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Limitations to the Generality of Cocaine Locomotor Sensitization

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Abstract

Repeated exposure to cocaine often leads to tolerance to effects on operant behavior, whereas sensitization often develops to effects on locomotor activity. The purpose of the present set of experiments was to examine if locomotor sensitization to cocaine would develop in the presence or absence of an operant contingency in rats. In Experiment 1, rats lever pressed on an FR schedule of reinforcement, and were administered chronic cocaine. Tolerance to effects of cocaine on lever pressing developed in most subjects. No subjects developed locomotor sensitization even when the operant contingency was removed. Experiment 2 examined effects of chronic cocaine administration in rats with no exposure to an operant contingency. Tolerance developed to locomotor effects of cocaine in some subjects, but none developed sensitization. In Experiment 3, rats were exposed to a shorter drug regimen, and given time off before a sensitization-test session. Some, but not all subjects showed locomotor sensitization during the test session. The present results, therefore, show that locomotor sensitization to cocaine is not an inevitable consequence of repeated exposure to the drug.

Keywords

tolerance; sensitization; cocaine; rat; locomotor behavior

Repeated drug exposure often leads to tolerance, which is a loss of drug effect relative to the initial impact, or sensitization, which is an increase in drug effect relative to the initial impact (Carlton, 1983). Tolerance is often viewed as an adjustment to a disturbance caused by initial drug effects, whereas sensitization is viewed as a facilitation of a drug effect. The development of tolerance or sensitization may depend on the original drug effect, and the frequency of drug administration. With repeated intermittent drug administration, tolerance often develops to effects that disrupt behavior, whereas sensitization often develops to effects that facilitate behavior (Stewart & Badiani, 1993).

Past research on repeated exposure to cocaine has found that tolerance often develops to effects on explicitly reinforced operant, or purposive, behavior such as lever-pressing for food, or milk drinking from a bottle (e.g., Smith, 1990; Wolgin & Hertz, 1995; Woolverton, Kandel, & Schuster, 1978). In contrast, sensitization is a common finding when effects of

repeated cocaine exposure have been examined on locomotor activity (e.g., Covington & Miczek, 2001; Gosnell, 2005; Haile, During, Jatlow, Ko-sten, & Kosten, 2003). Sensitization to effects of cocaine on locomotor activity has been found in a variety of species including rats (e.g., Covington & Miczek, 2001), mice (e.g., Reith, Benuck, & Lajtha, 1987), dogs (Downs & Eddy, 1932), fruit flies (McClung & Hirsch, 1998), Japanese quail (Levens & Akins, 2004), and pigeons (Pinkston & Branch, 2003, 2006b). When cocaine is administered intermittently (once per day), sensitization to locomotor effects frequently develops, but when cocaine is administered continuously (e.g., via minipumps), tolerance to locomotor effects frequently develops (e.g., King, Joyner, Lee, Khun, & Ellinwood, 1992; Reith et al., 1987).

In humans, low doses of cocaine often produce motor hyperactivity. Prolonged use of larger doses can produce stereotyped motor behavior, and potentially lead to extreme psychomotor activation (Julien, 2005). Clinical reports about cocaine abuse, however, usually point to tolerance as an accompaniment to abuse. The behavior of humans is often operant (Skinner, 1953), and it is therefore not surprising that tolerance has been associated with the development of cocaine abuse and dependence in humans (Fischman, Schuster, Javaid, Hatano, & Davis, 1985; Johanson & Fischman, 1989) given that tolerance is a common finding in drug effects on nonhuman operant behavior (e.g., Smith, 1990; Wolgin & Hertz, 1995; Woolverton et al., 1978).

Little research has examined effects of cocaine on both operant and locomotor behavior simultaneously. Pinkston and Branch (2003) examined effects of cocaine on key pecking and locomotion in pigeons. They found that when an operant contingency was in place, tolerance developed to the effects of cocaine on key pecking, and little change in locomotor behavior occurred after a chronic (daily) drug regimen. A separate group of pigeons that was never exposed to an operant contingency developed sensitization to effects of cocaine on locomotor behavior after the same chronic drug regimen (Pinkston & Branch, 2003). In a related experiment, pigeons were exposed to a schedule of reinforcement in which a fixed number of key pecks was followed by grain presentation when the key was illuminated one color, and key pecks were not explicitly reinforced when the key was illuminated another color [multiple fixed ratio extinction schedule (mult FR EXT)]. After chronic cocaine administration, subjects did not show locomotor sensitization in either component. When the FR component was switched to EXT (mult EXT EXT), locomotor sensitization developed (Pinkston & Branch, 2006a). The results of these experiments suggest that locomotor sensitization to cocaine in pigeons may not develop when an operant contingency is present.

