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ACUTE AND CHRONIC EFFECTS OF COCAINE ON THE SPONTANEOUS BEHAVIOR OF PIGEONS

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The present experiment examined the effects of acute and daily cocaine on spontaneous behavior patterns of pigeons. After determining the acute effects of a range of doses, 9 pigeons were divided into three groups that received one of three doses of cocaine daily, either 1.0, 3.0, or 10.0 mg/kg cocaine. Measures were taken of spontaneous locomotion, pecking, preening, and emesis. Under daily administration, cocaine induced consistent and substantial enhancements of its locomotor effects in all 9 pigeons, consistent with the phenomenon of locomotor sensitization. The maximum locomotor output did not differ according to the size of the daily dose. Locomotion was not elevated following tests of the saline vehicle, suggesting the effect was due to cocaine, not to a change in baseline or reactivity to the injection procedure. Cocaine dose-dependently decreased preening when given acutely, and those effects were not altered by repeated cocaine administration. Pecking occurred at very low rates and was unresponsive to cocaine treatment. Cocaine-induced emesis showed a dose-dependent increase under initial tests with cocaine, and those effects were attenuated following daily exposure. In a final condition, cocaine was replaced with daily saline for 30 days to assess the persistence cocaine-related increases in locomotion. Approximately half of the pigeons continued to show enhanced effects even after 30 days without cocaine, so although persistence was obtained, it showed marked intersubject variability. The data indicate that the effects of repeated cocaine administration on the behavior of pigeons shows parallels with many effects commonly reported with rodents (i.e., increased locomotion following repeated treatment, decrease in preening or grooming, persistence following drug withdrawal).

Key words: cocaine, sensitization, locomotion, preening, pecking, emesis, pigeon

Repeated treatment with cocaine often enhances its motor-stimulating effects, a phenomenon known as sensitization (Pierce & Kalivas, 1997; Robinson & Becker, 1986; Segal & Kuczenski, 1992; Stewart & Badiani, 1993; Woolverton & Weiss, 1998). Although the majority of research on sensitization has been conducted with rodents and primates, recent work has demonstrated sensitization to the locomotor stimulating effects of cocaine with birds (Geary & Akins, 2007; Pinkston & Branch, 2003). The finding that sensitization can be obtained in both avian and mammalian species is important, as it may suggest common pharmacological and behavioral processes have been conserved across evolution. In fact, neuroanatomical research supports such a conclusion and has shown that midbrain dopamine structures and their striatal targets, structures that are central to sensitization phenomena (Pierce & Kalivas, 1997 and Vezina, 2004), are homologous between birds and mammals (Reiner, 2002; Veenman, 1997).

In contrast, very little is known about cross-species commonalities in many other behavioral effects of cocaine. At present, only the enhanced locomotor effects have been studied. In addition to locomotion, examinations of repeated cocaine exposure with rodents and primates have shown that multiple responses may be affected. Repeated cocaine administration often leads to a disruption or suppression of grooming (Antoniou, Kafetzopoulos, Papadopoulou-Daifoti, Hyphantis, & Marselos, 1998; Carey, DePalma, & Damianopoulos, 2003; Cooper & van der Hoek, 1993) and the emergence of stereotyped behavior patterns (Kilbey & Ellinwood, 1977; Randrup & Munkvad, 1974; Segal & Kuczenski, 1992; White, Doubles, & Rebec, 1998). The ability of cocaine to effect similar changes in birds has not been well studied. In the present experiment, we attempted to replicate and extend our earlier research on pigeon locomotion

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(Pinkston & Branch, 2003). Additionally, we analyzed videotaped sessions to document changes in responses not captured by automated recording so as to provide a more complete account of the behavioral effects of acute and repeated cocaine exposure.

METHOD

Subjects

Nine experimentally naïve homing pigeons served as subjects. They were maintained at 80% of their laboratory free feeding weights, a deprivation level which is close to that of feral pigeons (Poling, Alling, & Nickel, 1990). An additional reason for using food deprivation was to make sure the crop was empty prior to drug administration; this was important because of emetic effects we observed in earlier pilot work and in the present experiment (see below). Body weight was maintained via feedings given immediately after experimental sessions. Between experimental sessions, each subject was housed individually in a temperature- and humidity-controlled colony room that provided a 16:8-hr light:dark cycle. Water and health grit were continuously available in the home cage.

Apparatus

The apparatus was a custom-built chamber for pigeons. The chamber walls were constructed of clear Plexiglas™. The floor of the chamber was made out of six moveable stainless steel panels. One edge of the panel was hinged to the frame of the chamber. The free end rested on a microswitch (Microswitch, V-1131). If the pigeon stepped anywhere on the panel, the microswitch was depressed. Thus, movement could be quantified by the movement of the pigeon from one panel to another. Additional details of the construction of the chamber and validation of its ability to measure locomotion has been published elsewhere (Pinkston & Branch, 2006). During experimental sessions, the plates were covered with paper (Sheperd Specialty Paper, Inc., four-ply poly pads) to catch excreta.

The chamber was housed in a wooden shell (47 cm × 64 cm × 45 cm). Ambient illumination was provided via six 1.1-W lights mounted inside the shell. Three lights were placed on the ceiling on each side of the long axis of the shell, equally spaced down its length. The top of the shell was open. A b/w camera (Panasonic WV-BL200) was mounted over this opening so that each pigeon's behavior could be recorded. The camera was connected to a VHS recorder (Emerson, EVR 20) located next to the chamber. White noise at 95 dB to mask extraneous sounds was present in the room where the chamber was located. Experimental events were controlled and data recorded by an experiment controller system operating under ECBASIC (Palya & Walter, 1993).

Procedure

General. Experimental sessions were conducted 7 days per week at the same time each day. Each session was preceded by a 5-min blackout. During this time, the chamber was dark and no data were recorded. After the blackout was over, the session began with onset of the houselights and lasted for 30 min. After a session was over, the pigeon was removed from the chamber and returned to the colony room where it was fed. Prior to drug testing, each pigeon was exposed to 10 habituation sessions to gather baseline data on unconditioned, spontaneous movement and to ensure stability in all behavioral measures prior to cocaine tests.

