TOLERANCE TO COCAINE FOLLOWING CHRONIC ADMINISTRATION OF A BEHAVIORALLY INACTIVE DOSE

By

VANESSA MINERVINI

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To my family

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Vanessa Minervini

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A procedure often used to demonstrate the development of tolerance is chronic (i.e., repeated) pre-session drug administration. The magnitude of the dose selected for repeated administration is of critical importance to researchers. Tolerance typically does not develop to a cocaine dose if the acute (i.e., initial) effects of that dose eliminate responding; therefore, the dose that researchers have often selected for chronic administration is the largest dose that disrupts and reduces, but does not abolish, responding. Some evidence suggests that tolerance may develop after chronic administration of relatively smaller doses, however. The purpose of the present experiment was to assess systematically effects of pre-session chronic (i.e., daily) administration of a behaviorally-inactive dose. Specifically, response rates and post-reinforcement pauses of five pigeons key pecking under a three-component multiple fixed-ratio schedule of food reinforcement were observed under chronic cocaine administration. After baseline responding was established, we evaluated the effects of a range of doses during acute (i.e., drug administrations spaced by at least 5 days) administration. The largest dose that failed to alter responding acutely was

administered chronically. After 30 consecutive sessions of chronic administration smaller and larger doses occasionally were substituted for the chronic dose. After assessments of the during-chronic dose-effect curves were completed, pigeons received pre-session saline (drug vehicle) administration for 30 consecutive sessions (i.e., a withdrawal phase), and then the effects of the series of doses on responding were re-determined. All subjects developed tolerance to doses of cocaine that had initially caused large decreases in rate, with the magnitude of the effects varying across components of the multiple schedule and subjects. Specifically, tolerance generally was greatest in the components with smaller ratios. Following a withdrawal phase, tolerance was usually diminished. Overall, the results demonstrate that under these conditions, repeated experience with deleterious effects of cocaine on food-maintained responding is not a necessary factor in the development of tolerance.

CHAPTER 1
INTRODUCTION

Classified as a central nervous system stimulant, cocaine exerts its effects principally by blocking dopamine reuptake in the brain. Some physiological effects of cocaine include increased heart rate, body temperature, and blood pressure. Additionally, the blood vessels constrict and the pupils dilate (National Institute on Drug Abuse, 2010). A complete understanding of the effects of cocaine, however, includes not only its physiological action but also its behavioral action. Research conducted in the field of behavioral pharmacology, an interdisciplinary field incorporating the research methodology of the experimental analysis of behavior with pharmacology, has long-standing findings demonstrating interactions between drugs and behavior where the goal is to determine behavioral mechanisms of drug action.

Despite its classification as a stimulant, cocaine's behavioral action depends on the environment. In an operant-conditioning paradigm, the environment includes the prevailing schedule of reinforcement. Under schedules of reinforcement that engender low baseline response rates, acute administration of psychostimulants usually elevates responding, and under schedules of reinforcement that engender high baseline response rates, acute administration of psychostimulants generally slows responding. Therefore, environmental factors like the schedule of reinforcement can cause an interaction between the drug and behavior, largely determining the effects that a drug exerts on behavior, rather than its effects depending solely on known pharmacological properties (Barrett, 1976; Dews, 1955, 1958; Gonzales & Goldberg, 1977; Kelleher & Morse, 1964, 1968). For example, cocaine can produce dose-dependent rate-decreasing effects on responding maintained by fixed-ratio (FR) food reinforcement and

dose-dependent rate-increasing effects on responding maintained by fixed-interval (FI) food reinforcement.

The acute effects of cocaine will determine what type of changes in behavior can be considered as tolerance. In general, tolerance is defined as a decreased sensitivity to drug effects after repeated dosing (i.e., chronic administration). A large dose that formerly produced an effect no longer may be effective, or a larger dose may be needed to produce effects comparable to initial effects at smaller doses. Tolerance to cocaine's rate-increasing effects would mean that during chronic administration rates decrease, whereas, conversely, tolerance to cocaine's rate-decreasing effects would mean that rates increase. Under an FR schedule, typical control levels are characterized by a "break and run" pattern of responding; fixed-ratio schedules engender performance that consists of a pause (i.e., a period of nonresponding) at the start of a ratio followed by rapid responding until a reinforcer is earned. Cocaine's acute effects on responding under an FR arrangement are that pausing increases and rates decrease (MacPhail & Seiden, 1975; Johanson, 1978). Therefore, tolerance to cocaine's pause-increasing and rate-decreasing effects would be characterized by a decline in pausing and recovery of response rates.