In a related study, Wolgin and Hertz (1995) examined effects of cocaine on milk drinking and locomotion in rats. After 60 daily administrations of cocaine, subjects showed tolerance to effects of cocaine on milk drinking and locomotion. Sensitization only developed for effects of cocaine on stereotyped head movements (Wolgin & Hertz, 1995). The limited results to date, therefore, suggest that neither tolerance nor sensitization is an inevitable result of chronic, intermittent cocaine administration. Instead, the outcome appears to depend on behavioral variables.

The purpose of the present set of experiments was to explore further the conditions under which tolerance and sensitization develop to effects of cocaine, and extend the findings of Pinkston and Branch (2003, 2006a) to rats. Rats are a species commonly used to study cocaine locomotor sensitization (Covington & Miczek, 2001; Gosnell, 2005; Haile et al., 2003), but tolerance has also been found to cocaine's effects on operant behavior in rats (e.g., Smith, 1990; Wolgin & Hertz, 1995; Woolverton et al., 1978). To the best of our knowledge, no research has examined effects of cocaine on locomotor behavior and lever pressing simultaneously in rats. Because the behavior of humans is often operant (Skinner, 1953), but also includes locomotor behavior (that may be less governed by operant contingencies), it is important to study drug effects on the two kinds of behavior concurrently. The specific purpose was to examine if locomotor sensitization would develop in the presence or absence of an operant contingency in rats.

Experiment 1

Method

Subjects—Subjects were four male, experimentally naïve, and drug naïve Long Evans rats (Harlan, Indianapolis, IN). All subjects were approximately 6 months of age at the beginning of the experiment, and were housed in individual plastic home cages in a windowless colony room on a 12/12 hr light/dark cycle (lights on at 8 a.m.). The colony room was maintained between 22 °C and 25 °C. Subjects had access to water at all times in the home cage, and were maintained at 85% of their free-feeding body weight by post session feeding (Lab Diet 5001; rodent diet) delivered immediately after each session if needed. The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Florida.

Apparatus—Experimental sessions were conducted in one open field activity chamber (MED Associates, Inc. Activity Monitor 5) measuring 48.0 cm by 48.0 cm by 30.5 cm. The chamber was enclosed in a sound attenuating cubicle, and was equipped with a stainless steel waste pan and grid floor. One 4.5-cm response lever extended 1.5 cm into the chamber and was located on the intelligence panel 22 cm from the ceiling, 23 cm from the left wall, and 15.5 cm from the right wall. The lever required approximately 0.32 N to register a response. A 28-V DC house light centered 2.5 cm from the ceiling and centered left to right on the intelligence panel illuminated the chamber when the FR schedule was in effect. Sucrose pellets (45 mg, P. J. Noyes, Inc.) were dispensed individually into a 5.0 cm by 5.0 cm by 3.5 cm recessed food cup located 19.5 cm from the ceiling, 15 cm from the left wall, and 21.5 cm from the right wall on the intelligence panel. The sucrose-pellet base was nonnutritive (cellulose). A fan in the experimental room, and a fan in the sound-attenuating chamber produced noise to mask extraneous sounds. Experimental events were arranged and recorded by MED-PC software on a computer located in the experimental room.

A Med-pc Activity Monitor 5 recorded locomotor behavior. The apparatus contained three 16-beam infrared arrays. Beam breaks were used to calculate horizontal and vertical movement. Distance traveled within each session was calculated. In order for activity to qualify as distance traveled rather than resting time or stereotypy, subjects had to move a minimum of 7.5 cm in one direction.

Procedure

Training: Lever pressing was trained through an automated procedure. Trials began with the illumination of the stimulus light. One lever press resulted in immediate sucrose pellet delivery, and the termination of the stimulus light for 2 seconds. The stimulus light was then illuminated and another trial began. A random time (RT) schedule was superimposed over the lever-press requirement such that a response-independent sucrose pellet delivery occurred every 100 seconds on average. Sessions were terminated after 60 food deliveries. After 1 week of daily sessions, response rates were above 10 responses per minute, and the automated procedure was discontinued. Subjects were then exposed to FR schedules, beginning with FR 2. The ratio requirement was incremented by one or two responses each session until FR 20 was reached. Ratio training took approximately 12 sessions. One subject's (173) response rates were almost completely suppressed after Hurricane Jeanne, presumably because of the changes in air pressure. This subject was put back on ratio training beginning with FR 2, but was unable to maintain high rates of responding. This subject's lever pressing was reinforced on FR 12 for the remainder of the experiment.

