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Effect of acute and repeated cocaine exposure on response matching capabilities of Sprague–Dawley rats responding for sucrose on concurrent schedules of reinforcement

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ABSTRACT

Cocaine exposure impairs the ability to match responding when rewarded and non-rewarded response options are reversed. However, it is unclear whether the impairment can also be observed when two rewarded responses differing in delay or magnitude of reward are reversed. Therefore, we tested the effect of acute (Experiment 1) and repeated (Experiment 2) cocaine on response matching between options dynamically varying in reinforcement schedule. Male Sprague–Dawley rats responded on concurrent fixed ratio 25 (FR25) and variable ratio 15 (VR15) schedules for sucrose. On tests, a progressive ratio (PR) schedule replaced the VR15, creating a within-session dynamic reversal point. In Experiment 1, acute cocaine (0, 1, 3 or 15 mg/kg IP) did not alter response matching. In Experiment 2, rats chronically exposed to cocaine (30 mg/kg/day × 5 days, IP) were tested after a 10-day withdrawal period on three sets of FR25/PR matching tasks with varying rates of PR escalation. Cocaine pre-exposure significantly increased perseverative matching errors, although repeated testing compensated the impairment. These results suggest that prior exposure to cocaine can produce perseverative behavior even when animals are required to match two well-learned and rewarded response options. The implications for addictive behaviors are discussed.

1. Introduction

Responding is considered "perseverative" when it continues outside the appropriate context, in the absence of desired consequences, or in the presence of significant costs, such as in the case of addictions (Jentsch et al., 2002; Ridley, 1994). Perseveration is common in patients with frontal lobe damage (Hornak et al., 2004; Lombardi et al., 1999) and is also associated with a number of psychiatric disorders such as Alzheimer's (Pekkala et al., 2008), Parkinson's disease (Gauntlett-Gilbert et al., 1999), and obsessive–compulsive disorders (Roh et al., 2005).

In drug addiction, perseverative responding to drugs and drug-related cues may represent a form of cognitive-behavioral impairment central to the pathology (Lane et al. 2007; Loh et al. 1993; Ridley 1994). Cocaine dependent individuals appear especially prone to perseverative behaviors. In fact, when compared to individuals addicted to other drugs, they displayed significantly more perseverative errors on a probabilistic reversal learning task (Ersche et al., 2008). In this task, participants were given a choice between two options, one correct and one incorrect. After the contingencies were reversed, cocaine users made more responses on the previously correct option. Similarly, perseverative responding in the form of "chasing," defined as continued gambling to recoup losses (Lesieur, 1984), is a key characteristic of pathological gambling (Leiserson and Pihl, 2007), and there is high co-morbidity between cocaine abuse and pathological gambling (Hall et al., 2000; Kausch, 2003).

Studies in animals have suggested that perseverative responding may be the result of cocaine exposure. Vervet monkeys were trained on a reversal learning task in which they displaced one of three objects in order to obtain a food reward (Jentsch et al., 2002). After learning the initial object-reward contingency, the food reward was moved to one of the previously non-rewarded objects, creating three response options: correct responses on the newly rewarded object, perseverative errors on the previously rewarded object, and acquisition errors on the never rewarded object. Chronic cocaine exposure increased perseverative errors only (Jentsch et al., 2002).

Chronic cocaine administration has also been found to cause perseverative-like responding in rats. Using a go/no–go task in which they were required to make or withhold responses to a food well following presentation of a odor cue predictive of reward or punishment, Schoenbaum et al. (2004) found that prior exposure to cocaine impaired learning reversal of the odor-outcome contingency. Using a cross-maze, Goto and Grace (2005a) tested the ability of rats to switch from a visual directed task (i.e. turn towards visual cue) to a response directed task (i.e. always turn right), and they found that chronic cocaine caused impairments in switching between strategies.

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Central to these behavioral effects of cocaine may be its action on central dopaminergic (DA) activity. In fact, chronic administration of cocaine enhances (Kalivas and Duffy, 1993a; Pettit et al., 1990) its ability to elevate mesocortical DA levels (Hurd et al., 1989; Hurd and Ungerstedt, 1989), and enhanced DA activity has been associated with perseveration (Goto and Grace, 2005b). There are even intriguing reports of sudden emergence of perseverative-like behaviors in Parkinson's patients treated with various DA agonists (Dodd, Klos et al. 2005; Drapier, Drapier et al., 2006).

However, in most animal studies mentioned above, the behavioral impairments may have resulted from a combination of cocaine-induced perseveration, and an inability to overcome avoidance of previously negative, or unrewarded, response options (i.e., learned non-reward). The need to distinguish between these two mechanisms was highlighted by Roesch et al. (2007) who reported no impairment by cocaine exposure on response matching tasks involving a choice between two appetitive options varying in either delay or magnitude of reward. That is, cocaine-treated animals showed hypersensitivity to changes in delay and magnitude of reward, but their ability to switch responding on the basis of altered outcomes was not impaired. This result is clearly opposite to the findings of experiments using reversal learning tasks where cocaine-treated animals appear impaired in switching from reinforced to un-reinforced response options.