Assessment of cocaine's effects on locomotion. Each pigeon was exposed to several doses of cocaine. Doses of 0.3, 1.0, 3.0, 10.0, and 13.0 mg/kg, and the saline vehicle were tested. The dose of 13.0 mg/kg may seem peculiar. We were hesitant to include higher doses as we had observed lethal effects in some homing pigeons following administration of 18.0 mg/kg; 13.0 was selected because it is halfway (log spacing) between 10.0 and 18.0 mg/kg. Drug administrations were spaced by 5 days, and doses were administered initially in a descending order. At least two determinations of the effects of each dose were conducted to assess the reliability of the drug's effect; no more than four tests were made of any dose.

Once assessment of the initial effects of cocaine was completed, the 9 pigeons were divided into groups of 3 to examine the effects of repeated cocaine administration. Doses of 1.0, 3.0, and 10.0 mg/kg were selected as daily doses. We selected doses based on previous work in our lab examining cocaine on both pigeon operant behavior and locomotion. A

dose of 1.0 mg/kg is often without a behavioral effect in our lab, 3.0 mg/kg partly suppressed operant behavior and has been shown to induce locomotor sensitization in pigeons (Pinkston & Branch, 2003), and 10.0 often completely suppresses operant behavior. The daily dosing regimen began 5 days following the completion of assessment the acute dose–response function. Each pigeon was next given the selected dose prior to each daily session for 30 consecutive days. Once this initial period of the repeated dosing was completed, the other doses originally tested were administered again, in a context of continued administration of the chronic dose. Retests were accomplished by substituting these other doses for the daily dose. For example, if a bird had been given 1.0 mg/kg cocaine daily for 30 days, subsequent tests of 13.0, 10.0, etc. mg/kg were made every 5th day by substituting one of those doses for 1.0 mg/kg, and data from days prior to substitutions were used to analyze the effects at the daily dose. Substitutions were always given in a descending sequence. Each dose, including saline, selected for retest was given at least twice to ensure reliability in the effects; no dose was tested more than four times. Once dose-response functions had been redetermined, we halted cocaine injections to study behavior under withdrawal from daily cocaine. Cocaine administration was replaced by daily saline administrations for 30 days. At the end of the 30 days, cocaine dose–response functions were redetermined once more.

Observational analysis of behavior. During the course of assessing cocaine's acute effects on locomotion, we videotaped the habituation sessions, all sessions on days when cocaine or vehicle was administered, and all days immediately prior to those where cocaine or vehicle tests were made. We recorded three categories of behavior from videotaped sessions: pecking (wall or floor), preening, and emesis. The categories were selected based on pilot data and were also informed from the literature. Pecking and emesis were collected as counts; preening was recorded by duration. Videotapes were analyzed by one of the authors (JWP). Interobserver agreement was computed from video analysis by independent trained observers and was calculated for a random 50% of sessions by regressing the observer's data against the author's. Agreement across all categories of behavior was always very high ($r > .94$ for all comparisons).

Drug preparation and administration. Cocaine hydrochloride, obtained from the National Institute on Drug Abuse, was dissolved in 0.9% saline, which served as the vehicle. On days when cocaine was administered, injections were given immediately before entry into the chamber and were made into the breast muscle in a volume of 1.0 ml/kg. During daily administration, the site of injection alternated between the left and right breast. Doses are expressed terms of the salt.

RESULTS

Effects of Acute and Chronic Cocaine on Locomotion

Visual analysis of the data from the adaptation phase (not shown) suggested that day-to-day levels of locomotion were stable for all pigeons by at least the last 5 days of the phase. Individual linear regressions performed over the data from the last 5 days indicated that none of the slopes differed significantly from zero for any pigeon. The means of the last five sessions ranged from 0.32–2.87 panel activations per min across pigeons; single-day values ranged from 0.03–4.00 activations per min.

The locomotor effects of acute and repeated cocaine administration are shown in Figure 1. Note that the *y*-axes have been scaled separately for each pigeon. In general, acute tests of cocaine did not stimulate locomotion (filled circles). Only the function for one pigeon (7) showed locomotion to increase as dose increased. Following repeated treatment, however, cocaine resulted in vertical shifts in the dose–response function (open squares). Surprisingly, shifts occurred under all daily dosing conditions, including 1.0 mg/kg. In general, tests of the saline vehicle made during dose–response determinations were unchanged from values obtained under acute tests. Slight elevations under vehicle may be seen in the data from Pigeons 5 and 200, but these increases are not nearly as large as the changes in cocaine's effects, suggesting that the effects were due to cocaine and were not some general reaction to the repeated injections (see also the third determination of dose–response functions shown below). The only difference that was observed across groups was a tendency for the range of increases to be larger for the group exposed to daily 10.0 mg/