It has been demonstrated that number of environmental and behavioral factors modulate whether and the degree to which behavioral tolerance develops. Some of these variables include repeated administration (Branch & Dearing, 1982; Branch, Walker, & Brodkorb, 1999; Schama & Branch, 1994; Woolverton, Kandel, & Schuster, 1978a), whether the dose is administered pre- or post-session (Marusich & Branch, 2009; Pinkston & Branch, 2004, 2010; Weaver, Dallery, & Branch, 2010; Woolverton,

Kandel, & Schuster, 1978b), the reinforcement schedule type and context (e.g., Barrett, 1976; Kelleher & Morse, 1964; 1968; Gonzales & Goldberg, 1977; Smith, 1986; Schuster, Dockens, & Woods, 1966; Waller, 1961), the degree of stimulus control (e.g., Laties, 1972; Thompson, 1977; Weiss & Laties, 1966), the subjects' deprivation level (e.g., Hughes, Pitts, & Branch, 1996; Ross & Schaal, 2002; Schaal & Branch, 1992; Schaal, Miller, & Odum, 1995), the reinforcer magnitude (Durgin, Porter, Bradley, Laraway, & Poling, 2009; Ginsburg, Pinkston, & Lamb, 2011; Pinkston, Ginsburg, & Lamb, 2009), the response effort (e.g., Hughes, Sigmon, Pitts, & Dykstra, 2005; Makhay, Alling, & Poling, 1994), and the reinforcement-schedule parameter (e.g., Hoffman, Branch, Sizemore, 1987; Hughes & Branch, 1991; McMillan, 1969; Nickel, Alling, & Poling, 1993; Van Haaren & Anderson,1994; Yoon & Branch, 2004).

Though exactly how environmental variables function—contributing to tolerance or lack thereof—remains to be elucidated, the reinforcement-loss hypothesis proposed by Schuster et al. (1966) has accumulated much empirical support and has endured as an viable explanation. According to the reinforcement-loss hypothesis, tolerance is thought to be a functional mechanism in that it develops only when a drug's behavioral effects result in a decreased rate of reinforcement. If an organism experiences the prevailing contingencies of a schedule in the presence of behaviorally deleterious drug effects (i.e., behavior is disrupted severely enough such that reinforcement is markedly reduced or not obtained), it can learn to adjust its behavior accordingly to compensate for the cost associated with drug-induced losses.

Schuster et al. (1966) demonstrated that amphetamine tolerance developed in the differential-reinforcement-of-low-rates (DRL) component, but not in the fixed-interval (FI)

component, in a multiple schedule. Physiological mechanisms of tolerance, such as changes in metabolism or neurotransmitter receptor sites, cannot fully explain the obtained results given that differential tolerance occurred. Amphetamine's acute effects increased responding in both components, thereby diminishing reinforcement rates in the DRL context but not in the FI context, which led Schuster et al. to suggest that behavioral tolerance occurs only when the effect of the drug is such that behavior becomes incompatible with the contextual contingencies, and contact with reinforcement decreases. Since the inception of the reinforcement-loss hypothesis as an explanation of tolerance, differential tolerance has been demonstrated across drugs, species, and responses in a multitude of studies (Bowen, Fowler, & Kallman, 1993; Carlton & Wolgin, 1971; Demellweek & Goudie, 1982; Emmett-Oglesby & Taylor, 1981; Foltin & Schuster, 1982; Galbicka, Kautz, Ritch, Wolgin & Wade, 1995; Hughes, Popi, & Wolgin, 1998; Nickel, Alling, Kleiner, & Poling, 1993; Poling & Nickel, 1993; Salisburry & Wolgin, 1985; Schuster et al., 1966; Schuster & Zimmerman, 1961; Smith 1986, 1990; Wolgin, 2000; Wolgin & Wade,1995).