Therefore, the current study was designed to investigate the effects of cocaine on response matching in a reversal-type task where animals dynamically selected between two different levers (A and B) differing in schedule of reinforcement. More specifically, following the principle of the matching law (i.e., rats preferentially respond to a lever with the lowest response-reinforcement contingency requirements; Herrnstein and Loveland, 1975), rats were initially given the opportunity to develop a preference for one of two levers (Lever A) because of its association with a more favorable reinforcement schedule. Then, the response requirements on this lever were gradually increased within session, eventually making the alternate lever (Lever B) the more favorable response option. In this situation, a point of response "equivalence" was defined as the point where the response-reinforcement contingency on the two levers is identical. Therefore, animals were expected to respond on Lever A until this point, and then switch responding to Lever B. Responses made on Lever A after the equivalence point were operationally defined as "perseverative" because they were no longer associated with a more favorable outcome. Alternatively, responses made on Lever B prior to the equivalence point were considered "conservative" because they did not maximize the number of reinforcers obtained. This testing design controls for learned non-reward because animals always choose between two response options that are both well learned and both reinforced, and this is essential to verify whether the reversal impairments reported after cocaine exposure reflect cognitive inflexibility (Schoenbaum et al., 2004) or inability to overcome avoidance of previously negative, or unrewarded, response options. Experiment 1 tested the effect of acute cocaine on this novel response matching task because cocaine can potentially alter PR responding for food (Brown and Stephens, 2002), and it causes premature responding (van Gaalen et al., 2006) which could lead to impairments in response matching. Experiment 2 tested the effects of repeated cocaine administration on response matching to further characterize cocaine-induced impairments noted in reversal learning tasks (see Stalnaker et al., 2009 for review).

2. Methods and materials

2.1. Subjects

Subjects were adult male Sprague–Dawley rats (Charles River, QC) weighing 275–300 g at the beginning of all experiments. They were single-housed, maintained on a reverse light/dark cycle (8:00 am lights off; 8:00 pm lights on), and behavioral testing occurred during their dark cycle. Initially, rats were allowed to habituate to the facility for 6 days and were then handled twice for approximately 10 min before the beginning of the experiments. Two days prior to the beginning of testing, rats were food restricted to 85% of their free-feeding weight, with increases of 20 g/week to allow normal growth. Animals were fed immediately following testing sessions, and were given approximately 10 g of food per day. All experiments were approved by the Animal Care Committee of the University of Guelph and were carried out in accordance with the recommendations of the Canadian Council on Animal Care.

2.2. Apparatus

2.2.1. Operant conditioning chambers

Sixteen Plexiglas operant conditioning chambers (model ENV-008CT, Med Associates, Lafayette, IN) were each enclosed in larger sound-attenuating plywood boxes (model ENV-018 M, Med Associates). Each operant conditioning chamber had two retractable levers (10 cm apart and 8 cm above the floor of the box), which were both "active" in that each activated the feeder, but with different schedules of reinforcement (see below). The chamber also had two house lights (28 V): one was located on the same wall of the levers and the other was located on the opposing wall, both lights were illuminated throughout the duration of each test. Each chamber was equipped with a food hopper, mounted on the exterior of the chamber, which delivered sucrose pellets (45 mg Dustless Precision Pellets; Bio-Serv, Frenchtown, NJ) in a magazine feeder located between the two levers.

2.2.2. Locomotor activity chambers

Horizontal and vertical locomotion was monitored using 12 custom made chambers (15.75″×16.125″×11.25″) constructed of semi-transparent Plexiglas and lit by individual LED lights (42 diodes). Each chamber was covered by black wire mesh to allow video tracking. The tracking software employed was EthoVision (version 3, Noldus Information Technology, The Netherlands).

2.2.3. General procedures

The task developed to assess response-matching capability was based on the observation that normal rats are sensitive to response–reinforcement contingencies and they tend to prefer (i.e., allocate more responding) more advantageous response options. The procedure used in these experiments involved three training phases and one test phase.

2.3. Phase 1 — training on 1st lever

Training sessions consisted of a 5 min habituation period in the absence of lights or levers, followed by a 1 h session during which the lights were activated and a single lever was introduced in the chamber. Rats pressed this lever for sucrose pellets delivered according to a continuous reinforcement schedule (Fixed Ratio 1 — FR1 — one pellet for each response). This type of training continued until rats responded consistently throughout the entire duration of the session (approximately 5 days). The schedule was then gradually increased to a fixed ratio 25 schedule (FR25 — 25 responses per pellet) over 5 days. Training sessions with the FR25 were maintained until responding was consistent throughout the entire duration of at least 2 consecutive sessions.

2.3.1. Phase 2 — training on 2nd lever

These training sessions began immediately after responding stabilized on the 1st lever. On each session of this phase, the alternate lever was introduced in the chamber, and responses were reinforced according to a variable ratio 15 schedule (VR15 — an average of 15 responses for each pellet). Training sessions with the VR15 were maintained for each rat until their responding was consistent throughout the entire duration of at least 2 consecutive sessions. A variable schedule was used to habituate the animals to unpredictable changes in response–reinforcement contingency, and this was deemed necessary to

prevent immediate shift in responding to the FR25 level on test days (see below).

2.3.2. Phase 3 — training with both 1st and 2nd levers simultaneously available

Rats were given 3 sessions with both levers presented simultaneously: the 1st on the same FR25 schedule and the 2nd on the same VR15 schedule. Pilot studies in our laboratory indicated that rats distinguish between the two schedules and preferentially respond on the VR15 lever. Rats that failed to emit at least 75% of total responding in 1 h on the 2nd lever by the end of the third test session were removed from the experiment (approximately 10% of subjects tested).