Baseline: Experimental sessions began with a 5-min blackout during which lever-pressing had no consequence, followed by an FR 20 schedule of reinforcement (FR 12 for subject 173) for 15 minutes or until 40 reinforcers were obtained, whichever occurred first. Completion of each FR was reinforced with one sucrose pellet. Responding was judged to be stable by visual analysis of graphs of daily response rates after approximately 40 sessions. For the remainder of the experiment, sessions ended after 15 min exposure to the FR 20 (or FR 12) schedule of reinforcement to synchronize session end time for the operant and activity-recording portions of the experiment.

Drug regimen: Acute effects of cocaine were determined by administration of cocaine twice per week. Saline and cocaine doses of 30.0 mg/kg, 17.0 mg/kg, 10.0 mg/kg, 3.0 mg/kg, and 1.0 mg/kg were administered in descending order on Tuesdays and Saturdays during acute dosing. A fixed order of dosing was used to aid in revealing any systematic differences (there were none) across repeated determinations of effects of each dose (Sidman, 1960). Each dose was administered a minimum of two times during the initial dose-effect determination. Any dose that produced variable effects was repeated until the mean effect was judged to be reasonably representative (cf. Pinkston & Branch, 2006b; Raiff & Dallery, 2006; Ward, Bailey, & Odum, 2006). Some subjects (170, 173) were also administered 0.3 mg/kg cocaine because the original set of cocaine doses did not produce a full range of effects from complete suppression of lever-pressing to no effect on lever-pressing.

After acute effects of cocaine were determined, each subject was administered a dose of cocaine chronically for 30 sessions that originally produced a minimum of a 50% rate decrease in FR responding, and also produced a moderate increase in distance traveled. The chronic doses used were similar to those used in previous experiments that found locomotor sensitization to cocaine in rats (e.g., Carey, DePalma, & Damianopoulos, 2005; Haile et al., 2003). The dose-response function was then redetermined as described above. Specifically, chronic dosing continued, punctuated by twice weekly administration of other doses of

cocaine or saline used in acute dose-response function determination administered in descending order.

Once dose-response determinations were completed, the operant lever pressing was extinguished, meaning the response lever was still present but lever pressing had no programmed consequences for the next 30 sessions. Lever pressing and distance traveled continued to be recorded, and all subjects continued chronic dosing with the same dose they were chronically administered in the previous phase of the experiment. The dose-effect curve was then redetermined as described above.

Drug procedure: Cocaine hydrochloride (obtained from the National Institute on Drug Abuse) was dissolved in sterile 0.9% sodium chloride solution. Doses were determined by the weight of the salt, and the injection volume was 1 ml/kg. Drug was administered via intraperitoneal (ip) injections, immediately before the 5-min blackout.

Results

Figure 1 displays average lever-pressing response rate and total distance traveled within a session for Experiment 1, with both measures calculated as the percent of saline vehicle, plotted as a function of dose of cocaine. Each panel shows data from an individual subject, except the bottom panels show data averaged across all subjects. Table 1 shows saline vehicle distance traveled used to calculate the dose-response functions in Figure 1. Percent saline values were determined on an individual-subject basis by dividing the average response rate or average distance traveled under effects of a particular dose for a subject by the average response rate or average distance traveled during saline vehicle for that subject and multiplying this value by 100. Percent of saline vehicle values were used because of the large range in saline values for individual subjects (see Table 1). Saline values from acute administration were used to calculate percent saline values for acute administration, and saline values from chronic administration were used to calculate percent saline values for chronic administration. During acute cocaine administration, all subjects showed dose-dependent decreases in rate of lever pressing, with the largest dose producing near complete suppression. Acute administration of cocaine produced dose-related increases in distance traveled, with peak distance traveled after administration of 10.0 mg/kg (Subjects 171, 173), 17.0 mg/kg (Subject 170), or 30.0 mg/kg cocaine (Subject 172).

After 30 days of chronic administration of cocaine, all subjects except 172 showed tolerance to the effects of cocaine on lever pressing, as indicated by a shift in the dose-response function to the right. Distance traveled generally decreased for all subjects after chronic cocaine administration. When the lever-pressing contingency was removed and chronic drug dosing continued, lever-pressing rates reached near zero, and are therefore not plotted. The removal of the lever-pressing contingency had little effect on distance traveled as compared to that during chronic administration when the contingency was in place, except for Subject 171, which showed essentially no change from baseline in distance traveled after administration of all doses of cocaine during lever-press extinction.

