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Differences in the behavioral time course of effects of rate-increasing and rate-decreasing doses of cocaine in pigeons

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Abstract

Although past research has examined the time course of plasma levels of cocaine in a variety of species, the time course of behavioral effects of cocaine on operant behavior has not been carefully described. The purpose of the present study was to examine the time course of effects of cocaine on operant behavior of pigeons, using a method that allowed comparison of dose–response functions, in individual subjects, within a session. Five pigeons responded under a multiple Fixed Interval 10 min Fixed Ratio 30 (FI 10 min FR 30) schedule of food presentation, with each component presented 10 times per session. Following acute administration, dose–response functions remained stable for about 45 min. Effects of acute cocaine administration also revealed that behavioral effects of large doses of cocaine diminished later in sessions, but effects were evident for at least 2 h. Exposure to chronic (i.e., daily) cocaine administration of a rate-decreasing dose led to tolerance that was characterized by diminished potency. Effects of formerly rate-decreasing doses diminishing earlier in the session compared to acute administration, and formerly rate-increasing doses resulted in rates similar to those under the saline-vehicle control from the session outset.
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Keywords: Cocaine; Pigeon; Time course; Tolerance; Operant behavior

The time course of drug action is an important factor in behavioral pharmacological studies. Because most experiments seek to examine the peak effects of a drug, the time from drug administration to peak drug effect is a vital piece of information. Additionally, the length of behavioral sessions needs to be shorter than the length of peak drug effect if effects are to be summarized accurately by session-wide measures, a class of measures frequently used.

Multiple factors are involved in the time course of a drug's effects. For example, different routes of administration can lead to different speeds of onset of drug effects and consistency in drug effects (Carlton, 1983). Absorption of the drug into the tissue, distribution of the drug in the system, metabolism of the drug, and elimination of the drug all play a role in the time course of drug effects. While a drug may still be detectable in the system long after administration, the drug may no longer have the prescribed effect (Julien, 2005).

Only a few studies have examined behavioral effects of cocaine on operant behavior across time. Byrd (1980) examined effects of cocaine (0.1–10.0 mg/kg) in chimpanzees responding under a multiple Fixed Ratio 30 Fixed Interval 10 min (mult FR 30 FI 10 min) schedule of reinforcement in a 2 h session. Lower doses of cocaine had little effect, and the highest dose produced a complete cessation of responding for the entire session (Byrd, 1980). In a similar experiment with squirrel monkeys, Gonzalez and Goldberg (1977) examined effects of cocaine on operant behavior in a 3 h mult FR FI sessions and a second-order schedule. The effects of cocaine on FI schedules and second-order schedules lasted well over 2 h (Gonzalez and Goldberg, 1977).

In addition to the few experiments on time-course evaluations using operant behavior, a small number of studies have

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examined the time course of locomotor increases produced by cocaine administration. Geary and Akins (2007) found that acute administration of cocaine produced locomotor increases in Japanese quail that persisted for a 150 min session. Repeated exposure to cocaine led to locomotor sensitization, which was evident for a minimum of 90 min (Geary and Akins, 2007). Lau et al. (1999) found locomotor increases in rats administered cocaine i.v. that lasted 60 min. Ansah et al. (1996) administered i.p. injections of cocaine to rats and found locomotor increases that lasted up to 200 min. Locomotor sensitization developed following repeated exposure to cocaine, but the time course of locomotor effects did not change (Ansah et al., 1996).

Another approach to examining the temporal length of effects of cocaine has been to administer the drug well before the session begins. MacPhail and Seiden (1975) exposed rats to an FR 40 schedule with cocaine (3.3 mg/kg–53.3 mg/kg) administered 15, 30, 60, or 120 min before the session. Shorter pretreatment times resulted in more response suppression. Responding after 120 min pretreatment of cocaine was unaffected except when the highest dose (53.3 mg/kg) was administered. Moderate doses decreased rates somewhat, even when administered 60 min pre-session.

In the only published experiment examining the time course of effects of cocaine in pigeons (Jarbe, 1993), subjects responded in a drug discrimination paradigm based on injections of 3.0 mg/kg cocaine and saline administered 15 min pre-session during training. After training, discrimination tests were conducted 15, 60, and 120 min after drug administration with 1.0 and 3.0 mg/kg cocaine. The discriminative stimulus effects of cocaine were moderately decreased 60 min after cocaine administration, consistent with effects of a reduced dose, and almost nonexistent 120 min after cocaine administration.

Although past research has shown that effects of cocaine on operant behavior can last over 2 h, the time course of behavioral effects of cocaine has not been carefully described in pigeons, a species often used in research in behavioral pharmacology. The present experiment was conducted to provide a characterization of the time course of cocaine's action on the behavior of pigeons since that has not been explored in past research. Specifically, we used a method that permitted assessment of the dose–response function at different times after drug administration. Additionally, because drugs can have different effects on responding maintained by FI schedules compared to FR schedules of reinforcement (e.g., Dews, 1955), a time-course analysis using a mult schedule was conducted. Therefore, the specific purpose of the present experiment was to examine the behavioral time course of cocaine in pigeons exposed to a mult FI FR schedule of reinforcement.

1. Methods

1.1. Subjects

Subjects were 5 male, racing homer pigeons (Double "T" Farm, Glenwood, IA). All subjects had previous experience with interlocking schedules of reinforcement, and were aged approximately 12 to 18 months at the beginning of the experiment. All were drug naive. Subjects were housed in individual home cages in a windowless colony room on a 16.5/7.5 h light/dark cycle (lights on at 7 am). The colony room was maintained between 19.4°C and 22.8°C. Subjects had access to vitamin enriched water at all times in the home cage, and were maintained at 80% of their free-feeding body weight by post session feeding (Purina ProGrains® for Pigeons) 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, and followed the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85–23, revised 1985).