2.3.3. Phase 4 — test with both 1st and 2nd levers simultaneously available

For this test, both levers were inserted in the chamber. The schedule on the 1st lever remained FR25, however, the schedule on the 2nd lever (i.e., previously VR15) was substituted with a progressive ratio (PR) schedule (response ratio $= (5 \times e^{(0.2 \times \text{reward number})}) - 5$; Roberts and Bennett 1993). In this situation, the "equivalence" point of responding is defined as the point at which response-reinforcement contingencies of the two levers is identical (i.e. 25 responses/reinforcer; see Fig. 1A). Ideally, animals should respond on the 2nd lever (PR lever) until the equivalence point is reached, and then switch responding to the 1st lever (FR25). Therefore, responses on the 2nd lever after the equivalence point can be considered "perseverative" because they are no longer associated with a more favorable response-reinforcement contingency. Alternatively, responses made on the 1st (FR25) lever prior to the equivalence point can be considered "conservative" because, at the initial stage of the PR schedule, the response–reinforcement contingency is move favorable on the 2nd lever (PR). These responses can be considered as "errors" because they deviate from optimal number of responses per reinforcer, and therefore reduce the maximum number of reinforcers obtainable.

2.4. Experiment 1: acute cocaine

2.4.1. Experiment 1A: effects of acute cocaine on locomotor activity

In this experiment, the locomotor response to an acute cocaine challenge was tested in 12 rats. This test involved an injection of vehicle followed by 1 h of observation in the activity chamber, and then an injection of 3, 5, 9, or 15 mg/kg cocaine (IP) followed by another hour of observation. The results of this locomotion study were used to determine the doses used for Experiment 1B.

2.4.2. Experiment 1B: effects of acute cocaine on response matching to changing reinforcement contingencies

In this experiment, 41 rats were employed to assess the effect of acute cocaine administration on conservative and perseverative errors. Therefore, just prior to the first response-matching test, all rats received an injection of vehicle to establish a baseline level of performance with concurrent FR25 and PR schedules. Following this test, rats received 3 additional days of training with concurrent FR25 and VR15 schedules (Phase 3 above) to re-establish a preference for the VR15 lever. The animals were then assigned to one of 4 dose groups: 0 (vehicle; $n = 12$), 1 ($n = 8$), 3 ($n = 11$), and 15 mg/kg ($n = 10$) cocaine, and given a second FR25/PR test 5 min following drug administration.

2.4.3. Experiment 2: effects of repeated cocaine on response matching to changing reinforcement contingencies

In this experiment, 40 rats were employed to assess the effect of repeated cocaine administration on conservative and perseverative errors. A modified version of the task was employed to specifically investigate whether frequency of errors could be affected by repeated testing and by rate of PR escalation. This experiment had three phases.

2.4.4. Phase 1 — pre-training

Initial training for this experiment was as described above, but testing involved 18 sessions. This was necessary to manipulate rate of escalation of the PR schedule, and hence vary how rapidly the equivalence point could be reached. Three different PR schedules were used escalating at different rates (see Fig. 2): PR1, response ratio $= (5 \times e^{(0.2 \times \text{reward number})}) - 5$; PR2, response ratio $= (5 \times e^{(0.05 \times \text{reward number})}) - 5$; PR3, response ratio $= (5 \times e^{(0.02 \times \text{reward number})}) - 5$. The order of PR schedule presentation was counter-balanced across animals, and all rats received 6 tests on each PR schedule (hence 18 tests) before (baseline) and after the period of cocaine treatment. At the end of this pre-training phase, rats were assigned to two groups on the basis of overall responding and total responding on the PR lever.

