-axis values are different for the cocaine and water plots. $*p<0.05$ indicate a significant difference between reinforcer magnitude. See text for detailed description

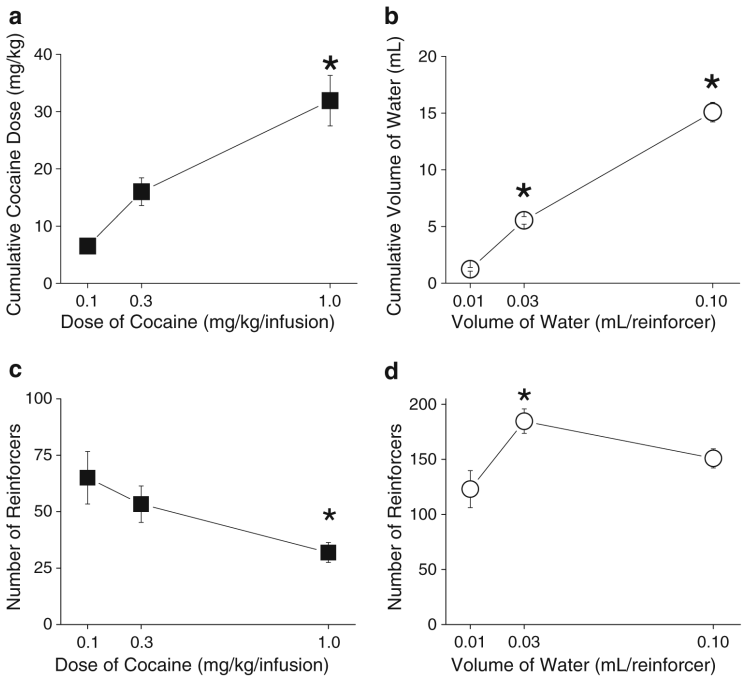

Fig. 2.

These plots indicate the cumulative amount of water and cocaine reinforcers earned during the consumption periods. The *top panels* shows the cumulative amount of cocaine/water consumed as a function of cocaine dose (**a** 0.1, 0.3, and 1.0 mg/kg/inf) or water amount (**b** 0.01, 0.03, and 0.1 mL) per reinforcer available during the consumption phase. The *bottom panel* shows the number of reinforcers earned as a function of cocaine dose (**c** 0.1, 0.3, and 1.0 mg/kg/inf) or water amount (**d** 0.01, 0.03, and 0.1 mL) per reinforcer available during the consumption phase. Note that the *Y*-axis values are different for the cocaine and water plots. *$p<0.05$ indicate a significant difference between reinforcer magnitudes. See text for detailed description

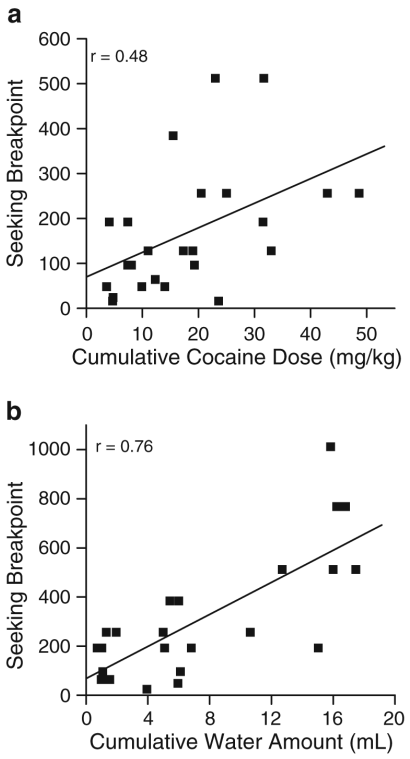

Fig. 3.

Scatter plots showing associations between the seeking BP and cumulative consumption of water and cocaine in experiment 1. Cumulative reinforcement of cocaine or water is represented on the *X*-axis, and seeking breakpoints are represented on the *Y*-axis. **a** Plot indicates that there was a significant positive association between cumulative dose of cocaine self-administered and the BtwPR BP. **b** Plot indicates that there was a significant positive association between cumulative amount of water earned and the BtwPR BP. Note that the Y axis values are different for the cocaine and water plots. See text for detailed description

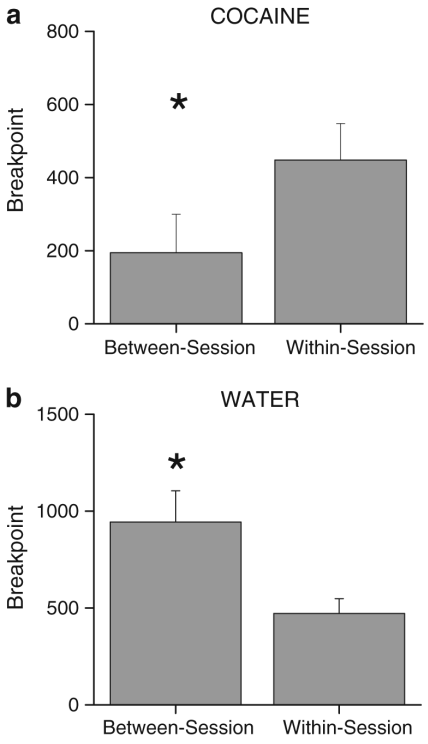

Fig. 4.

These plots compare BtwPR-seeking BP and WinPR BPs across reinforcer type (cocaine or water) in experiment 2. **a** Rats emitted a greater amount of effort to gain access to one infusion of 1.0 mg/kg of cocaine (as measured by the within-session breakpoints) compared to the amount of effort to gain access to a period of cocaine SA (as measured by the between-session breakpoints). **b** Rats emitted greater amount of effort to gain access to a period of water reinforcement (as measured by the between-session breakpoints) compared to the amount of effort for one presentation of 0.l mL of water (as measured by the within-session breakpoints). *p<0.05 indicate that the BtwPR BP is significantly different from the WinPR BP. See text for detailed description