1.2. Apparatus

Three different operant-conditioning chambers for pigeons were used. All chambers were enclosed in sound-attenuating cubicles, and were equipped with grid floors. Sessions for three subjects were conducted in a custom built standard three-key operant test chamber measuring 30.5 cm by 33.5 cm by 32.0 cm. The 2-cm diameter center key was used in this experiment, and was located on the panel 9.0 cm from the ceiling and equidistant from both sidewalls. To register a response, the key required approximately 0.05 N. Two 28-V DC houselights were located 2.0 cm from the ceiling and 2.0 cm from each sidewall on the panel, and illuminated the chamber during the experimental session. Mixed grain could be made available through a 6.0 cm by 5.0 cm aperture centered near the base of the panel 21.0 cm from the ceiling.

Experimental sessions for two subjects were conducted in two similarly constructed BRS/LVE Inc. (Model PIP-010-016) standard three-key operant test chambers measuring 31.0 cm by 36.5 cm by 35.0 cm. The center key in each chamber measured 2.5-cm in diameter, and was located on the panel 8.7 cm from the ceiling, equidistant from both sidewalls. To register a response, the key required approximately 0.11 N. A 28-V DC houselight was centered 2.2 cm from the ceiling at the center of the panel, and illuminated the chamber during the experimental session. Mixed grain could be made available through a 5.5 cm by 5.0 cm aperture centered near the base of the panel 20.0 cm from the ceiling.

A speaker in the experimental room produced white noise (95 dB) to mask extraneous sounds. Experimental events were arranged and recorded by EC-BASIC (Palya et al., 1995) software on a computer located in another room. A cumulative recorder in another room recorded responses as a function of time during daily sessions.

1.3. Procedure

1.3.1. Training

Because the chambers and key colors were new to them, the subjects were trained, through the method of successive approximations, to peck the center key when it was illuminated red or green. Key color alternated after each food presentation. After all subjects reliably pecked the key, subjects were put on an FR 1 schedule for one session, with the stimulus light alternating red and green after each peck. Key pecks were reinforced with 3 s

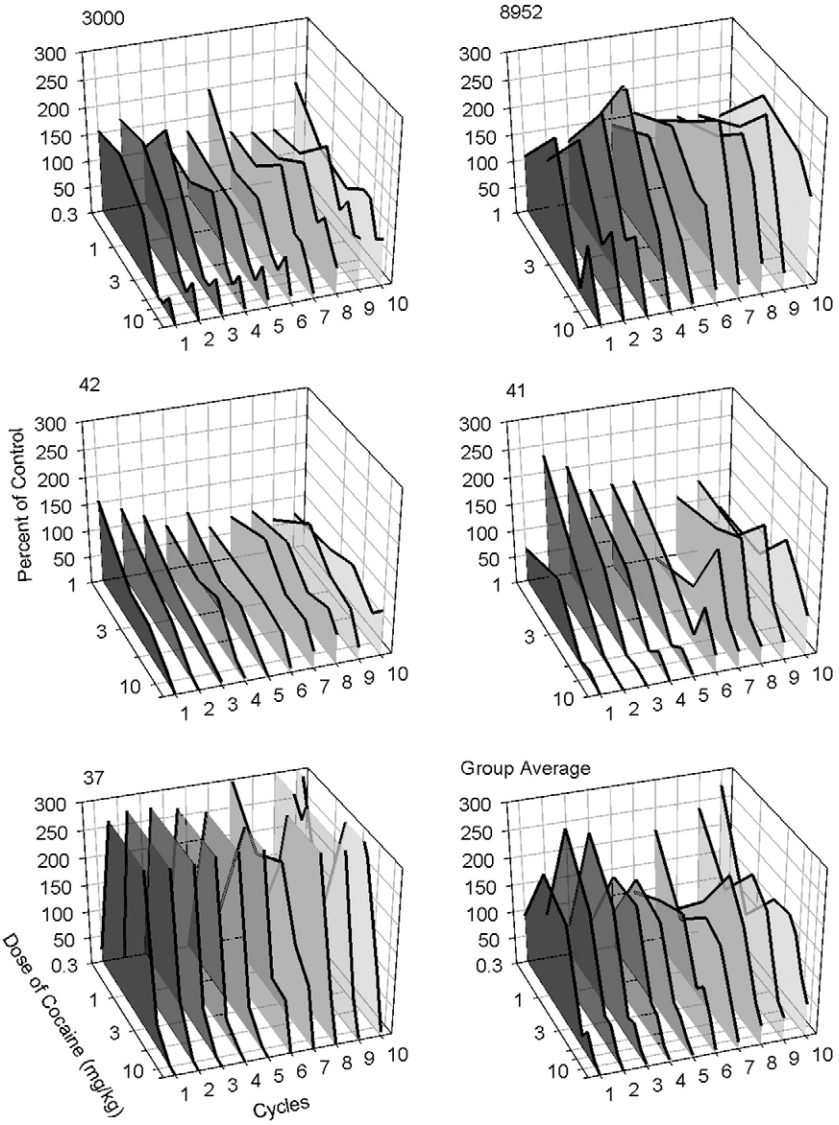

Fig. 1. Three-dimensional plots of the rate of responding (percent of saline-vehicle rate) plotted as a function of dose of cocaine (log scale) and cycle of the FI schedule within the session during the acute phase. Each panel shows data from an individual subject except the bottom right panel shows data averaged across all subjects.

access to mixed grain. The key light and houselights were extinguished during food presentation.