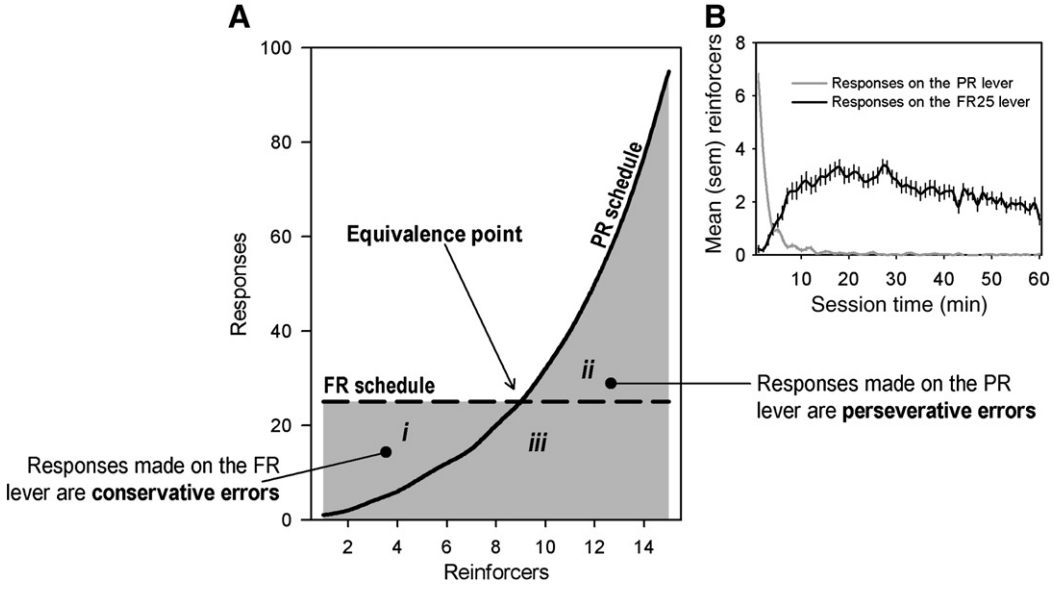

Fig. 1. A: Theoretical relationship between responding on two concurrent schedules of reinforcement and obtainable reinforcers. The "ideal" pattern of responding involves a selection of the PR lever up to the equivalence point and then a switch to the FR25 lever. Conservative errors are responses made on the FR25 lever before the equivalence point and perseverative errors are responses made on the PR lever after the equivalence point. B: Mean (sem) reinforcers (sucrose pellets) obtained on the PR and FR25 levers over time during the baseline test session of Experiment 1b.

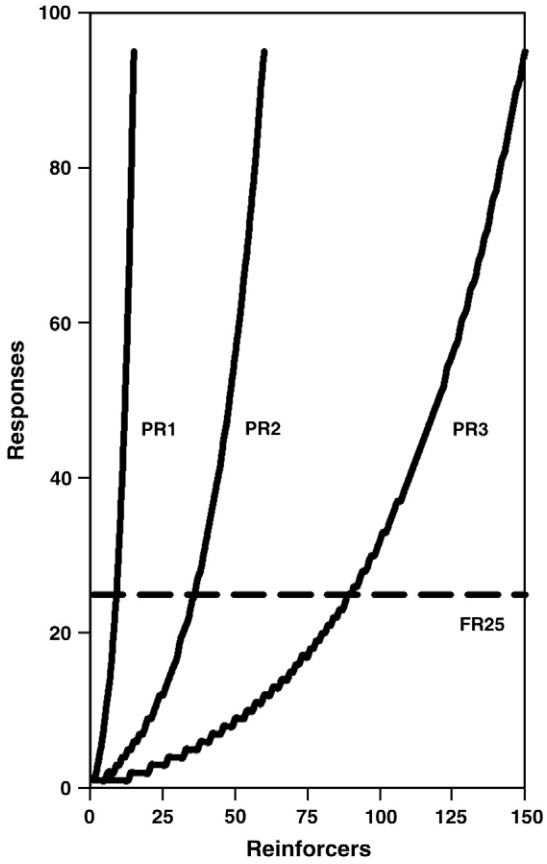

Fig. 2. Rate of response–reinforcement escalation for the three progressive ratios tested in Experiment 2: PR1 — Response ratio = $(5 \times e^{(0.2 \times \text{reward number})}) - 5$; PR2 — Response ratio = $(5 \times e^{(0.05 \times \text{reward number})}) - 5$; PR3 — Response ratio = $(5 \times e^{(0.02 \times \text{reward number})}) - 5$.

2.4.5. Phase 2 — cocaine treatment and test of locomotion

The groups received one injection a day of 0 ($n = 21$) or 30 ($n = 19$) mg/kg cocaine (IP) for 5 days administered in the housing colony. This regimen was selected because of its effectiveness in inducing locomotor sensitization (Kalivas and Duffy, 1993a,b). To verify sensitization in our experiment, all rats were tested in activity chambers 24 h after the last cocaine injection. This test involved an injection of vehicle followed by 1 h of observation, and an injection of 15 mg/kg cocaine (IP) followed by another hour of observation. Animals were left undisturbed in the home cages for 10 days before the beginning of Phase 3.

2.4.6. Phase 3 — testing

Response matching tests included 18 sessions and involved the same procedures described in Phase 1 above.

2.5. Drugs and dosages

Cocaine HCL (Dumex, Toronto, On) was dissolved in physiological saline. The doses selected for Experiment 1B were based on the results of Experiment 1A (see Results). In addition, 1 and 3 mg/kg were selected on the basis of studies indicating that these doses have minor effects on responding for food reward in rats (Harris et al., 1978). As mentioned above, the selection of dose/regimen employed in Experiment 2 was based on previous studies of cocaine-induced sensitization (Kalivas and Duffy, 1993a,b).

2.6. Statistical analysis

For Experiment 1B, perseverative and conservative errors were analyzed using separate two-factor mixed design ANOVAs (Drug Group: independent factors; Test: repeated factor), and in Experiment 2 they were analyzed using separate three-factor mixed design ANOVAs (Drug group: independent factor; Test Session: repeated factor; and PR Schedule: repeated factor). The second factor (i.e., Test Session) was included to detect possible changes in responding due to repeated testing on a given PR schedule. Significant interactions or main effects were analyzed by multiple comparisons using Fisher LSD with an alpha level of 0.05. Group differences were analyzed using parametric (*t*-test) or non-parametric (Mann–Whitney *U* test) planned comparisons depending on whether the assumption of normal distribution was violated. Planned comparisons were anticipated to analyze groups at the different FR25/PR tests. For both Experiment 1A and 2, to equate for baseline individual differences in locomotion expressed following vehicle (i.e., saline) injections, locomotion data were expressed and analyzed as percent change from the 1st h following vehicle injection to the 1st h following the drug challenge, and group differences were analyzed using a *t*-test. Statistics were calculated using SigmaStat (version 3.0 for Windows, SPSS Inc) and GB-STAT School Pak (Dynamic Microsystems, INC, 1997). The exact values of non-significant statistical analyses are not reported.