The finding that the reinforcement schedule modulates tolerance is interesting because the multiple schedule arrangement reveals that the presence and absence of tolerance can occur within a single session, thus indicating that simple, general pharmacological effects cannot be a complete account. Such an effect even has been extended to schedule-parameter dependent tolerance to the disruptive effects of cocaine. Hoffman et al. (1987) trained three pigeons to respond under a three-component multiple FR schedule with food reinforcement. When cocaine was administered acutely, it produced dose-dependent, rate-decreasing effects in all three

components. Following chronic administration of a dose that suppressed—but did not entirely eliminate—responding, tolerance developed in the small- and medium- ratio components. Little to no tolerance developed in the large-ratio component. These results somewhat were consistent with the reinforcement-loss hypothesis in that response rates recovered during chronic administration and subjects were able to adjust behavior to achieve reinforcement. The results were inconsistent with the reinforcement-loss hypothesis, however, because tolerance failed to occur in the large-ratio component even though reinforcement loss occurred in that component. Follow-up studies by Branch (1990) and Schama & Branch (1989) revealed that differences in reinforcement rate across components were not associated with differential development of tolerance. Findings reported by Yoon and Branch (2004) and Hughes et al. (2005) showed that differences in unit price also were not associated with differential development of tolerance. Our present understanding of the effect obtained by Hoffman et al., therefore, is that the response requirement is the relevant variable that controls the extent to which tolerance develops.

Typically, for most drugs of abuse, the acute effects are dose-dependent, so it is necessary to assess the effects of a range of doses on responding. A dose-response function, with dose expressed on the x-axis and quantifiable behavior expressed on the y-axis, graphically depicts a drug's effects. Based on this function, a dose is selected for chronic administration. The best dose at which one can observe the development of tolerance during chronic administration is between the effective-dose (ED) 25 and the ED 75 (Schuster, 1978). An ED_{25} is a dose that alters (i.e., increases or decreases) responding by 25% relative to baseline, and an ED_{75} would be a dose that alters

responding by 75% relative to baseline (see Method section for a full description of the equation). Thus, for rate-decreasing drugs, typically the largest dose that reduces responding without eliminating it entirely has been selected for chronic administration. Because previous research on repeated administration of cocaine has indicated that tolerance can develop with relatively lower doses but usually does not develop with higher doses that abolish responding (Bowen, Fowler, & Kallman, 1993; Branch, Wilhem, & Pinkston, 2000; Stafford & Branch, 1996), the systematic manipulation and assessment of the chronic dose selection is of critical importance in understanding factors that contribute to the development of tolerance or lack thereof.

In the behavioral literature on drug action, surprisingly few studies have attempted to assess the role of the chronic dose when it is administered pre-session. Bowen et al. (1993) found that acute cocaine administration dose-dependently decreased responding in a milk-drinking task in rats. Rats then either received 8.0 mg/kg, 16.0 mg/kg, or 32.0 mg/kg cocaine chronically. They found that dose-specific tolerance occurred to the lowest dose tested (i.e., 8.0 mg/kg), but that tolerance failed to generalize when higher doses were substituted for the chronic dose. Following the moderate-dose chronic administration, tolerance was observed across a range of doses tested, and the highest dose tested (32.0 mg/kg) produced hardly any tolerance. Stafford and Branch (1996) reported similar findings. They assessed cocaine's acute rate-decreasing effects under an FR 30 schedule in pigeons. Then, pigeons were divided into three groups: The pigeons either received a small, medium, or large chronic dose for 40 consecutive sessions. They found a shift in the dose-response function, indicative of tolerance, when the chronic dose was small. Evidence of tolerance to larger doses occurred even

when the chronic dose was low enough such that its effect on response rate was indistinguishable from that of baseline responding. The combined results from these studies illustrate that the degree of tolerance is affected by the dose selected for chronic administration; however, neither study addressed this variable in the context of a multiple schedule, which also has been shown to modulate the degree of tolerance (e.g., Hoffman et al., 1987).