Following the one session of FR 1, subjects then underwent ratio and interval training. The FI component was signaled by the illumination of a red key light, and the FR component was signaled by illumination of a green key light. Components were separated by a 30-s inter-component interval in which all lights were out and key pecks had no arranged consequences. During training, the mult FI FR schedule was altered across sessions. Interval length and ratio requirements were systematically increased across sessions for all subjects until subjects reliably responded on mult FI 10 min FR 30. The FI schedule incremented by increments of 25 s to 2 min per session, and the FR schedule incremented by one to five responses per session. Training was completed in seven to 18 sessions for all subjects. After ratio and interval training was complete, subjects were exposed to baseline conditions. Throughout training and baseline, components were presented in strict alternation beginning with the FI component. Each component was presented 10 times each within each session, and components alternated after each reinforcer was earned. Both the FI and FR components included a 1 min limited hold, such that a new component began if reinforcement was not obtained 1 min after the interval expired, and 1 min after the FR component began.

1.3.2. Baseline

Experimental sessions began with a 5-min blackout, during which key pecking had no programmed consequence. This was followed by a mult FI 10 min FR 30 schedule of reinforcement. Sessions lasted between 110 and 130 min excluding the 5 min blackout. Sessions were conducted seven days a week at approximately the same time each day. After 35–66 sessions, responding was determined to be stable by visual inspection of graphs of daily session-wide response rates.

Table 1
Average responses per minute following saline-vehicle administration for each cycle of each component of the multiple schedule

Subject					
Cycle	3000	42	37	8952	41
Acute FI					
1	6.55 (10.21)	22.23 (5.58)	0.15 (0.17)	6.50 (7.10)	28.43 (15.64)
2	17.73 (22.93)	28.23 (14.97)	1.20 (2.40)	21.38 (14.94)	22.53 (12.17)
3	15.12 (17.71)	33.63 (31.02)	0.05 (0.10)	5.75 (11.30)	31.23 (8.72)
4	12.63 (19.76)	60.63 (18.82)	1.63 (3.25)	16.20 (8.02)	15.33 (17.57)
5	112.43 (183.69)	14.47 (9.65)	10.33 (20.12)	4.85 (5.57)	24.23 (12.72)
6	21.75 (24.15)	30.57 (7.82)	8.38 (13.23)	5.35 (7.86)	38.03 (17.61)
7	29.10 (16.77)	37.87 (10.87)	4.95 (6.07)	17.85 (10.72)	21.47 (22.66)
8	37.63 (18.92)	27.23 (12.02)	12.13 (11.15)	6.60 (3.94)	37.97 (2.80)
9	14.05 (9.00)	38.83 (22.85)	10.05 (9.21)	16.90 (13.47)	22.10 (10.71)
10	15.45 (6.55)	33.80 (6.40)	20.22 (22.03)	18.33 (5.23)	28.57 (3.20)
Mean	*28.24 (60.68)*	*32.75 (17.75)*	*6.91 (11.90)*	*11.97 (10.48)*	*26.99 (13.44)*
Acute FR					
1	85.36 (78.97)	191.5 (22.26)	0.00 (0.00)	136.03 (9.00)	237.47 (26.33)
2	128.32 (89.39)	194.07 (19.69)	8.50 (17.00)	178.65 (83.11)	208.33 (8.57)
3	98.07 (106.78)	189.03 (16.42)	0.00 (0.00)	163.83 (88.91)	224.57 (32.12)
4	68.11 (49.13)	193.33 (22.48)	0.25 (0.50)	148.43 (39.41)	144.53 (60.61)
5	153.30 (100.20)	186.13 (45.51)	18.53 (37.05)	143.25 (48.22)	220.47 (37.76)
6	129.56 (124.74)	187.53 (18.47)	45.73 (52.25)	157.98 (21.01)	200.87 (71.91)
7	113.66 (117.69)	176.33 (8.24)	31.18 (62.35)	152.98 (37.22)	178.03 (35.19)
8	96.32 (96.23)	174.83 (4.15)	53.48 (62.55)	145.90 (34.27)	185.63 (21.80)
9	78.06 (102.44)	191.13 (14.42)	51.00 (36.28)	136.53 (39.92)	216.57 (48.40)
10	125.46 (93.95)	184.60 (11.12)	74.15 (51.04)	158.18 (41.29)	189.60 (24.97)
Mean	*107.62 (89.76)*	*186.85 (18.73)*	*28.28 (43.59)*	*152.17 (45.68)*	*200.60 (42.92)*
Chronic FI					
1	4.98 (2.12)	16.87 (10.63)	0.00 (0.00)	0.92 (0.53)	34.69 (12.98)
2	66.81 (5.37)	23.46 (38.65)	0.59 (0.45)	7.68 (12.81)	16.45 (15.65)
3	28.62 (36.85)	24.75 (37.46)	0.00 (0.00)	6.82 (11.65)	15.54 (21.98)
4	43.21 (7.46)	37.46 (17.92)	0.05 (0.07)	16.09 (13.28)	15.34 (7.14)
5	11.87 (8.76)	40.38 (5.31)	0.41 (0.32)	4.45 (3.63)	12.49 (5.67)
6	43.99 (23.19)	39.54 (6.60)	0.05 (0.06)	11.87 (11.47)	6.09 (8.61)
7	45.39 (16.52)	24.57 (19.64)	1.50 (2.12)	9.54 (5.87)	19.69 (6.50)
8	35.19 (15.43)	45.34 (14.74)	0.32 (0.45)	10.60 (2.13)	26.10 (19.28)
9	27.48 (7.91)	33.53 (15.00)	9.22 (12.53)	4.05 (4.21)	7.73 (1.93)
10	51.29 (2.19)	37.03 (12.61)	14.00 (19.79)	3.21 (3.71)	10.03 (0.19)
Mean	*35.88 (21.47)*	*32.29 (17.30)*	*2.61 (7.20)*	*7.52 (8.21)*	*16.41 (12.20)*
Chronic FR					
1	128.85 (1.47)	124.36 (45.82)	0.00 (0.00)	155.70 (14.58)	159.18 (5.57)
2	134.94 (7.16)	141.85 (10.92)	1.00 (1.41)	166.75 (11.61)	187.95 (65.60)
3	121.61 (6.89)	136.97 (16.48)	0.00 (0.00)	162.52 (23.46)	236.30 (11.74)
4	119.15 (29.21)	126.62 (26.59)	32.49 (45.95)	158.46 (5.31)	159.60 (16.47)
5	151.40 (2.47)	147.51 (40.97)	0.00 (0.00)	154.90 (17.03)	163.42 (22.66)
6	125.74 (27.84)	129.78 (10.04)	0.00 (0.00)	150.26 (23.87)	197.91 (5.46)
7	121.56 (78.05)	129.99 (26.03)	47.03 (66.51)	141.71 (28.68)	166.29 (0.77)
8	146.95 (9.89)	126.68 (26.47)	0.00 (0.00)	145.51 (29.36)	198.22 (45.70)
9	113.04 (27.69)	133.14 (29.95)	34.13 (48.26)	137.38 (21.88)	225.59 (2.34)
10	153.94 (27.12)	138.92 (29.71)	0.00 (0.00)	144.51 (20.42)	181.41 (8.33)
Mean	*137.71 (26.34)*	*133.58 (24.76)*	*11.46 (28.19)*	*151.77 (19.62)*	*187.59 (33.13)*