An Extra Sum of Squares *F* test (Motulsky & Christopolous, 2004) was conducted to assess the difference between the acute versus chronic functions for lever pressing and distance

traveled for the group average. The procedure compared whether the data for each dependent measure were better described by one straight line fitted to all the data after both acute and chronic drug administration (null hypothesis), or by two straight lines, one fitted to the data from acute drug administrations, and one fitted to the data from chronic drug administration (alternative hypothesis). A straight line (as opposed to a curve) was chosen because it is the most parsimonious function, and it yielded good fits to the data for lever pressing ($r^2 = .77-.84$), and moderate (yet still statistically significant) fits to the data for distance traveled ($r^2 = .25-.46$). The test yielded a significant $F(2, 40) = 7.64, p < .05$ for lever pressing; and a not significant $F(2, 40) = 2.03, p > .05$ for locomotion, supporting the view that the data were better described by separate lines fit to the data after acute and chronic drug administration for lever pressing but not for locomotion. The same test was conducted on distance traveled comparing all the data from chronic administration with an operant contingency and with no operant contingency combined versus individual fits for with and without an operant contingency. The test was not significant [$F(2, 40) = 1.45, p > .05$], indicating that the data from chronic administration with and without an operant contingency were not well described by two separate lines. The same test was also conducted on distance traveled comparing the data from acute administration with an operant contingency and chronic administration with no operant contingency. The test was significant [$F(2, 40) = 6.33, p < .05$], indicating that the data from acute administration with an operant contingency and chronic administration without an operant contingency were better described by separate lines fit to the data after acute and chronic without an operant contingency.

Experiment 2

The results of Experiment 1 are consistent with Pinkston and Branch (2003) who found that pigeons exposed to an operant contingency did not develop locomotor sensitization. In contrast, the results of Experiment 1 were not entirely consistent with those of Pinkston and Branch (2006a) with respect to effects of cocaine on locomotor behavior. They found, as did we, that when an operant contingency was operative, locomotor sensitization was not evident. Yet, when their operant contingency was switched from an FR requirement to EXT, locomotor sensitization was observed. On the contrary, when the operant contingency was removed in Experiment 1, there was little effect on locomotor behavior, and no indication of sensitization. The prior presence of an operant contingency in Experiment 1 may have somehow prevented the development or expression of locomotor sensitization. Therefore, the purpose of Experiment 2 was to examine if rats with no exposure to an operant contingency would develop locomotor sensitization using the same drug regimen as that used in Experiment 1.

Method

Subjects—Subjects were six male, experimentally naive, and drug naive Long-Evans rats aged five months at the beginning of the experiment. Subjects were housed and maintained as in Experiment 1. The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Florida.

Apparatus—The same apparatus as described for Experiment 1 was used in Experiment 2.

Procedure

Baseline: Subjects were placed into the experimental chamber daily with no programmed contingencies. Sessions began with a 5 minute blackout, followed by 15 minutes with the house light on. Distance traveled was measured using Med-pc Activity Monitor 5. After 30 sessions of exposure, stability of distance traveled was assessed. Distance traveled was deemed stable if the means from the most recent three blocks of three sessions did not all show an increasing or decreasing trend. Distance traveled was judged as stable after 44 sessions for all subjects.

Drug regimen: Once locomotor behavior stabilized, acute cocaine dosing was assessed as in Experiment 1, except that acute doses were administered on Wednesdays and Saturdays. Subjects were then randomly assigned a chronic dose of 3.0 mg/kg or 10.0 mg/kg cocaine (3 subjects/dose). These doses were chosen because they were used in Experiment 1. All subjects were administered their chronic dose for 30 consecutive sessions. The dose-response function was then redetermined as in Experiment 1, except that probe doses were administered on Wednesdays and Saturdays.

Drug procedure: The same drug procedure described for Experiment 1 was used in Experiment 2.

Results

Figure 2 shows average total distance traveled within a session for Experiment 2 as a function of dose of cocaine. Each panel shows data from an individual subject, except the bottom left panel shows data averaged across all subjects. Table 2 shows saline vehicle distance traveled used to calculate the dose-response functions in Figure 2. Percent saline values were calculated as in Experiment 1. Percent of saline vehicle values were used because of the large range in saline values for individual subjects (see Table 2). Acute administration of cocaine produced dose-related increases in distance traveled for all subjects, with peak distance traveled after administration of 17.0 mg/kg cocaine for all subjects except Subject 193, which showed peak distance traveled after 30.0 mg/kg cocaine. After chronic administration of cocaine, distance traveled either decreased (Subjects 192, 194, 196), or changed little (Subjects 193, 195, 197) as compared to effects of acute administration.