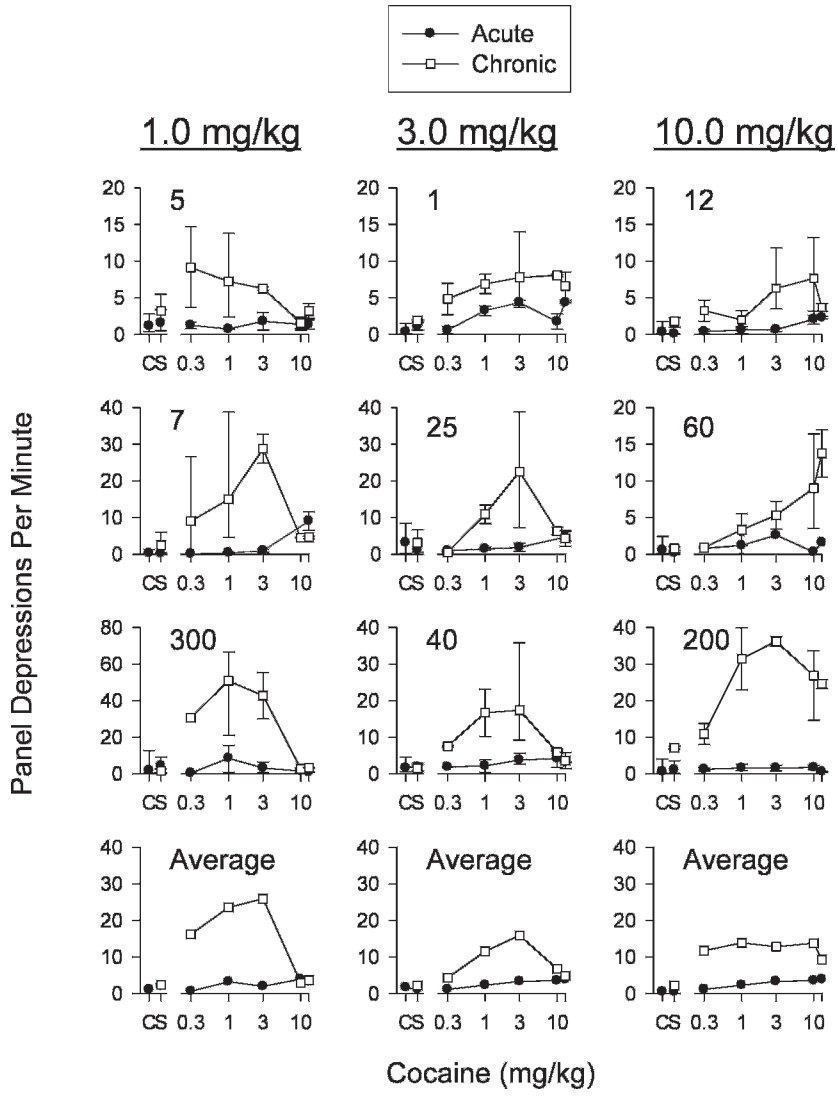

Fig. 1. Effects of acute and chronic cocaine on locomotion. For each pigeon, counts of panel activations are plotted against dose of cocaine. Averaged data across the group are shown at the bottom of each column. Filled circles indicate the effects of cocaine given acutely; open squares indicate the effects of cocaine following 30 daily injections. The dose given daily is indicated by the label at the top of each column. Points above ''C'' and ''S'' indicate data obtained during nondrug control sessions and observations of the saline vehicle, respectively. Note that the y-axis is scaled differently for each pigeon. Error bars denote the range of values.

kg. Specifically, the effects at the 10.0 and 13.0 mg/kg doses were increased for the 3 pigeons that received the 10.0 mg/kg dose repeatedly, for 1 pigeon exposed daily to the 3.0 mg/kg dose (25), and for no pigeons exposed repeatedly to the lowest dose.

A mixed-model ANOVA with one between-subject factor (Daily Dose) and two within-subject factors, one representing the dose-effect curve repeatedly determined in all subjects (Dose Curve) and one representing the dosing Regimen (Acute vs. Chronic), was applied to the group-average data. Note that data from nondrug control sessions were excluded from statistical analyses because there was no counterpart to them during daily cocaine treatment. The ANOVA revealed a significant effect of the Regimen, $F(1,6) = 8.8$, $p < .006$, and a significant Dose Curve X Regimen interaction, $F(5,30) = 5.6$, $p < .001$,

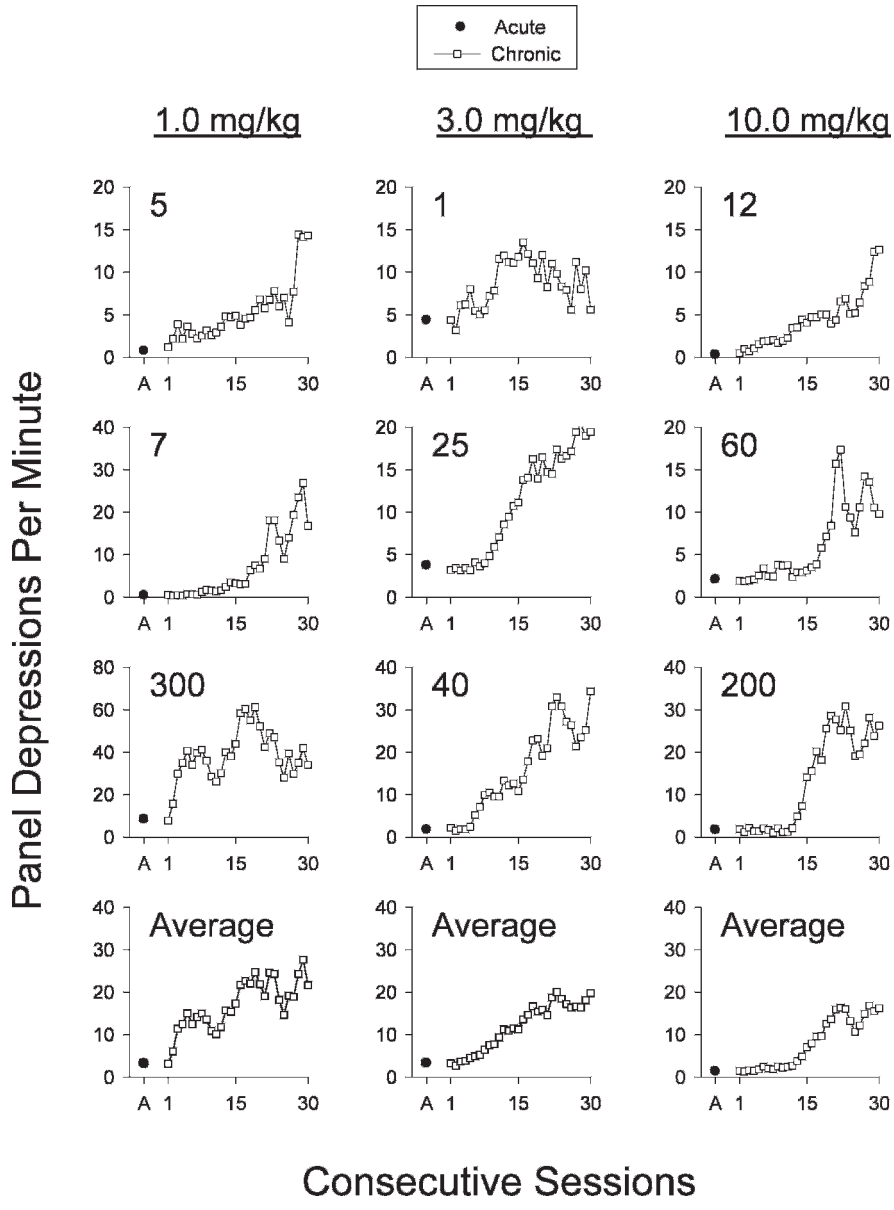

Fig. 2. Effects of repeated testing of cocaine on locomotion. Panel depressions per min are plotted across the 30 days of repeated exposure to cocaine (open squares). Average effects of the daily dose of cocaine obtained during acute determinations are replotted above the filled circles and labeled ''A'' in each graph. Column labels indicate the dose given daily. Note the y-axis has been scaled individually for each bird.

corroborating the impression that the functions did shift, but did not do so in parallel. No other effects or interactions were significant.