The mean, calculated as the average of all 10 cycles (italicized), was used to calculate percent control data for all figures. Data from individual subjects are presented in columns. Data from schedule components and acute and chronic drug administration are presented in rows. Data in parentheses are the standard deviations of the mean.

1.3.3. Drug regimen

After responding was judged to be stable, acute effects of cocaine were assessed. During the acute-administration phase of the study, saline and cocaine doses of 10.0 mg/kg, 5.6 mg/kg, 3.0 mg/kg, and 1.0 mg/kg were first administered in descending order, with an injection occurring every 7 days. Each dose was administered twice to permit observation of any systematic changes in the dose–response functions and in the time course of the drug effects across successive determinations. (There were none). Doses that produced variable effects across the first

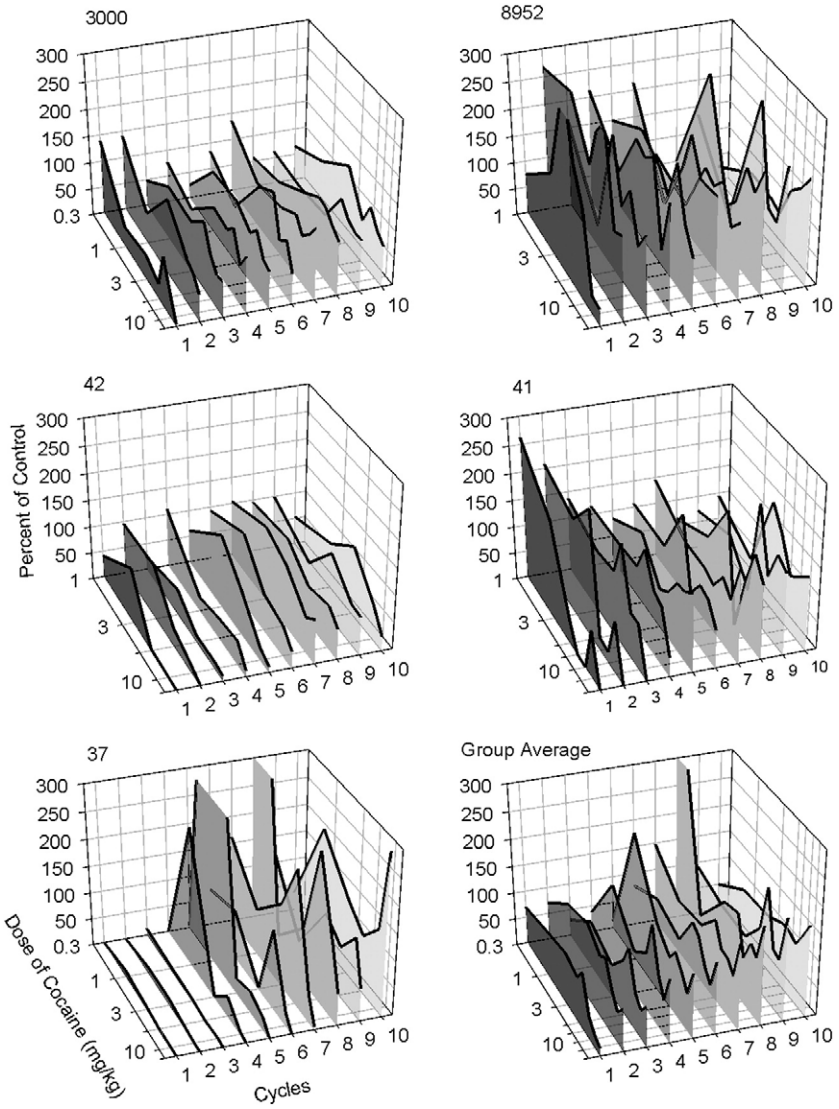

Fig. 2. Three-dimensional plots of the rate of responding plotted as a function of cycle of the FI schedule within the session during the chronic phase. Details are as in Fig. 1.

two administrations were tested again, occasionally several times, until we judged the mean effect to be representative. The maximum number of times any dose was administered was eight times. Doses of 13.0 mg/kg, 7.4 mg/kg and 0.3 mg/kg were also assessed for some subjects when the initial range of doses did not produce a full range of effects from complete suppression of key pecking to no effect (Subject 3000 received 13.0, 7.4, 0.3 mg/kg; Subject 42 received 13.0 mg/kg; Subject 37 received 13.0, 0.3 mg/kg; Subject 8952 received 7.4 mg/kg; Subject 41 received 7.4 mg/kg). It should be noted that no systematic changes in effects were observed across repeated administrations of any dose, suggesting that the seven sessions between administrations was sufficient to prevent any lingering effects.