3. Results

3.1. Experiment 1A: effects of acute cocaine on locomotor activity

The ANOVA indicated a significant effect of drug dose [$F(3, 12) = 7.84$, $p < 0.01$] and multiple comparisons revealed that while 9 and 15 mg/kg produced greater change in activity than 3 and 5 mg/kg, there was no difference between 9 and 15 mg/kg or 3 and 5 mg/kg (see Table 1). Since there were no behavioral differences between the doses at the high and the low ends of the spectrum, only the extreme doses were tested in Experiment 1B.

3.2. Experiment 1B: effects of acute cocaine on response matching to changing reinforcement contingencies

The typical pattern of responding during tests with concurrent FR25/PR schedules is represented in Fig. 1B; rats preferentially respond on PR lever for the initial portion of the session and then shift to the FR25. Fig. 3A represents mean number of total errors committed on test after acute vehicle and after acute cocaine. The top panels display perseverative errors, and the ANOVA revealed a significant main effect of Test (after vehicle vs. after cocaine; [$F(1,37) = 9.66$, $p < 0.01$]), but no effect of Drug Dose. The bottom panels display conservative errors, and the ANOVA revealed a significant interaction between Drug Dose and Test [$F(1,37) = 3.66$, $p < 0.05$]. Multiple comparisons indicated that there

Table 1
Results of locomotion activity tests performed in Experiment 1A and Experiment 2. The values represent mean (sem) percent change in locomotion from baseline to drug tests. In Experiment 1A, four different groups received a 1 h test after vehicle followed by a 1 h test following an injection of cocaine. The asterisk represents a significant difference from the 3 mg/kg group. In Experiment 2, animals were pre-treated (5 injections in 5 days) with vehicle or cocaine (30 mg/kg) and then tested for locomotion after a vehicle injection (1 h) and after a cocaine injection (1 h; 15 mg/kg).

Experiment 1A	
3 mg/kg	−23.4 (1.9)
5 mg/kg	−4.7 (7.1)
9 mg/kg	61.5 (15.0) *
15 mg/kg	72.3 (15.4) *
Experiment 2	
After vehicle exposure	28.6 (5.0)
After cocaine exposure	53.5 (8.4) *

was a significant increase in the number of conservative errors in rats injected with 15 mg/kg cocaine. But, when the pattern of responding induced by 15 mg/kg cocaine was analyzed over time (Fig. 3B), it was found that this dose suppressed lever pressing on both levers for the initial 40 min of the session (see panel ii). Further, to quantify a possible non-selective effect of 15 mg/kg cocaine on operant responding, percent change in total responding from vehicle to cocaine test sessions was analyzed using a one-factor ANOVA. Indeed, there was a significant effect of cocaine dose [$F(3, 37) = 22.78$, $p < 0.001$], and the largest change was observed in rats injected with 15 mg/kg cocaine (72% decrease), with the other doses showing non-significant changes (0 mg/kg = 0.3% increase; 1 mg/kg = 9% decrease; 3 mg/kg = 8% decrease).

3.2.1. Experiment 2: effects of repeated cocaine exposure on response matching to changing reinforcement contingencies

Fig. 4 represents mean perseverative and conservative errors made by vehicle- and cocaine-treated rats on tests 1, 3 and 6 given 10 days after the period of injections. For perseverative errors (top panels), the ANOVA revealed a main effect of PR Schedule [$F(2, 76) = 8.73$, $p < 0.01$], suggesting that perseverative errors increased as the rate of PR escalation