Figure 2 shows the changes in locomotion across the 30 days of repeated cocaine treatment. Importantly, at the start of the daily regimen, cocaine's effects were not different from that observed during acute dosing. In several instances, moreover, elevations in locomotion were not observed until after several administrations of cocaine. Of note is that all 9 subjects showed an increase, with the relative magnitude of increase ranging from a factor of 2 (doubling) to a factor of about 15.

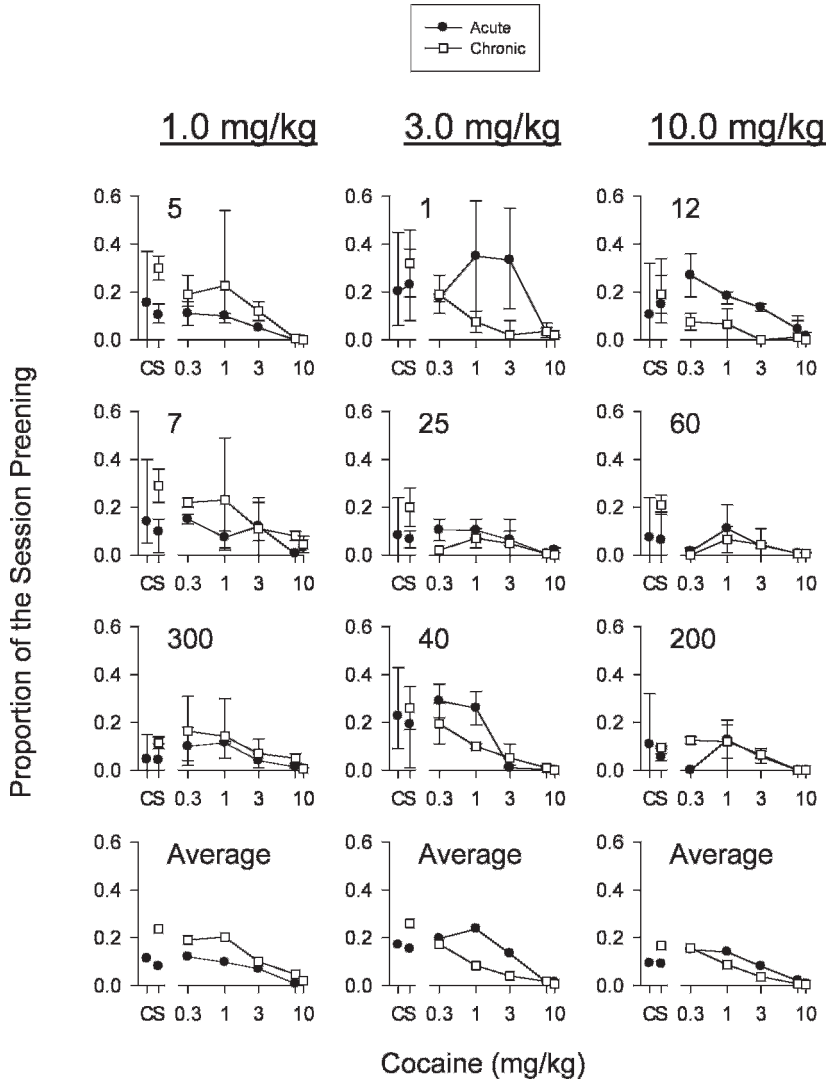

Fig. 3. Effects of acute and chronic cocaine on preening. Proportion of the 30-min session spent preening is plotted on the y-axis against dose of cocaine on the x-axis. Averaged data across the group are shown at the bottom of each column. Other details are the same as in Figure 1.

Effects of Cocaine on Pecking, Preening, and Emesis

We analyzed videotaped sessions in order to learn more about cocaine's effects on pigeon behavior other than locomotion. First, cocaine had no systematic effect on pecking. We observed only a few pecks during the habituation phase. Pigeons rarely made more than 15 pecks in any one session (range 0–48 pecks). During both acute and daily tests with cocaine, the number of pecks rarely exceeded more than 10 pecks over the session (range 0–34), and often no pecks were recorded. A mixed-model ANOVA, similar to that described above, found no significant effects or interactions. So, over the range of doses studied here, cocaine did not alter spontaneous pecking.

Preening, in contrast, was decreased dose-dependently by cocaine. Figure 3 shows the effects of cocaine before (filled circles) and after (open squares) repeated exposure. For all pigeons, preening was eliminated, or nearly so, by the largest doses of cocaine. Following repeated exposure to cocaine, dose–response functions generally were unchanged. A mixed-