During the chronic-dosing phase of the study, each pigeon was first administered 10.0 mg/kg cocaine immediately before the session for 30 consecutive sessions. This dose was chosen as a chronic dose because it initially produced a moderate rate-decreasing effect on FI and FR responding for all subjects that persisted for a minimum of approximately 60 min. Daily dosing then continued, punctuated at one-week intervals by tests with other doses to re-determine the dose–response curve. All doses administered during re-determination were administered a minimum of twice and in descending order, beginning with an administration of saline, followed by the highest dose previously administered. If the original set of doses did not produce the full range of effects, higher doses (Subjects 8952 and 41 received 13.0 mg/kg and 17.0 mg/kg) were assessed until a dose produced a minimum of a 50% decrease in rate of responding on both components of the schedule. Subject 3000 died during dose–response curve re-determination. Additional tests were also made with some doses to confirm the reliability of effects.

1.3.4. 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

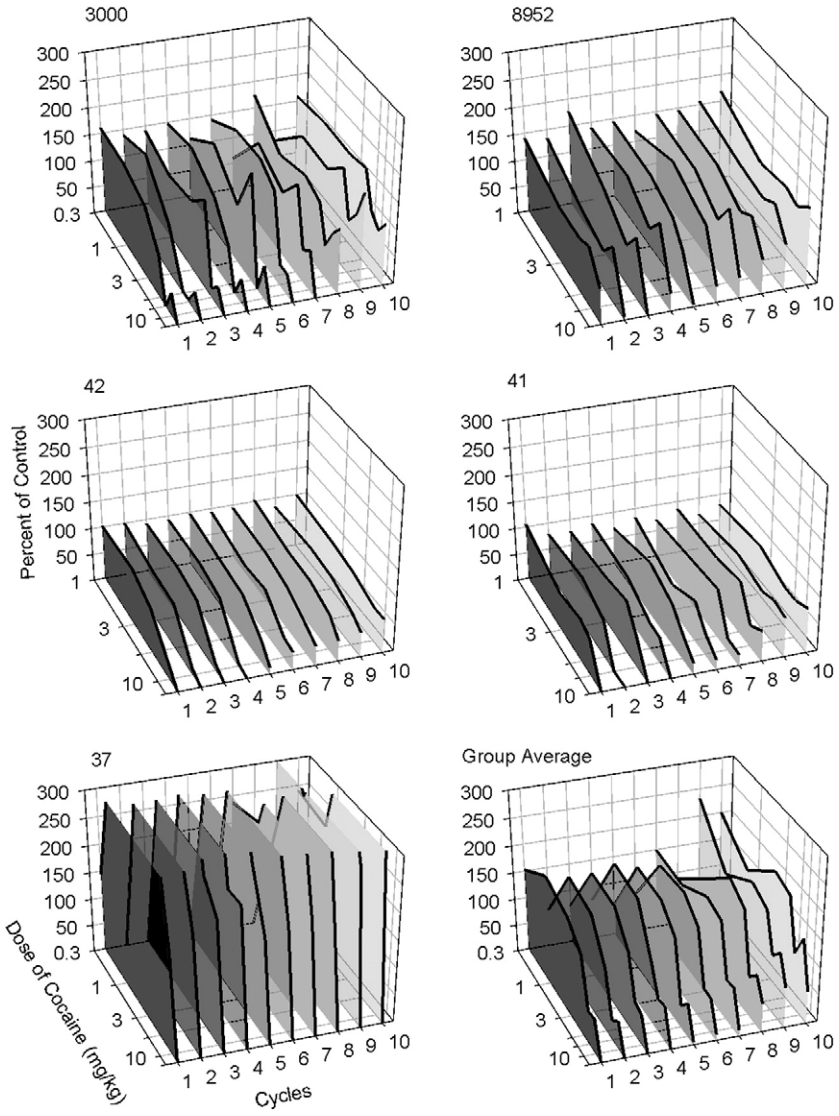

Fig. 3. Three-dimensional plots of the rate of responding plotted as a function of cycle of the FR schedule within the session during the acute phase. Details are as in Fig. 1.

intramuscular (IM) injections in the breast muscle, immediately before the 5-min pre-session blackout. During daily administration, injections alternated sides of the breast.

2. Results

Fig. 1 shows the dose–response function at successive cycles to illustrate effects of cocaine on FI performance across the session during the acute phase. Response rate, calculated as the percent of saline-vehicle rate of responding, is plotted as a function of dose of cocaine and cycle of the FI component within the session. Average rates of responding for each subject following saline-vehicle administration are presented in Table 1, which also shows cycle-by-cycle means that illustrate the range of variability across successive presentations of the FI schedule. Each panel shows data from an individual subject, except the bottom right panel shows data averaged across all subjects. Note that the group-average graph is skewed by the data from Subject 37, which was the only animal to show consistent large increases in rate at intermediate doses, and which had the lowest baseline response rate (Table 1). Acute administration of cocaine produced both increases (smaller doses) in rate of responding for some subjects (3000, 8952, 41, 37) and decreases (larger doses) in rate of responding for all subjects in the FI component. Dose–response functions were generally similar across the first 4 or 5 cycles. After that, rate-decreasing effects of large doses typically diminished across the session for all subjects. Rate increases tended to remain fairly stable, or diminish slightly as the session progressed.