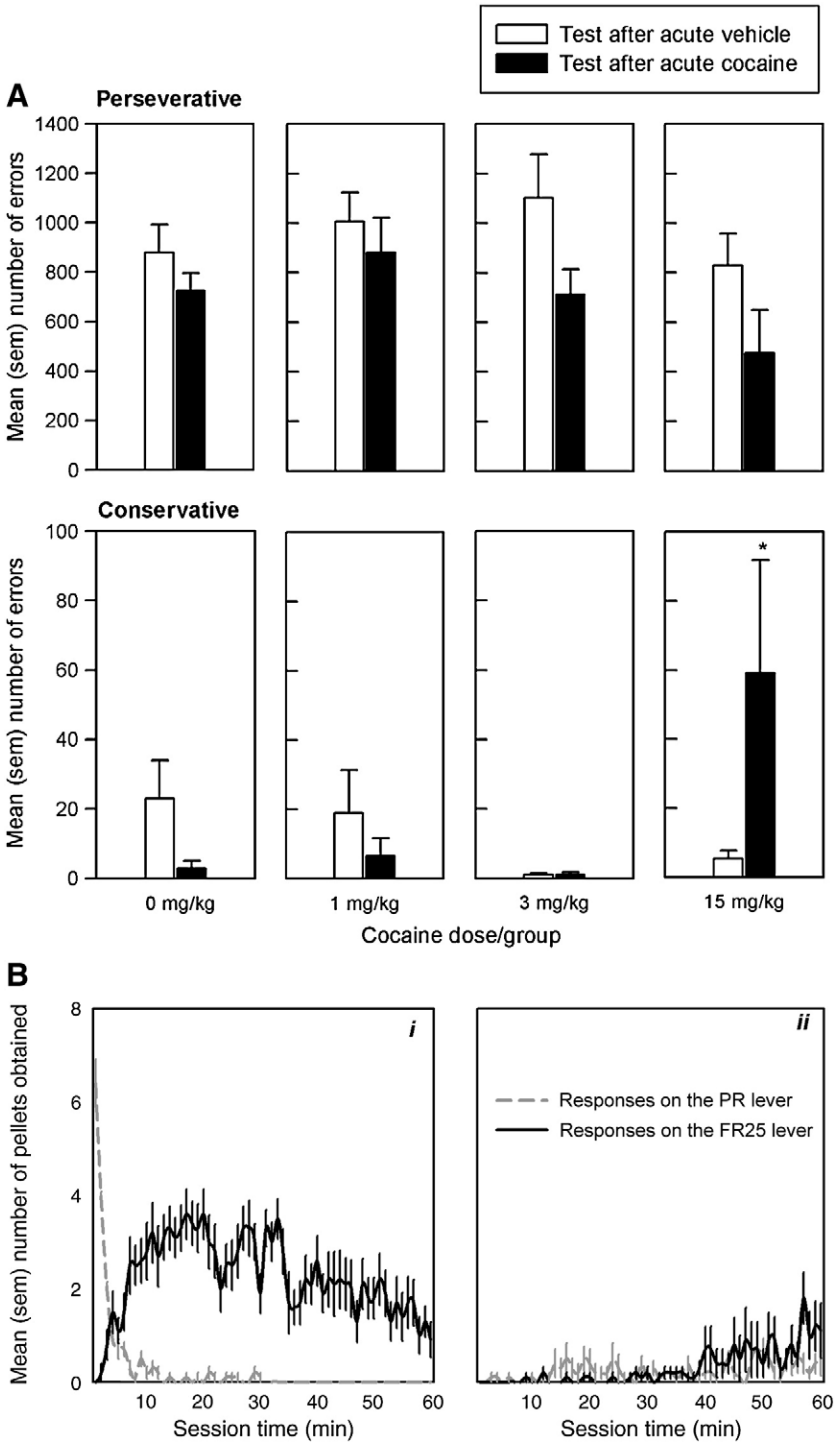

Fig. 3. A. Mean (sem) perseverative (top panels) and conservative (bottom panels) errors on the baseline (test after acute vehicle) and cocaine (test after acute cocaine: 0, 1, 3, or 15 mg/kg) test sessions. The asterisk represents a significant difference between tests ($p < 0.05$). B: Mean (sem) sucrose pellets obtained on the PR and FR25 levers by the 15 mg/kg cocaine group on the baseline (panel i) and cocaine (panel ii) test sessions.

decreases. There was also a significant interaction between Test Session and Drug Group [$F(2, 76) = 3.41$, $p = 0.038$]. This interaction was caused by cocaine-treated animals making significantly more perseverative errors on test 1, and planned comparisons showed this effect was mainly driven by significant differences in responding on PR2. There were no group differences on tests 3 and 6. For conservative errors (bottom panels) there was a significant effect of Drug Group [$F(1, 38) = 7.36$, $p = 0.01$] with vehicle-treated animals making significantly more errors than rats treated with cocaine. There was also a interaction between Test Session and PR Schedule [$F(4, 152) = 4.38$, $p<0.01$], with both groups making fewer conservative errors during test 1 on the PR1 schedule.

Unlike in Experiment 1, there were no significant differences in total number of responses on both levers between groups across PR schedules.

3.3. Locomotion

To assess the effect of cocaine pre-exposure on sensitivity to its stimulatory properties, mean percent change in locomotion from vehicle baseline induced by a cocaine (15 mg/kg) challenge in vehicle- and cocaine-treated rats was analyzed (see Table 1): animals pre-treated with cocaine showed a significantly greater locomotor response to the cocaine challenge [$t(38) = 2.37$, $p = 0.02$].

4. Discussion

In this study, the effects of acute and repeated cocaine exposure on response matching capability in rats were assessed in a task whereby animals dynamically selected a response option on the basis of the most favorable response–reinforcement contingency. On test days, rats were required to choose between one lever on a progressive ratio (PR) and a second lever on a fixed ratio 25 (FR25). When the response requirement on the PR lever became equal to the FR25, an equivalence point was reached, and after this point rats had to shift their responding from the PR to the FR25 lever to maximize the number of reinforcements obtained. Perseverative errors were responses made on the PR lever after this point, and conservative errors were responses made on the FR25 lever prior to this point. In Experiment 1, it was found that acute cocaine administration enhanced conservative errors at the highest dose, but this was probably the result of non-specific suppression of operant responding. In Experiment 2, when animals were tested drug-free after withdrawal from a sensitizing regimen of cocaine exposure, it was found that cocaine administration increased perseverative errors, although this effect was modulated by the rate of PR escalation and was significantly reduced by repeated testing.