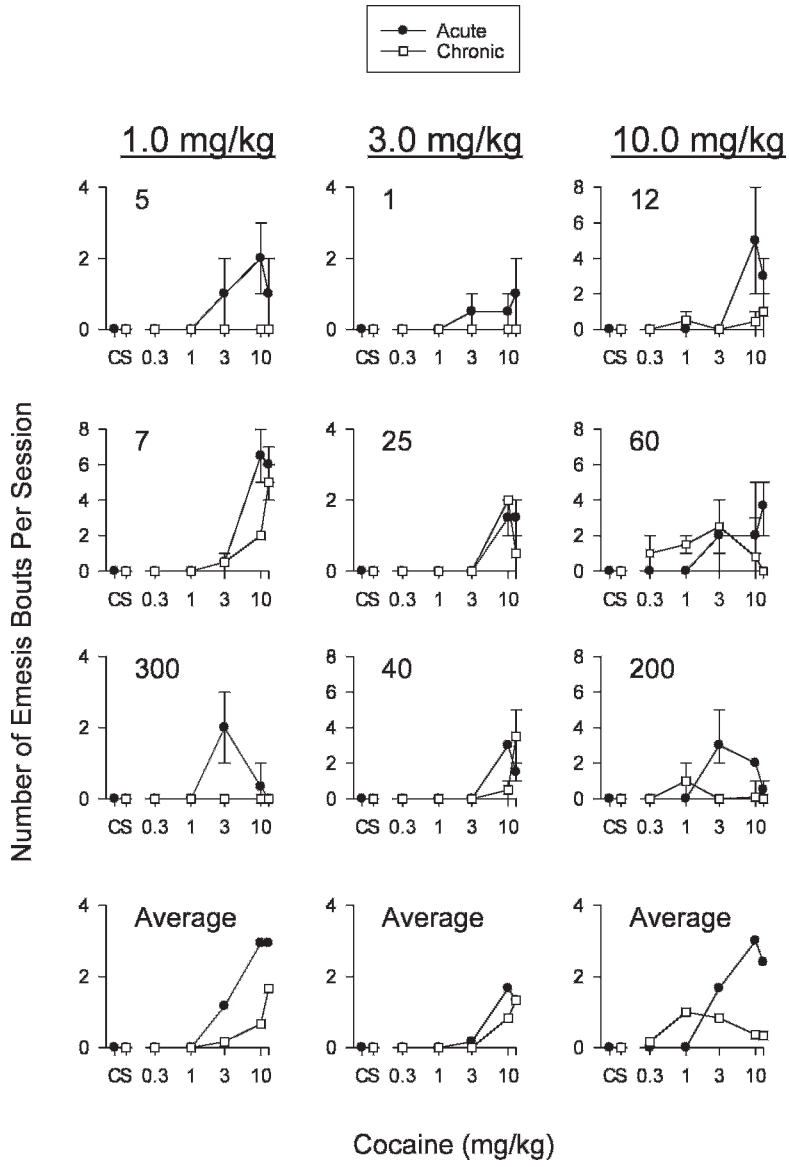

Fig. 4. Effects of acute and chronic cocaine on emesis. Number of emetic episodes are plotted on the y-axis as a function of cocaine on the x-axis. Averaged data across the group are shown at the bottom of each column. Other details are the same as in Figure 1.

model ANOVA revealed a significant effect of dose on preening, $F(5,30) = 24.9$, $p < .001$, but this effect did not change with repeated exposure to cocaine or the daily dose, nor was there any significant interaction among terms.

From the videotapes, we counted the number of emetic bouts that occurred in response to cocaine. Emetic bouts revealed a systematic and orderly relationship to cocaine administration, shown in Figure 4. Note that y-axes have been scaled individually for each pigeon. During initial tests with cocaine, emetic episodes occurred with increasing frequency as dose increased (filled circles); daily cocaine exposure attenuated those effects (open squares), although there appeared some slight increases in emetic response at smaller doses when pigeons were given daily 10.0 mg/kg cocaine. A mixed-model ANOVA, similar to that described above, revealed that the dose-

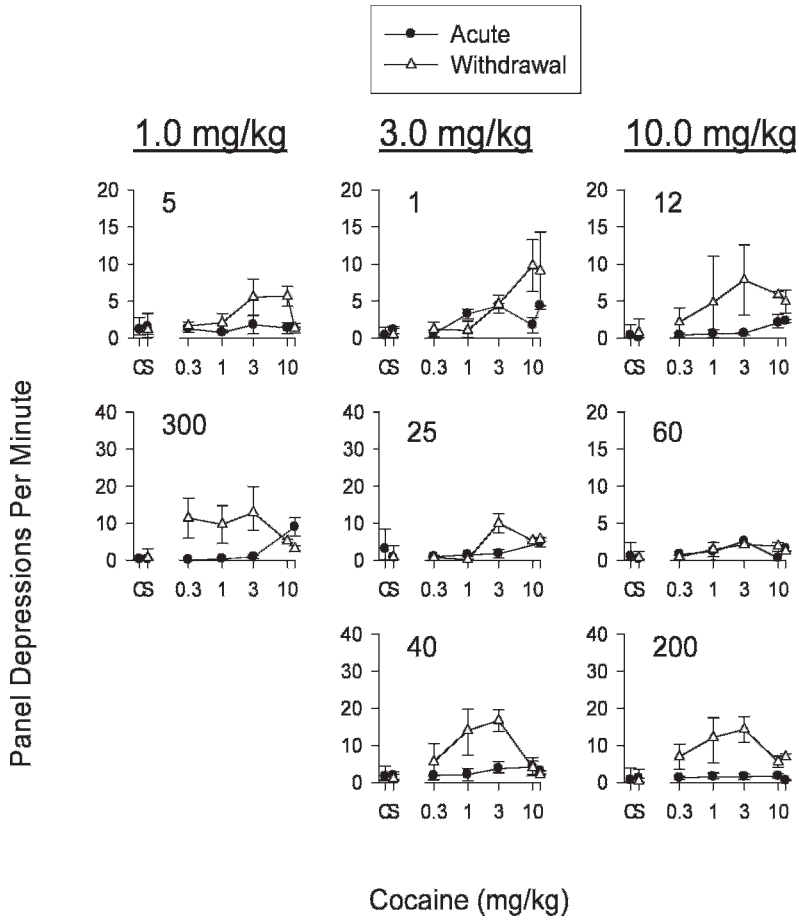

Fig. 5. Retention of cocaine-related increases in locomotion. Dose–response functions obtained following 30 daily injections of the saline vehicle are shown (open triangles) with the acute dose–response functions obtained for each pigeon (replotted from Figure 1). Details are the same as in Figure 1.

dependent increases in emesis were significant, $F(5,30) = 4.8$, $p < .002$, and that the attenuation following daily treatment was significant, $F(1,6) = 19.8$, $p < .004$. There was no main effect of daily dose or interaction.

Effects of Withdrawal of Daily Cocaine on Locomotion

Because the literature has suggested that changes in cocaine's locomotor-stimulating effects can be long lasting (e.g., Henry & White, 1995), we sought to examine if our observed increases were persistent in pigeons. So, following daily cocaine, the saline vehicle was substituted for cocaine and given for 30 days. At the end of 30 days, the dose–response functions were redetermined a third time. Pigeon 7 died of unknown causes during the middle of the daily saline regimen, and so no data were available from that bird. Data from the remaining pigeons are shown in Figure 5. Data from the acute determinations are replotted from Figure 1 for comparison.

The data show that elevations in the dose–response function did not persist for 2 pigeons (5 and 60). Following daily saline, the dose–response functions for those 2 birds approximated the effects seen during acute determinations. Two additional pigeons (25 and 1) showed some enhanced effectiveness of cocaine at one or two doses. Data from the remaining 4 pigeons, however, indicated that the shifts in the dose–response function were still evident 30+ days after cocaine was discontinued. The loss of pigeon 7 makes it difficult to assess a role for the daily dose. At least 1

pigeon in each group retained the elevated sensitivity to cocaine's locomotor effects, suggesting that all doses were at least capable of inducing relatively long-lasting changes in cocaine's effects. Also clear, however, is that the persistence was not observed in every animal. One final feature of the data deserves comment. The effects of the saline vehicle remained at levels observed during the acute determinations of cocaine, suggesting that baseline levels of locomotion remained constant throughout the experiment.