Fig. 2 shows similar plots for the FI component following the chronic phase. Following chronic administration of cocaine, most subjects' (3000, 8952, 41, 37) rate-increasing effects were diminished, as indicated by response rates nearer to saline-vehicle control rates for most subjects as compared to during acute administration. Rate decreases at larger doses, especially those later in the session, were attenuated after chronic administration. For Pigeons 37 and 42, rate-decreasing effects were actually more pronounced early in the session. For rate increases, the changes

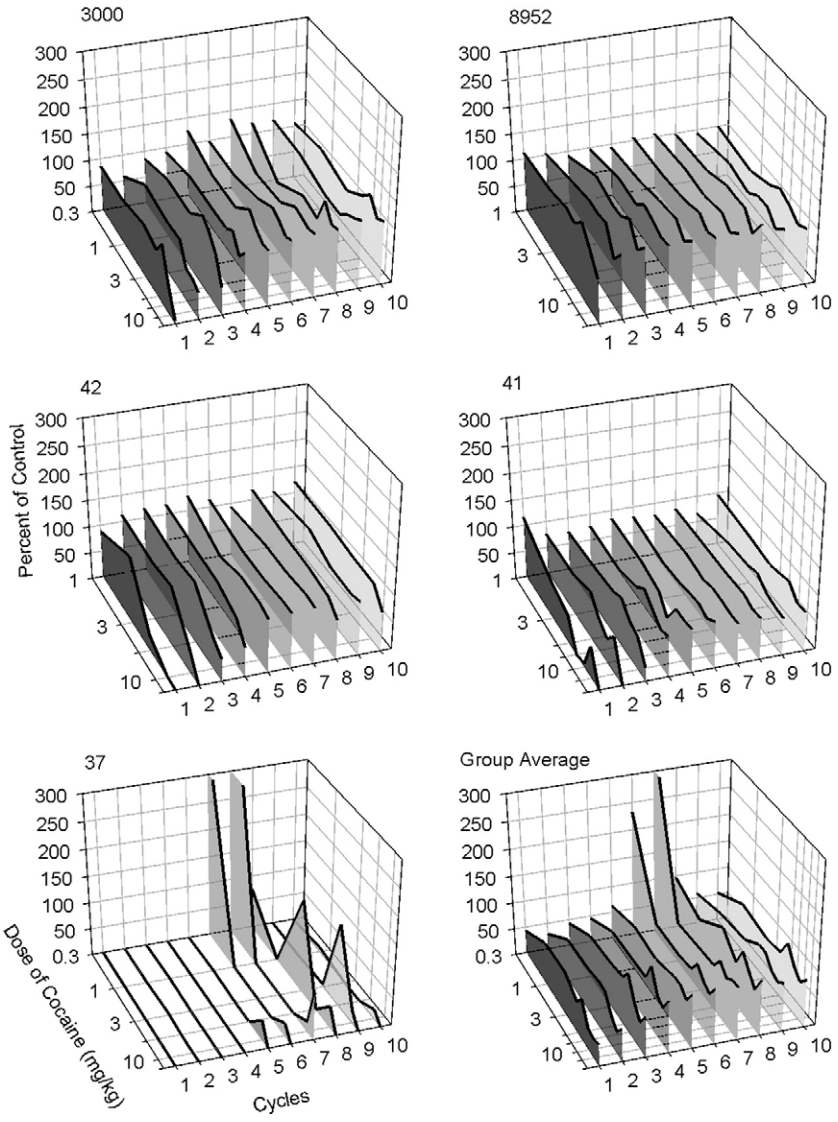

Fig. 4. Three-dimensional plots of the rate of responding plotted as a function of cycle of the FR schedule within the session during the chronic phase. Details are as in Fig. 1.

were apparent from the beginning of a session. Rate decreases were still evident, however, at the larger doses, but those decreases did not persist as long into the session as they did following acute administration. Essentially, after chronic administration the largest doses produced effects like those of small doses. Subject 42's behavior showed little change in the FI component following chronic administration of cocaine.

Fig. 3 shows similarly constructed plots for the acute phase during the FR component. The group-average data is presented in the bottom right panel, and is again heavily influenced by the data of Subject 37, which had an uncharacteristically low baseline rate in the component (Table 1). In the FR component, acute administration of cocaine produced dose-dependent decreases in rate of responding at larger doses for all subjects, and increases at smaller doses for some subjects (3000, 8952, 37). Like the FI component, dose–response functions were generally similar across the first 4 to 5 cycles, and decreases in FR rate under larger doses became smaller in magnitude as the session progressed during the acute phase. In cases where small to moderate doses of the drug increased rates, rates often remained elevated throughout the session.

Fig. 4 shows three-dimensional plots for the FR component during the chronic phase. Chronic administration of cocaine led to tolerance to the rate-increasing and decreasing effects of cocaine in the FR component for all subjects, except Subject 37, which showed apparent sensitization to rate-decreasing effects. In general, chronic administration resulted in a flattening of the dose–response functions, with most data points eventually falling near saline-control levels. As with acute effects, diminished effects of rate-increasing doses were evident at session outset and rate-decreasing effects of larger doses diminished across cycles, with the attenuation generally beginning earlier in the session than under acute-administration conditions.

Fig. 5 compares within-session effects of cocaine during the acute phase and after the chronic phase for selected rate-increasing and rate-decreasing doses within the session from selected subjects. These particular doses were chosen because they produced a minimum of a 50% increase or 50% decrease in