In Experiment 1B, it was first established that drug-free rats do respond primarily on the PR lever at the beginning of the session and then switch to the FR25 lever soon after reaching the equivalence point (see Fig. 1B). That rats preferentially respond on a lever associated with a more favorable schedule of reinforcement is consistent with the matching law (Herrnstein and Loveland, 1975), and with the results of effort-based discounting studies (Floresco et al., 2008) showing that rats detect changes in response requirements and adjust their behavior accordingly. Following an acute challenge with cocaine at 1 or 3 mg/kg, it was found that both conservative and perseverative errors were not altered. In contrast, 15 mg/kg produced a significant increase in conservative errors, but it also caused a general suppression of operant

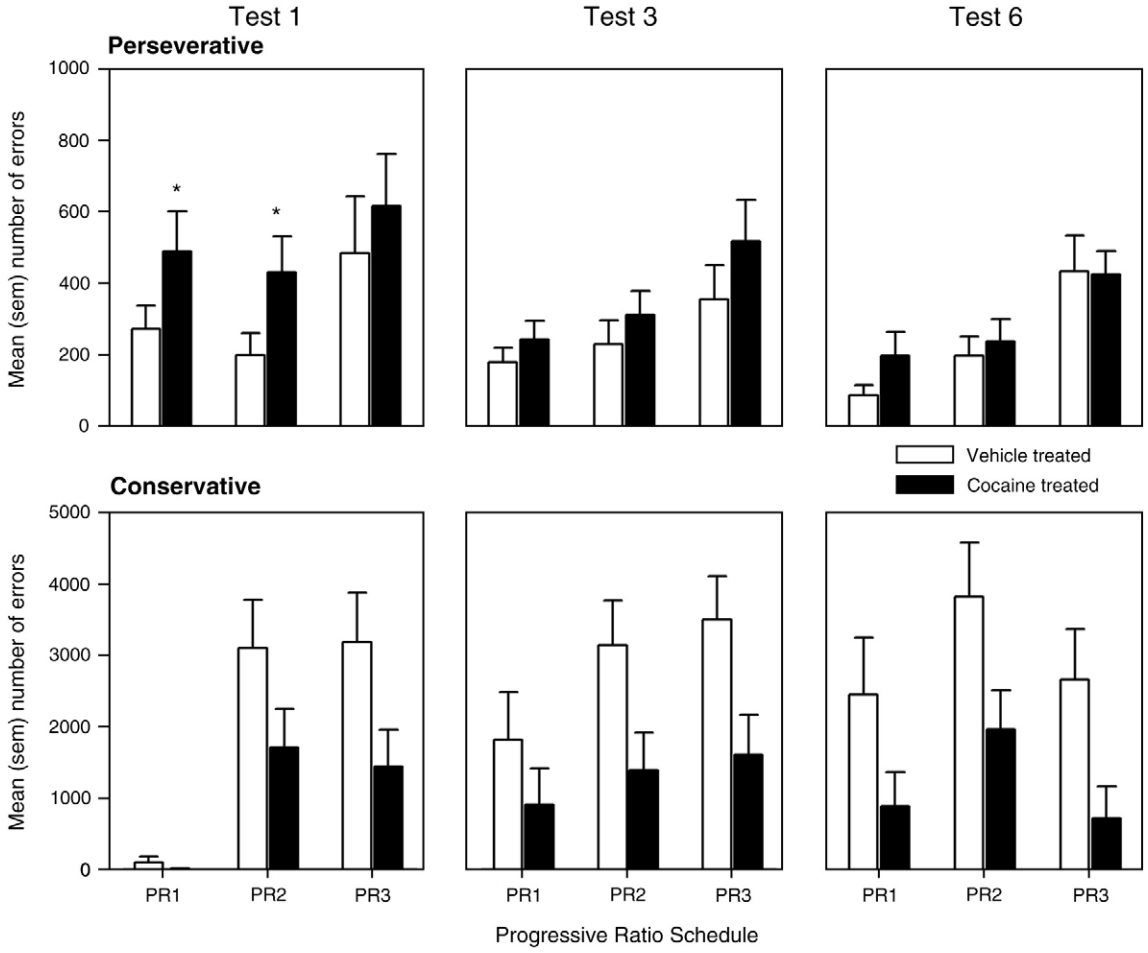

Fig. 4. Mean (sem) perseverative (top panels) and conservative (bottom panels) errors on the first, third and sixth tests in animals previously treated with vehicle or cocaine. At the time of testing, all animals were drug free. The asterisk represents a significant difference between groups ($p<0.05$).

responding (see panel ii of Fig. 3B). This confirms that it is difficult to assess the effects of cocaine on tasks that require operant responding for sucrose/food because cocaine can alter performance both by altering activity (Flagel and Robinson, 2007) and/or food consumption (Balopole et al., 1979).

In Experiment 2, animals were pre-trained and tested on the FR25/PR task, then exposed to cocaine, and after a 10-day withdrawal period, they were re-tested on the same FR25/PR task, drug-free. Locomotion analysis revealed sensitization to the stimulatory properties of cocaine; animals treated with cocaine showed a significantly greater response to a cocaine challenge (15 mg/kg) than animals chronically treated with vehicle. Cocaine sensitization was selected because of the established link between sensitization, DA hyperactivity, and impairments in reversal learning (Stalnaker et al. 2006, 2007, 2009). Also, cocaine sensitization can lead to a hypersensitivity of the mesocorticolimbic DA system that can be long lasting (Kalivas and Duffy, 1993a; Pettit et al., 1990). This was important to our experiment because it allowed conducting our tests while animals were in a hypothesized state of heightened DA reactivity (Avena et al., 2008; Fallon et al., 2007), but free of cocaine. In addition, psychomotor-induced sensitization is believed to increase following termination of drug injections (Flores and Stewart, 2000; Kolta et al., 1985; Paulson and Robinson, 1995). Therefore, although we did not re-assess locomotor sensitization at time closer to response-matching testing, we can assume that the system remained sensitized based on previous literature regarding the timeline of this process.