An Extra Sum of Squares *F* test (Motulsky & Christopolous, 2004) was conducted on distance traveled comparing all the data from acute and chronic administration combined (null hypothesis) versus individual straight-line fits for acute and chronic administration (alternative hypothesis). This produced moderate (yet still statistically significant) fits to the data for distance traveled ($r^2 = .32-.35$). The test was significant [$F(2, 47) = 5.07, p < .05$], indicating that the data from acute and chronic drug administration were better described by two separate lines. The decrease in distance traveled for most subjects after chronic cocaine administration indicates that tolerance, and not sensitization, had developed to the locomotor increasing effects of cocaine for these subjects.

Experiment 3

There are many differences between our Experiments 1 and 2, and those that have found locomotor sensitization to cocaine in rats (e.g., Covington & Miczek, 2001; Gosnell, 2005; Haile et al., 2003), including the number of exposures to the experimental apparatus before any drug administration, number of chronic dosing days (and administrations), number of days off chronic administration before the test for locomotor sensitization, the number of different doses experienced, and whether or not subjects were free feeding. Experiments 1 and 2 used a drug regimen and procedure similar to that of Pinkston and Branch (2003, 2006b), that included many (30+) exposures to the experimental session before drug administration, a minimum of 30 days of chronic cocaine administration, and zero days off chronic administration before testing for locomotor sensitization. In contrast, experiments that have found locomotor sensitization to cocaine in rats typically involved free-fed subjects, generally used one 60-min exposure to the experimental session before drug administration, 5 to 10 days of chronic cocaine administration, and up to 15 days off chronic administration before a test for sensitization (e.g., Covington & Miczek, 2001; Gosnell, 2005; Haile et al., 2003). Therefore, the purpose of Experiment 3 was to use a drug and measurement regimen similar to that of past experiments that have found locomotor sensitization to cocaine in rats.

Method

Subjects—Subjects were 18 male, experimentally naïve, and drug naïve Long-Evans rats aged approximately 100 days at the beginning of the experiment. Subjects ran through the experiment in three successive cohorts of six. All subjects were free-fed for the duration of the experiment. Subjects were housed as in Experiment 1. The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Florida.

Apparatus—The same apparatus as described for Experiment 1 was used in Experiment 3.

Procedure

Habituation: The single habituation session began with a 5 minute blackout, followed by 60 minutes with the house light on. No contingencies were arranged. Distance traveled was measured using Med-pc Activity Monitor 5. No saline or cocaine was administered.

Drug regimen: After the habituation session, subjects were randomly assigned to the saline or cocaine group (9 subjects/group, 3 in each cohort). Subjects in the saline group were administered saline immediately before the experimental session for five consecutive daily sessions, and subjects in the cocaine group were administered 10.0 mg/kg cocaine immediately before the experimental session for five consecutive sessions. Experimental sessions were conducted at approximately the same time each day. After the five chronic dosing days, subjects remained in their home cage with no experimental sessions, and no drug or saline administration for 14 consecutive days. Then subjects were exposed to the experimental chamber for one test session. All subjects were administered 10.0 mg/kg cocaine immediately before the test session.

Drug procedure: The same drug procedure described for Experiment 1 was used in Experiment 3.

Results

Figure 3 displays distance traveled during each session for subjects in both groups in Experiment 3. The majority (seven of nine) of the subjects in the cocaine group showed an increase in distance traveled in the first session of cocaine administration compared to the habituation session, although the effect was marked in only three rats. During the chronic cocaine regimen, subjects in the cocaine group displayed a variety of effects, including a general increase in distance traveled (Subjects 238, 248), a general decrease in distance traveled (two subjects), or variable effects of cocaine. During the test session, six out of nine subjects in the cocaine group showed an increase in distance traveled compared to the first session preceded by cocaine administration. For the cocaine group-average, distance traveled during the first day of cocaine administration was slightly less than that of the last day of chronic dosing. The group-average showed a slight increase in distance traveled on the test day compared to that of the last chronic dosing day, but this was primarily because of the large increase in distance traveled by Subject 241 (see Figure 3). Therefore, sensitization was not reliably evident in a within-subject or within-group analysis; however, group means did increase across cocaine administrations indicating a tendency of the data toward sensitization.