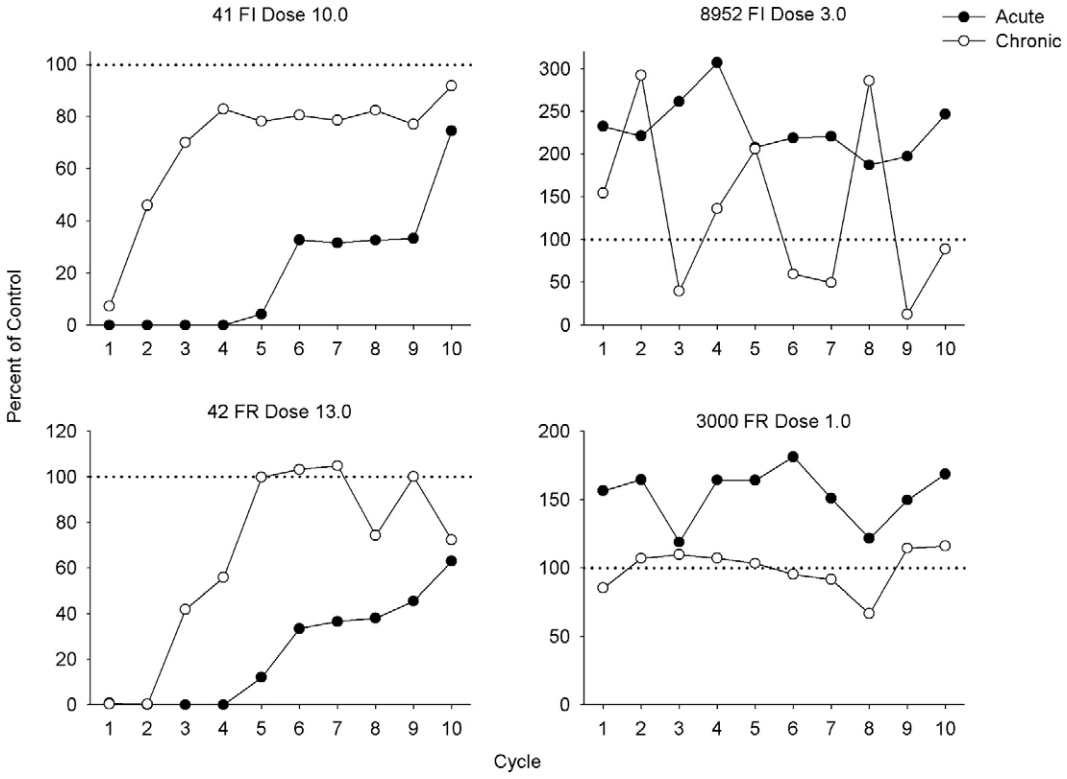

Fig. 5. Response rate, expressed as percent of saline-vehicle rate, as a function of cycle of each component within the session from representative subjects. Each graph shows effects of a single dose of cocaine. Data from selected rate-decreasing doses are presented in the left column and data from rate-increasing doses are presented in the right column. Filled circles display acute effects, and open circles show effects after chronic administration. A dotted line is provided at the 100% level for reference. Note different *y*-axis scales for different subjects.

rate of responding during acute administration. As suggested by Figs. 1 and 3, effects of rate-decreasing doses diminished across a session. Complete suppression lasted for about 4 or 5 cycles, or approximately 57–70 min when the drug was administered acutely. After chronic administration of cocaine, however, response rate decreases, although still present at the beginning of the session, recovered more quickly within the session compared to acute effects. This pattern was evident for both FI and FR components. In contrast, effects of doses that acutely produced increases in rate remained fairly stable throughout the

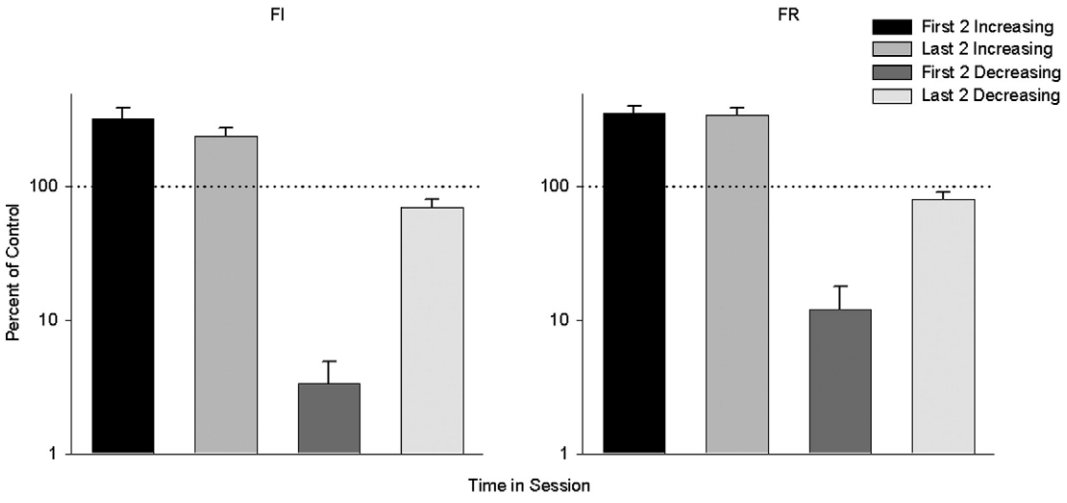

Fig. 6. Average response rate following acute drug administrations, expressed as percent of saline-vehicle control rate, as a function of time in session. Data from the FI component are presented in the left graph and data from the FR component are presented in the right graph. Data summarized are for all doses that initially produced greater than a 50% increase in rate or 50% decrease in rate. Each bar represents the average of two presentations of the component. Error bars represent the standard error. The dotted line represents 100 percent of saline-vehicle control rate. Note log scale on *y*-axis. FI increasing $N=5$; FI decreasing $N=8$; FR increasing $N=5$; FR decreasing $N=8$.

session, suggesting that the peak rate-increasing effect lasted for at least 115 min. Following chronic administration, rate-increasing effects of cocaine were decreased in magnitude, with rates more similar to that of saline-vehicle occurring throughout the session for both FI and FR components as compared to acute effects.

Fig. 6 shows a group-average comparison of effects of acute cocaine administration at the beginning (average of first two presentations of a component) and end (average of last two presentations of a component) of the session for rate-increasing and decreasing doses of cocaine. Effects are averaged across all subjects, and doses that produced a minimum of a 50% increase or 50% decrease (for the total session) in rate compared to saline-vehicle rate were included in the analysis. Fig. 6 has logarithmic *y*-axis to facilitate comparison of the relative changes in effects of rate-increasing doses and rate-decreasing doses in the two components. As suggested by the representative data in Fig. 5, effects of rate-increasing doses did not significantly change from the beginning of the session to the end of the session for both the FI and FR components [FI: $t(18)=1.12$; $p>.05$; FR: $t(18)=0.12$; $p>.05$], whereas rate-decreasing effects were attenuated as the session progressed. The differences from the beginning to the end of the session for rate-decreasing doses for both components were statistically significant [FI: $t(30)=-6.05$; $p<.05$; FR: $t(30)=-5.21$; $p<.05$].