Analysis of the performance of the vehicle-treated animals showed that as the rate of PR escalation increased, number of perseverative errors decreased. This probably resulted from greater ease in detecting changes in the PR schedule, and the equivalence point, when the increase in response requirements for successive reinforcements escalated rapidly. Vehicle-treated animals also made a large number of conservative errors, and these errors increased with repeated testing. This suggests that normal animals learned to anticipate the equivalence point and started switching earlier based on expected changes in response–reinforcement contingency.

Repeated cocaine exposure caused a significant increase in perseverative errors on both PR1 and PR2 tests, but not PR3. That is, impairments in response matching were observed only when animals responded on PR schedules that escalated more rapidly. Furthermore, it was found that perseverative errors decreased with repeated testing on PR1 and PR2 schedules, suggesting that the impairment caused by cocaine sensitization was compensated by repeated experience with the task. Although more permanent impairments may have been observed by using a more robust regiment of cocaine exposure, such as that used in other reversal studies (Stalnaker et al., 2006), it should be noted that the order of the PR tests were counterbalanced across rats, and therefore repeated experience did not eliminate the effect of cocaine, it only masked it. That is, experience was beneficial only as long as the response-matching task was kept constant; when rats were switched to a new schedule the deficit reemerged.

There are several mechanisms that could account for the cocaine-induced elevation in perseverative errors noted in our study. First, it is possible that cocaine exposure altered the motivational properties of the sucrose and this in turn increased likelihood to commit perseverative errors. After all, progressive ratio schedules have been used to measure the motivational property of the reinforcer (Hodos, 1961), and cocaine has been found to alter PR responding when acutely administered before a session (Brown and Stephens, 2002; Jones et al., 1995). However, our task included a second lever that was also reinforced by sucrose, and rats were not required to respond to a breaking point on the PR lever. Therefore, any change in general motivation for sucrose should have increased total number of responses (though no change was observed in this study) but not distribution of responses between levers. A second possibility is that cocaine exposure caused an increase in general locomotion. This also does not seem a likely explanation for our results because there were no differences between saline and cocaine-treated animals in overall rate of responding; the difference was in the allocation of the responses. Third, it is possible that cocaine exposure altered the ability to discriminate between the two levers, and therefore increased perseverative errors by chance. Again, this interpretation appears unlikely because we observed a systematic distribution of errors in cocaine-treated animals: fewer conservative errors and greater perseverative errors grouped immediately following the equivalence point. Fourth, Leiserson and Pihl (2007) suggested that perseverative errors in humans reflect working memory impairments, and cocaine exposure produces memory deficits in rats (George et al., 2008). But, cocaine-treated animals were clearly able to learn the task as they showed significant improvements from test 1 to test 6 at both PR1 and PR2 tests. Interestingly, cocaine-treated rats also made fewer conservative errors, and this did not change with additional training. Failure to anticipate the equivalence point, and thus make fewer conservative errors, may represent a deficit in long term planning and appears homologous to the tendency of chronic drug users to make decisions based on immediate information without anticipating their long-term consequences (Barry and Petry, 2008; Verdejo-Garcia et al., 2007). Two final possible interpretations remain: cocaine exposure enhanced resistance to extinction (Beardsley et al., 1993; Gomez and Meisch, 2003) and therefore promoted additional responding on the PR lever, and/or cocaine exposure impaired ability to detect changes in the response–reinforcement contingencies. While it is impossible to distinguish between these two possibilities, we favor the second because we observed a consistent pattern of responding across test sessions, and this seems more consistent with a dynamic process of matching response options rather than responding on the PR lever to extinction before switching to the FR25 lever.

At a neurochemical level, it is possible that mechanisms responsible for the alteration in response matching capability are similar to those underlying cocaine-induced impairments in reversal learning. Thus, repeated cocaine administration may have altered activity of neurons sensitive to response-outcome in the orbitofrontal cortex (Stalnaker et al., 2006) and/or basolateral amygdala (Stalnaker et al., 2007). This may have resulted from altered DA activity in cortical, striatal and amygdalar regions as a result of repeated cocaine administration (Goto and Grace, 2005a). Firing rates of DA neurons in the ventral tegmental area increase when an unexpected reward is obtained, and decrease when an expected reward is not obtained (Schultz, 1998). Therefore, alterations in DA reactivity to drug or natural rewards (Harmer and Phillips, 1999) following cocaine exposure may impair the ability of this system to respond to changes in response–reinforcement contingency and lead to behavioral perseveration.

In conclusion, our results suggest that exposure to cocaine can increase perseverative errors in situations when animals are required to choose between two well learned and reinforced response options, and this is consistent with the results of reversal learning studies. But, our findings also suggest that tasks where animals must overcome avoidance of previously negative, or unrewarded, response options may reveal more pronounced and permanent deficits. Overall, these data suggest that heavy cocaine use could cause perseveration of inappropriate responding to appetitive stimuli. The involvement of DA in perseveration is of particular interest given that perseverative responding is a common feature of pathological gambling (Dickerson et al., 1987; Leiserson and Pihl, 2007), and there are reports of individuals with no prior gambling experience developing pathological gambling after treatment with DA agonists for Parkinson's disease (Dodd et al., 2005; Drapier et al., 2006), or restless leg syndrome (Tippmann-Peikert et al., 2007).

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