DISCUSSION

In the present study, we examined cocaine's effects on several behavior patterns of pigeons. In several respects, the general patterns replicate what has been reported with rodents, though some notable differences were obtained. Considering first cocaine's effects on locomotion, we found that daily, presession cocaine resulted in enhanced locomotor-stimulating effects across three different daily doses, reflected generally as vertical shifts in the dose–response function. Observations of the saline vehicle during daily cocaine, and later following cocaine withdrawal, indicated that baseline levels of locomotion generally were unaltered, ruling out changes in exposure to the experimental apparatus, or repeated injections per se, as a possible explanation of our results. Thus, our results are consistent with the notion that repeated cocaine administrations resulted in sensitization to its locomotor effects following repeated dosing.

Although birds and rodents both appear to show sensitization to cocaine's locomotor effects, there are some differences between our findings and those obtained with rodents. First, increases in locomotion were obtained with all three daily doses. The literature with rodents has suggested that sensitization is greater when larger doses are given (e.g., Hooks, Jones, Neill, & Justice, 1992; Todtenkopf & Carlezon, 2006). In fact, we were surprised that even the 1.0 mg/kg dose increased locomotion upon repeated exposure, as this dose has often been without any effect on explicitly reinforced operant behavior in many of our procedures (e.g., Marusich & Branch, 2009; Schama & Branch, 1989; Stafford, Branch, & Hughes, 1994; Walker & Branch, 1996). It is important to note, however, that the results do not reflect a general reactivity of pigeons to the injection procedure because tests of the saline vehicle yielded levels of locomotion that remained at baseline levels throughout the experiment. The similarity of outcomes across daily doses may be related to the adaptation/habituation period that preceded tests with cocaine. Preexposure to the testing environment has been shown to blunt cocaine's acute effects on rodent locomotion (Carey, DePalma, & Damianopoulos, 2005), and as noted earlier, cocaine had little effect on locomotion when given acutely in the present experiment. The literature with rodents, furthermore, has shown that sensitization is most robust and most easily detected in those animals that are insensitive to cocaine initially, so-called ''low'' responders (e.g., Carey, et al., 2005; Sabeti, Gerhardt, & Zahniser, 2003). In essence, all of our pigeons were ''low'' responders. Thus, it is likely that our habituation period resulted in reduced responsiveness to acute cocaine and increased our ability to observe sensitization at all the doses.

Additionally, we used a longer period of drug exposure than is common to research in sensitization, which is more typically 7–14 days. It may be that longer treatment increased the ability of the lowest dose to induce sensitization, although Figure 2 indicates that 2 of the 3 pigeons exposed to daily 1.0 mg/kg showed enhanced locomotion within the first 2 weeks of exposure. The selection of an initial 30 days of cocaine injections was made to keep parameters near to those used in our studies of tolerance to cocaine's effects on operant behavior and in our earlier work on sensitization. There has been an unfortunate split in the procedures and methods used to study tolerance and sensitization, making it difficult for either to inform the other (see Woolverton & Weiss, 1998). Our choice to use dosing procedures common to our work on tolerance was made to discover relationships that may be important to both tolerance and sensitization. Often the literature has shown that similar procedures may result in tolerance or sensitization depending on the response under study, reinforcement contingencies, stimulus conditions, and associative relationships (e.g., Goeders, Irby, Schuster, & Guerin, 1997; Leith & Kuczenski, 1981; Wolgin, 2000). In that respect, we feel the use of common procedures

within our lab is a virtue because it allows us to search for factors that contribute to the development of tolerance or sensitization in a systematic way. It will be important, however, for future research to compare these methods with more conventional ones in further studies of avian sensitization.

A second, and perhaps a more important, difference between birds and rodents is the apparent robustness of sensitization when studied in pigeons. All of the pigeons in the present experiment demonstrated sensitization. Additionally, repeated cocaine administration induced sensitization to all 4 pigeons of our previous study (Pinkston & Branch, 2003). The fact that we have observed sensitization in every pigeon studied in our lab stands in contrast to findings from the rodent literature. In rodents, psychomotor stimulant sensitization is often highly variable from individual to individual (Camp & Robinson, 1988; Cass et al., 1993; Woolverton & Weiss, 1998), and sometimes sensitization may fail to develop (e.g., O'dell, Khroyan, & Neiswander, 1996). Recent reviews of the literature have suggested that as many as 50% of rats may fail to show sensitization following repeated stimulant exposure (Gulley, Hoover, Larson, & Zahniser, 2003). Although there were individual differences in the magnitude of sensitization shown by our pigeons, all showed shifts in dose–response function (Figure 1) as well as changes in response to the repeatedly administered dose (Figure 2). The present results, therefore, indicate that, with pigeons, individual-subject designs can be used effectively to analyze sensitization to effects of cocaine, and, presumably, other drugs. In contrast, it does not seem at present that comparable single-subject experimentation is possible with rodents (see also Marusich, Branch, & Dallery, 2008).

Videotaped sessions from the present experiment provided the opportunity to analyze changes in other categories of behavior. First, we found that cocaine did not affect spontaneous pecking at the doses tested here; such data are in line with the observation that another indirect monoamine agonist, *d*-amphetamine, does not generally affect pecking, or does so only weakly (Goodman, 1981). In some sense, it is surprising that cocaine and amphetamine have such a weak effect on pecking because the direct dopamine agonist apomorphine is known to stimulate pecking in pigeons (e.g., Abelson & Woods, 1980; Acerbo & Delius, 2004; Pinkston, Madden, & Fowler, 2008). Such differences may be due to cocaine and amphetamine's action on multiple neurotransmitter systems. Second, cocaine dose-dependently decreased preening. The suppression of preening systematically replicates previous work showing that cocaine also suppresses spontaneous grooming in rodents (Antoniou et al., 1998; Carey, et al., 2003; Cooper & van der Hoek, 1993), and indicates the disruption of self-maintenance behavior is an additional property of cocaine that is common to birds and mammals. Decreases in preening did not appear due to any competition with locomotor effects because they occurred at the larger doses, even when those doses failed to induce locomotion (see Martin-Iverson & Fawcett, 1996, for additional discussion on evidence against competition theories in sensitization). Also, the dose–response function for preening was not shifted following the development of sensitization to cocaine's locomotor effects, again suggesting response competition played no role in cocaine's effects on preening.