Individual-subject data from the saline group showed little variation in the pattern across sessions for each rat with the majority of subjects showing a slight decrease in distance traveled across successive sessions. Subjects in both groups traveled a similar distance during the habituation session. During the test session, subjects in the cocaine group traveled more distance than subjects in the saline group on average, and this difference was statistically significant [cocaine group $M = 11818.09$ ($SE = 1694.66$); saline group $M = 8150.23$ ($SE = 600.28$); $t(16) = 2.31$; $p < .05$].

The difference between the average distance traveled during the habituation day and the average distance traveled during the first day of cocaine administration for each group (chronic Day 1 for cocaine group, test day for saline group) was similar for both groups, indicating that subjects in both groups showed a similar increase in distance traveled from the habituation session to the session after the first drug administration. Therefore, the day before the first drug administration subjects in the cocaine group traveled farther than subjects in the saline group.

Discussion

In summary, Experiment 1 showed that most rats developed tolerance to effects of cocaine on reinforced lever pressing, and showed either tolerance to locomotor effects or little change in locomotor effects of cocaine after chronic administration. Removal of the operant contingency had little effect on cocaine's effects on locomotion. In Experiment 2, rats with no exposure to an operant contingency either developed tolerance to effects of cocaine on locomotion, or showed little change in effects of cocaine on locomotion after chronic administration. In Experiment 3, rats were not exposed to an operant contingency, had fewer

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habituation days and fewer chronic dosing days than those in Experiments 1 and 2, were not food-deprived, and had time off drug and experimental sessions before testing for locomotor sensitization. Of those chronically administered cocaine, a majority showed locomotor sensitization (individual-subject sensitization) with sensitization defined as greater distance traveled during the test session than during the first session preceded by cocaine administration, and at the group-mean level showed locomotor sensitization when compared to the saline group (between-groups sensitization).

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When rats were given many “habituation” days, had experienced acute drug administrations of a variety of doses, had a minimum of 30 chronic dosing days, and no days off drug before testing for sensitization, no subject showed locomotor sensitization to cocaine even during the first few days of chronic administration, and many showed tolerance to locomotor effects of cocaine (Experiments 1 and 2). Statistical analyses (Extra Sum of Squares F test) support the conclusion that locomotor sensitization did not develop for subjects in Experiments 1 and 2. In fact, the analyses support the conclusion that subjects in Experiment 2 developed locomotor tolerance rather than sensitization. Locomotor sensitization was only found, and only in some subjects, when they were not exposed to an operant contingency, experienced only one habituation day, had a short chronic dosing regimen, had time off drug and experimental sessions before the test session, and were free-fed (Experiment 3). Although whether or not all these conditions were necessary for sensitization to develop was not determined. Even this procedure did not lead to locomotor sensitization in all subjects (six of nine showed sensitization), and the sensitization, when seen, was a relatively small effect as compared to the tolerance shown in Experiments 1 and 2 except for one subject (241). This regimen also resulted in between-groups sensitization, indicated by greater average distance traveled by the cocaine group relative to the average from the saline group during the test session. If the distance traveled during the habituation session is compared to the distance traveled during the session first preceded by drug administration, the results are similar for subjects in both groups. Nevertheless, the effects shown in Experiment 3 are similar in magnitude to those found in other experiments that have shown locomotor sensitization to cocaine (e.g., Covington & Miczek, 2001; Gosnell, 2005; Haile et al., 2003), and the chronic dose used was the same as that for some experiments that have found locomotor sensitization (Carey, DePalma, & Damianopoulos, 2003; Carey et al., 2005; Haile et al., 2003). Regardless of whether individual-subject or between-subjects sensitization is of interest, the locomotor sensitization found in Experiment 3 was a small effect, and was not found in all subjects.

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The results of Experiment 1 are not consistent with past experiments that examined the development of locomotor sensitization in the presence of an operant contingency. Sensitization simply never developed when a long (30+ days) chronic dosing regimen was used (Experiments 1 and 2). This is in contrast to the findings of Pinkston and Branch (2003, 2006a) who also found that locomotor sensitization did not develop in the presence of an operant contingency in pigeons, but found that when the operant contingency was removed, or if it was never present, locomotor sensitization did develop (Pinkston & Branch, 2003, 2006a). Although not conclusive, this points to a possible species difference in the development of locomotor sensitization to cocaine. To make a more definitive statement on

species differences, similar experiments would need to be conducted with each species in the same type of apparatus, and parametric examinations would likely be needed. Locomotor behavior was measured with infrared beams in a large operant chamber in the present set of experiments, whereas Pinkston and Branch (2003, 2006a; 2006b) used a standard size operant chamber with floor panel depressions used to measure locomotor behavior (cf. Pinkston & Branch, 2006b).