3. Discussion

Acute administration of the larger doses of cocaine produced rate decreases during the first portion of the session for all subjects in both components of the multiple schedule. In some subjects, small or intermediate doses resulted in rate increases in the FI component (Fig. 1), and in two subjects, such doses produced increases in rate in the FR component (Fig. 3). Rate decreases produced by acute administration of cocaine were generally attenuated as the session progressed in both the FI and FR component for all subjects. Rate increases, however, often persisted throughout the session in both schedule components for all subjects (Figs. 1, 3, and 5).

Chronic administration of cocaine led to tolerance in most subjects in the FI component, and all subjects in the FR component (Figs. 2 and 4), although the change was marginal in Subject 42. Tolerance to the rate-decreasing effects of cocaine was characterized by a quicker recovery of rates toward saline-vehicle control levels as the session progressed. Tolerance to the rate-increasing effects of cocaine was characterized by an absence of rate increases, with rates similar to saline-vehicle control levels throughout the session (Fig. 4). Therefore chronic administration of cocaine appears to have flattened the dose–response curves, especially for the FR component, but this tolerance can still be characterized as a shift in the dose–response curve to the right because administration of some higher dose of cocaine would eventually decrease responding.

The results of the present experiment show an apparent dissociation of the time course of rate-decreasing and rate-increasing effects of cocaine in that rate-decreasing effects subsided during the session, while rate-increasing effects persisted. That dissociation may be more apparent than real, however. The difference can be construed to be consistent with changes in plasma concentrations across the session. The case of attenuation of rate decreases is straightforward. Doses of cocaine that decreased rate of responding ranged from 7.4–13.0 mg/kg, which were the higher doses examined. The range of effective rate-decreasing doses, therefore, spanned about 0.3 log units. A half-log unit decrease in blood level, consequently, would reduce the effective dose to a level too low to result in rate decreases. That is, during the session, the amount of drug present in plasma after a large dose presumably decreased to concentrations consistent with smaller doses that did not decrease response rate. In those cases in which cocaine increased rates, by contrast, the increases were generally observed across a wider range of doses, 1.0–10.0 mg/kg, or about 1.0 log unit. As plasma concentrations declined across sessions, they may have remained in the range that could produce rate increases.

Not as easily reconciled, however, is the difference in patterns of tolerance for rate-increasing versus rate-decreasing doses. For rate-decreasing doses (the descending portion of the dose–response function) the change was adequately characterized as a shift to the right in the dose–response function. Rate increases, however, were essentially absent after chronic administration (see Fig. 5). If the curve had merely shifted right, rate increases would have been evident at doses larger than those seen under acute-administration conditions. One possibility is that the portion of the curve that acutely showed increases was shifted so far to the right after chronic administration that rate-increasing effects were masked by rate-decreasing effects. That is, the curve for rate-increasing doses shifted further to the right than the curve for rate-decreasing doses. To determine if that is a real possibility would require some method to block the rate-decreasing effect independently of the rate-increasing effect. In any event, the present data suggest different patterns of tolerance for rate increases versus rate decreases.

With regard to total duration of action, results of the present experiment are in accordance with past research investigating the behavioral time course of cocaine using both pigeons and other species (Byrd, 1980; Gonzalez and Goldberg, 1977; Jarbe, 1993; Macphail and Seiden, 1975) in that they confirm that behavioral effects of acute administration of cocaine may persist for 1–2 h. The present experiment is also consistent with the studies by Byrd (1980) and Gonzalez and Goldberg (1977) in that rate increases following acute administration persisted throughout the experimental session. The results are also congruent with previous research on the time course of locomotor effects of cocaine in rats. Ansah et al. (1996), Geary and Akins (2007), and Lau et al. (1999) found that locomotor effects of cocaine could last for 60–200 min depending on route of cocaine administration and species.

The basic mechanisms underlying the tolerance observed cannot be deduced from the current results. The fact that effects were reduced from session outset makes it less likely that tolerance was due to changes in pharmacokinetics, but only direct measurement of blood levels can confirm that (e.g., Lau et al., 2000). Early session reduction in effect is consistent with receptor-based interpretations, but learning processes cannot be ruled out. Arguing against a learning-process contribution,

however, is a lack of difference in effects in the two components of the multiple schedule. The most well-supported theory of learning-based tolerance is the reinforcement-loss hypothesis (Schuster et al., 1966; Wolgin, 1989), and that view would predict more dramatic tolerance in the FR component, at least to effects of a rate-reducing dose (which is what was given chronically). Response-rate reductions result directly in reinforcement-rate reductions (i.e., reinforcement loss) when FR schedules are in effect, but have less effect on reinforcement rate when FI schedules operate. In addition, Smith (1986) has shown that reinforcement loss has a greater effect the higher the initial rate of reinforcement. In the current study, the rate of reinforcement under the FR schedule was considerably higher than that under the FI schedule. Those circumstances would suggest that tolerance should be enhanced in the FR component, but no such difference was evident in the present study.

In conclusion, the present experiment found that acute behavioral effects of cocaine in pigeons can last over 2 h, and that peak acute effects can be observed for about 45 min. When, after repeated daily administration, tolerance developed to effects of cocaine, it was reflected primarily as a decrease in potency from the beginning of the session on. Effects of rate-decreasing doses diminished earlier in the session compared to acute administration, while rate-increasing effects were usually not observed following repeated administration. The present findings support these characterizations at the level of the entire dose–response function.

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