Third, our analysis of videotaped sessions revealed that large doses of cocaine induced bouts of emesis during acute administration. Although emesis is not a response that pigeons share with laboratory rats, as rats are in general incapable of vomiting (see Horn, 2008 for a recent review), it is not altogether surprising that cocaine induces emesis in pigeons. Emesis is a common clinical sign of acute cocaine toxicity in humans (Fischman, 1984), apparently due to dopaminergic stimulation of the medullary chemoreceptor zone (cf. Albibi & McCallum, 1983), and this is likely the same mechanism by which cocaine induces emesis in pigeons (Cheng & Long, 1974). On the other hand, we are not aware of prior documentation of the dose–response relationship between cocaine and emesis in pigeons, nor its effects following repeated treatment. The fact that emesis occurred under initial tests and that those effects were attenuated following repeated exposure suggest cocaine's emetic effects may play an important role in our studies of cocaine disruption and tolerance on schedules of food-maintained behavior. Because emesis may interfere with the ingestion and/or processing of food, it could partly explain the initial disruptive effects of

cocaine on operant behavior when given acutely. Attenuation of cocaine's emetic effects, furthermore, may contribute to the recovery of food-maintained behavior following repeated cocaine treatment. Certainly, cocaine's emetic effects cannot be the entire explanation of its effects on operant behavior, as those effects do not seem able to account for the differential tolerance that can develop under different parameters of ratio schedules (Hoffman, Branch, & Sizemore, 1987; Nickel, Alling, Kleiner, & Poling,, 1993). Nevertheless, it will be important for future research to investigate the possible role cocaine's emetic effects have on food-maintained behavior.

Lastly, prior work with rodents has shown that changes in sensitivity to cocaine may persist after drug withdrawal (e.g., Henry & White, 1995), so it was of interest to assess the retention of changes in cocaine's effects with pigeons. Of the 8 pigeons that participated in the final phase, 4 birds indicated some persistence of cocaine's effects, at least 1 pigeon from each dosing group. It is not clear if our findings that persistence was not an ''every animal'' effect is peculiar to birds. As sensitization research has tended to report grouped data, it is difficult to determine how many animals show persistence in studies with rodents. The fact that the induction of sensitization in rodents has indicated substantial individual differences (Cass et al., 1993; Marusich, et al., 2008; Segal & Kuczenski, 1987) suggests that there may also be individual differences in its retention, but they are lost in conventional data presentations. It will be important for future studies to examine how representative prior work is at the individual-subject level, especially as the longevity of sensitization is thought important to its possible roles in drug addiction (Kalivas & Volkow, 2005; Vezina, 2004). At the very least, our data suggest that enhanced locomotion induced by repeated cocaine administration can be persistent in pigeons, but it is subject to individual variation.

REFERENCES

Abelson, J. S., & Woods, J. H. (1980). Effects of apomorphine on elicited and operant pecking in pigeons. *Psychopharmacology, 71*, 237–241.

Acerbo, M. J., & Delius, J. D. (2004). Behavioral sensitization to apomorphine in pigeons (*Columba livia*): blockade by the D1 dopamine antagonist SCH-23390. *Behavioral Neuroscience, 118*, 1080–1088.

Albibi, R., & McCallum, R. W. (1983). Metoclopramide: pharmacology and clinical application. *Annals of Internal Medicine, 98*, 86–95.

Antoniou, K., Kafetzopoulos, E., Papadopoulou-Daifoti, Z., Hyphantis, T., & Marselos, M. (1998). d-Amphetamine, cocaine, and caffeine: a comparative study of acute effects on locomotor activity and behavioural patterns in rats. *Neuroscience and Biobehavioral Reviews, 23*, 189–196.

Camp, D. M., & Robinson, T. E. (1988). Susceptibility to sensitization. I. Sex differences in the enduring effects of chronic d-amphetamine treatment on locomotion, stereotyped behavior, and brain monoamines. *Behavioural Brain Research, 30*, 55–68.

Carey, R. J., DePalma, G., & Damianopoulos, E. (2003). Cocaine-conditioned behavioral effects: a role for habituation processes. *Pharmacology, Biochemistry, & Behavior, 74*, 701–712.

Carey, R. J., DePalma, G., & Damianopoulos, E. (2005). Acute and chronic cocaine behavioral effects in novel versus familiar environments: Open-field familiarity differentiates cocaine locomotor stimulant effects from cocaine emotional behavioral effects. *Behavioural & Brain Research, 30*, 321–330.

Cass, W. A., Gerhardt, G. A., Gillespie, K., Curella, P., Mayfield, R. D., & Zahniser, N. R. (1993). Reduced clearance of exogenous dopamine in rat nucleus accumbens, but not in dorsal striatum, following cocaine challenge in rats withdrawn from repeated cocaine administration. *Journal of Neurochemistry, 61*, 273–283.

Cheng, H. C., & Long, J. P. (1974). Dopaminergic nature of apomorphine-induced pecking in pigeons. *European Journal of Pharmacology, 26*, 313–320.

Cooper, S. J., & van der Hoek, G. A. (1993). Cocaine: a microstructural of its effects of feeding and associated behavior in the rat. *Brain Research, 608*, 45–51.

Fischman, M. W. (1984). The behavioral pharmacology of cocaine in humans. In J. Graboski (Ed.), *Cocaine: pharmacology, effects, and treatment of abuse* (pp. 72–91). NIDA Research Monographs No. 50. Washington, D. C.: US Government Printing.

Geary, E. H., & Akins, C. K. (2007). Cocaine sensitization in male quail: temporal, conditioning, and dose-dependent characteristics. *Physiology & Behavior, 90*, 818–824.

Goeders, N. E., Irby, B. D., Schuster, C. C., & Guerin, G. F. (1997). Tolerance and sensitization to the behavioral effects of cocaine in rats: relationship to benzodiazepine receptors. *Pharmacology, Biochemistry, & Behavior, 57*, 43–56.

Goodman, I. J. (1981). Amphetamine and apomorphine induced stereotyped behavior in adult pigeons. *Pharmacology Biochemistry & Behavior, 15*, 701–704.

Gulley, J. M., Hoover, B. R., Larson, G. A., & Zahniser, N. R. (2003). Individual differences in cocaine-induced locomotor activity in rats: behavioral characteristics, cocaine pharmacokinetics, and the dopamine transporter. *Neurophsychopharmacology, 28*, 2089–2101.

Henry, D. J., & White, F. J. (1995). The persistence of behavioral sensitization to cocaine parallels enhanced inhibition of nucleus accumbens neurons. *Journal of Neuroscience, 15*, 6287–6299.

Hoffman, S. H., Branch, M. N., & Sizemore, G. M. (1987). Cocaine tolerance: acute versus chronic effects as dependent upon fixed-ratio size. *Journal of the Experimental Analysis of Behavior, 47*, 363–376.