One potential reason why sensitization was not observed after the long chronic regimen in Experiments 1 and 2 may be that subjects developed sensitization during the first few administrations of cocaine. Within-session data from initial drug administration sessions, and data from successive acute administrations, however, did not provide any evidence for early development of sensitization. Successive administrations of cocaine during acute dosing did not consistently increase distance traveled, and did not increase distance traveled across all doses for any one subject. Even if acute dosing somehow produced some amount of sensitization, this sensitization would have been substantially diminished after chronic administration because statistically significant tolerance developed to locomotor effects of cocaine by the end of the chronic regimen (Experiment 2).

One limitation of the current set of experiments is that it did not isolate any one factor, or factors that were necessary for the development of locomotor sensitization. One possibility was the number of chronic dosing days. Zavala, Nazarian, Crawford, and McDougall (2000) found that cocaine locomotor sensitization developed in young rats regardless of whether the chronic dosing regimen lasted five or 10 days. Locomotor sensitization was more likely to be evident after a longer period without drug if a longer chronic dosing regimen (10 days) was used, indicating that longer chronic dosing regimens are more likely to produce persisting sensitization (Zavala et al., 2000). Another study found that two 7-day chronic dosing regimens produced more locomotor sensitization to cocaine than one 7-day chronic dosing regimen, suggesting that more exposure to cocaine leads to more sensitization (Davidson, Lazarus, Lee, & Ellinwood, 2002). This result is in apparent contrast to the current set of experiments in which relatively long chronic dosing regimens (Experiments 1 and 2) did not lead to locomotor sensitization, whereas a shorter chronic dosing regimen (Experiment 3) did lead to sensitization in some subjects. Most experiments that have found locomotor sensitization to cocaine in rats, including the present Experiment 3, have used a short chronic regimen lasting 5 to 10 days (e.g., Covington & Miczek, 2001; Gosnell, 2005; Haile et al., 2003). One experiment that found locomotor sensitization to cocaine in Japanese quail found that 10 chronic dosing days led to more sensitization than either 1 or 20 chronic dosing days. The amount of locomotor sensitization decreased when chronic dosing was continued from 10 to 20 days (Geary & Akins, 2007). Therefore, locomotor sensitization may only be a product of relatively short (5–14 days) chronic dosing regimens, rather than relatively long (30+ days) chronic dosing regimens.

The number of days without drug exposure after the chronic dosing regimen may also be important in the development of locomotor sensitization to cocaine. Zavala et al. (2000) found that cocaine locomotor sensitization could be found in young rats over either a 1-day drug abstinence period or a 7-day drug abstinence period; however, a longer chronic dosing regimen was required to produce sensitization with the 7-day drug abstinence period (Zavala

et al., 2000). A similar experiment found amphetamine-induced locomotor sensitization in adult male rats when there were 7 to 8 drug abstinence days, but not 21 to 28 drug abstinence days (Robinson, Becker, & Presty, 1982). The results of both these experiments suggest that shorter drug abstinence periods are more likely to lead to locomotor sensitization. Therefore, it is possible that if a shorter drug abstinence period was used in Experiment 3, more subjects would have shown sensitization, or would have shown a greater magnitude of sensitization. That possibility, however, seems unlikely given that there was no consistent difference between cocaine's effects in the last session of daily administration and its effects in the test.

It is also possible that at least one drug abstinence day is necessary for rats to show locomotor sensitization since sensitization was not observed in Experiments 1 and 2 that had no abstinence days, but there was no evidence of the development of sensitization during the period of chronic administration for any subject in either of these experiments. In contrast, Pinkston and Branch (2003, 2006b) found locomotor sensitization in pigeons with no drug abstinence days, making it difficult to determine the role of drug abstinence days in the development of locomotor sensitization.

An additional possibility not examined in the present set of experiments is whether cocaine locomotor sensitization is a result of Pavlovian processes. Previous research has shown that when cocaine is repeatedly paired with the experimental context in which locomotion is measured, cocaine locomotor sensitization developed. When cocaine was repeatedly administered in the home cage 2 hours after daily locomotor sessions, or saline was repeatedly paired with the session, distance traveled decreased across successive days (Carey et al., 2003). This suggests that the pairing of the drug with the experimental context may be the key factor in the development of cocaine locomotor sensitization. Another study found that when cocaine was administered in an unfamiliar environment (no preexposure) subjects traveled much farther than when cocaine was administered in a familiar environment (10 preexposures). Subjects with preexposure traveled similar distances to those administered saline. The increase in distance traveled because of administration of cocaine in an unfamiliar environment had ceased, however, after three successive sessions, at which point subjects in both cocaine groups traveled the same distance. The subsequent decrease in distance traveled across successive sessions preceded by cocaine administration may be explained by habituation to both the novelty of the environment and to the drug effect (Carey et al., 2005). Therefore, the lack of sensitization seen in Experiments 1 and 2 may be because of habituation to the environment before any drug testing, or habituation to the drug effect because of extended exposure. Although this may suggest that Pavlovian process can account for locomotor sensitization, it does not rule out the possibility that cocaine locomotor sensitization may be a product of an increase in the reinforcing efficacy of locomotor behavior while under effects of cocaine.

In conclusion, the present set of experiments found that locomotor sensitization to cocaine was not a robust effect in the circumstances we studied, and as such served to indicate limits to the generality of cocaine locomotor sensitization. A variety of procedures were used to try and produce locomotor sensitization, but only one produced any de-tectible amount of sensitization, and even this sensitization was not found in all subjects and was not

particularly dramatic in magnitude. The present results, therefore, show that locomotor sensitization to cocaine is not an inevitable consequence of repeated exposure to the drug. Future research could be directed at characterizing circumstances in which locomotor sensitization does and does not develop. Because of the paucity of experimental data on long-term effects of cocaine in humans it is difficult to determine whether sensitization often develops in humans. If sensitization contributes to the development of drug abuse in humans, then it seems likely, based on what is currently known that its contribution is limited to early drug effects.

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Figure 1.

Response rate is plotted as a function of dose (log scale) of cocaine in the left column, and distance traveled is plotted as a function of dose of cocaine in the right column for Experiment 1. Data are plotted as percent of values obtained after administration of saline vehicle. Black circles display the effects of cocaine during acute administration, white triangles show the effects after 30-plus days of daily cocaine administration with lever-pressing reinforced, and gray squares show the effects of daily cocaine administration when lever-pressing was not reinforced. The points above “S” indicate the average effects of

saline vehicle control, with error bars displaying the standard error of effects of saline vehicle. Error bars on the group average graph show the standard error. Numbers between the columns identify the subjects. Numbers to the right of the y-axes in the left column of graphs identify the dose of cocaine administered chronically for each subject.

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Figure 2.

Distance traveled is plotted as a function of dose of cocaine for Experiment 2. Data are plotted as percent of values obtained after administration of saline vehicle. Black circles display the effects of cocaine during acute administration, and white triangles show the effects after 30-plus days of daily cocaine administration. Numbers above the graphs identify the subjects, and numbers to the right of the y-axes identify the dose of cocaine administered chronically for each subject. All other details are as in Figure 1.

Table 1

Lever Presses Per Minute and Distance Traveled (in Meters) Following Saline Vehicle Administrations for All Subjects in All Phases in Experiment 1

	Subject			
Phase	170	171	172	173
Acute lever press	75.15	64.79	81.31	7.55
	81.97	70.05	68.32	2.42
Mean	78.56	67.42	74.81	4.98
Acute distance	9.05	1.56	2.15	8.30
	12.20	11.87	9.78	23.31
Mean	10.62	6.72	5.97	15.80
Chronic lever press	59.93	51.04	56.85	15.00
	120.40	29.32	48.42	14.69
	101.30	52.17	23.70	25.14
Mean	93.88	44.18	38.53	14.84
Chronic distance	16.11	6.40	11.33	9.93
	11.62	6.12	11.71	14.80
	11.98	0.79	23.87	15.76
Mean	13.24	4.43	15.67	12.36
Extinction distance	17.88	47.70	31.57	24.51
	11.88	33.54	20.21	24.35
	13.61	30.60	14.18	9.43
			13.32	18.29
Mean	14.45	37.28	19.82	19.15

Table 2
Distance Traveled (in Meters) Following Saline Vehicle Administrations for All Subjects in All Phases in Experiment 2

	Subject						
Phase	192	193	194	195	196	197	
Acute	15.03	19.21	5.35	12.30	11.00	11.45	
	24.12	26.30	8.43	15.25	11.80	14.21	
	25.24	17.04	4.90	30.08	10.47	17.47	
	19.27	22.62	6.20	16.39	8.59	9.93	
Chronic	26.70	25.46	4.52	20.87	14.12	13.02	
	37.73	29.56	4.19		15.73	16.26	
	24.68	23.37	5.60	18.98	11.95	13.72	
	32.78	37.76	6.26	37.71	27.16	14.38	
Mean	29.73	35.06	3.74	30.49	24.02	15.41	
	31.25	36.41	5.00	34.10	25.59	14.89	