Hooks, M. S., Jones, G. H., Neill, D. B., & Justice, J. B., Jr. (1992). Individual differences in amphetamine sensitization: dose-dependent effects. *Pharmacology, Biochemistry, & Behavior, 41*, 203–210.

Horn, C. C. (2008). Why is the neurobiology of nausea and vomiting so important? *Appetite, 50*, 430–434.

Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: a pathology of motivation and choice. *American Journal of Psychiatry, 162*, 1403–1413.

Kilbey, M. M., & Ellinwood, E. H. (1977). Reverse tolerance to stimulant-induced abnormal behavior. *Life Science, 20*, 1063–1075.

Leith, N. J., & Kuczenski, R. (1981). Chronic amphetamine: tolerance and reverse tolerance reflect different behavioral actions of the drug. *Pharmacology, Biochemstry, & Behavior, 15*, 399–404.

Martin-Iverson, M. T., & Fawcett, S. L. (1996). Pavlovian conditioning to psychomotor-stimulant induced behaviours: has convenience led us astray? *Behavioural Pharmacology, 7*, 24–41.

Marusich, J. A., & Branch, M. N. (2009). Environmental and pharmacological factors in the development of noncontingent tolerance to cocaine in pigeons. *Experimental and Clinical Psychopharmacology, 17*, 266–282.

Marusich, J. A., Branch, M. N., & Dallery, J. (2008). Limitations to the generality of cocaine locomotor sensitization. *Experimental & Clinical Psychopharmacology, 16*, 282–292.

Nickel, M., Alling, K., Kleiner, M., & Poling, A. (1993). Fixed-ratio size as a determinant of tolerance to cocaine: is relative or absolute size important? *Behavioural Pharmacology, 4*, 471–178.

O'dell, L. E., Khroyan, T. V., & Neisewander, J. L. (1996). Dose-dependent characterization of the rewarding and stimulant properties of cocaine following intraperitoneal and intravenous administration in rats. *Psychopharmacology, 123*, 144–153.

Palya, W. L., & Walter, D. E. (1993). A powerful, inexpensive experiment controller or IBM PC interface and experiment control language. *Behavioral Research Methods, Instrumentation and Computers, 25*, 127–136.

Pierce, R. R., & Kalivas, P. W. (1997). A circuitry model for the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Research Reviews, 25*, 192–216.

Pinkston, J. W., & Branch, M. N. (2003). Sensitization to cocaine in pigeons: interaction with an operant contingency. *Experimental & Clinical Psychopharmacology, 11*, 102–109.

Pinkston, J. W., & Branch, M. N. (2006). Validation of a mechanical apparatus for the measurement of avian walking. *Journal of Neuroscience Methods, 155*, 56–61.

Pinkston, J. W., Madden, G. J., & Fowler, S. C. (2008). Effects of white and infrared lighting on apomorphine-induced pecking in pigeons. *Behavioural Pharmacology, 19*, 347–352.

Poling, A., Nickel, M., & Alling, K. (1990). Free birds aren't fat: weight gain in captured wild pigeons maintained under laboratory conditions. *Journal of the Experimental Analysis of Behavior, 53*, 423–424.

Randrup, A., & Munkvad, I. (1974). Pharmacology and physiology of stereotyped behavior. *Journal of Psychiatric Research, 11*, 1–10.

Reiner, A. (2002). Functional circuitry of the avian basal ganglia: implications for basal ganglia organization in stem amniotes. *Brain Research Bulletin, 57*, 513–528.

Robinson, T. E., & Becker, J. B. (1986). Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Research, 396*, 157–198.

Sabeti, J., Gerhardt, G. A., & Zahniser, N. R. (2003). Individual differences in cocaine-induced locomotor sensitization in low and high cocaine locomotor-responding rats are associated with differential inhibition of dopamine clearance in nucleus accumbens. *The Journal of Pharmacology and Experimental Therapeutics, 305*, 180–190.

Schama, K. F., & Branch, M. N. (1989). Tolerance to effects of cocaine on schedule-controlled behavior: effects of fixed-interval schedule parameter. *Pharmacology, Biochemistry, & Behavior, 32*, 267–274.

Segal, D. S., & Kuzcenski, R. (1987). Individual differences in responsiveness to single and repeated amphetamine administration: behavioral characteristics and neurochemical correlates. *Journal of Pharmacology & Experimental Therapeutics, 242*, 917–926.

Segal, D. S., & Kuzcenski, R. (1992). Repeated cocaine administration induces behavioral sensitization and corresponding decreased extracellular dopamine responses in caudate and accumbens. *Brain Research, 577*, 351–355.

Stafford, D., Branch, M. N., & Hughes, C. E. (1994). Persistence of tolerance to effects of cocaine on schedule-controlled behavior in pigeons. *Behavioural Pharmacology, 5*, 581–590.

Stewart, J., & Badiani, A. (1993). Tolerance and sensitization to the behavioral effects of drugs. *Behavioural Pharmacology, 4*, 289–312.

Todtenkopf, M. S., & Carlezon, W. A., Jr. (2006). Contribution of drug doses and conditioning periods to psychomotor sensitization. *Psychopharmacology, 185*, 451–458.

Veenman, C. L. (1997). Pigeon basal ganglia: insights into the neuroanatomy underlying telencephalic sensorimotor processes in birds. *European Journal of Morphology, 35*, 220–233.

Vezina, P. (2004). Sensitization of midbrain dopamine neuron activity and self-administration of psychomotor stimulant drugs. *Neuroscience & Biobehavioral Reviews, 27*, 827–839.

Walker, D. J., & Branch, M. N. (1996). Effects of cocaine on briefly signaled versus completely signaled delays to reinforcement. *Journal of the Experimental Analysis of Behavior, 65*, 375–388.

White, I. M., Doubles, L., & Rebec, G. V. (1998). Cocaine-induced activation of striatal neurons during focused stereotypy in rats. *Brain Research, 810*, 146–152.

Wolgin, D. L. (2000). Contingent tolerance to amphetamine hypophagia: new insights into the role of environmental context in the expression of stereotypy. *Neuroscience & Biobehavioral Reviews, 24*, 279–294.

Woolverton, W. L., & Weiss, S. R. B. (1998). Tolerance and sensitization to cocaine: an integrated view. In S. T. Higgins, & J. L. Katz (Eds.), *Cocaine abuse: behavior, pharmacology, and clinical applications* (pp. 107–134). San Diego: Academic Press.

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