Pinkston and Branch (2004) aimed to assess tolerance to cocaine's rate-decreasing effects in a multiple FR 5 FR 100 schedule following pre-session chronic administration of a small dose. For all six pigeon subjects, they found that tolerance developed in the small-ratio component but not in the large-ratio component. That is, following chronic administration of a small dose, acute effects (i.e., decreased response rates at high doses) were attenuated. Of particular interest is that the small chronic dose produced no noticeable effect on response rates in the small-ratio component, suggesting that tolerance may develop after pre-session administration of a behaviorally-inactive dose. Unfortunately, one limitation in their study was the criterion for selection of the "small" dose. The chronic, pre-session small dose was chosen because in a previous condition of the experiment it was defined as one that did not affect within-session responding when administered post-session. The problem with the definition is twofold. First, by the end of the post-session chronic administration condition, responding had decreased in the large-ratio component for 3 of 7 subjects and had decreased in the small-ratio component for 1 subject. Second, when the small dose then was administered chronically pre-session, it reduced responding, albeit

slightly, in the large-ratio component; thereby the “small” dose still had some behavioral action on responding.

The purposes of the present experiment were to (a) evaluate the development of tolerance after chronic administration of a dose that failed to reduce responding acutely (i.e., a behaviorally-inactive dose) and (b) determine whether the fixed-ratio (FR) parameter modulated the degree of tolerance. To do so, we arranged a three-component multiple schedule, under which 5 pigeons’ responding was maintained by access to grain. Once baseline responding had stabilized, an acute dose-effect determination was conducted. The largest dose that failed to disrupt responding acutely then was administered chronically. To evaluate whether and the degree to which tolerance developed, we reassessed the effect of a series of doses on responding by conducting a during-chronic dose-effect determination. The development of tolerance to larger doses of cocaine following pre-session chronic administration of a behaviorally-inactive dose not only would confirm findings reported by Bowen et al. (1993), Stafford and Branch (1996), and Pinkston and Branch (2004), but also provide evidence against the reinforcement-loss hypothesis in that tolerance need not require learning and behavioral compensation due to the presence of decreased reinforcement rate under drug effects.

CHAPTER 2
METHOD

Subjects

Six experimentally-naïve adult male White Carneau pigeons (numbered 1078, 1082, 1163, 1166, 1186, and 1859) were obtained from from Double-T Farms, Glenwood, Iowa. We maintained the pigeons at 85% of their free-feeding body weight via post-session feedings consisting of mixed grain and pellets (Purina Pigeon Chow Checkers) in equal proportions. Outside of daily sessions, the pigeons were individually housed in a temperature- and humidity-controlled colony room with a 16:8-hr light:dark cycle. In their home cages, the pigeons freely had access to water and health grit. Due to a beak injury that failed to heal properly, one subject did not complete the experiment.

Apparatus

The experiment was conducted in two pigeon operant-conditioning chambers (interior dimensions 35 x 30 x 35 cm). The front panel of the chambers contained a houselight positioned 30-cm from the chamber floor, and 7 cm below the houselight were 3 horizontally-positioned keys. The keys measured 2.5 cm in diameter and were positioned 8 cm from the walls and 5.5 cm apart. Only the center key—illuminated white, red, or green—was used; its activation required a minimum force of 0.098 N. A 30-ms tone, produced by a Mallory Sonalert device, accompanied each successful response to the key. Located 10 cm directly below the center key and 11 cm from the chamber floor there was a 5-cm by 5.5-cm aperture through which access to a solenoid-operated hopper filled with buckwheat, milo, and hempseed could be provided. During reinforcer presentations, the aperture and raised hopper were illuminated, and all other

lights in the chamber were extinguished. In one of the chambers, an additional 5-cm by 5.5-cm aperture for pellet delivery was located 3.5 cm to the left of the grain aperture, but it served no function in this experiment. White noise at approximately 95 dB masked extraneous sounds in the rooms containing the operant chambers. In an adjacent room, computers running EC-BASIC software (Palya & Walter, 1993) controlled experimental events and recorded data, and cumulative-response recorders provided live-time data collection.

Procedure

Training

After the pigeons reliably approached and ate from the raised hopper, responses to the center key (illuminated white) were shaped by reinforcing successive approximations. Once key pecking was established, the following session consisted of a fixed-ratio 1 schedule with the center key illuminated white and lasted until the pigeon earned 60 reinforcers.

General procedure

To arrange a 3-component multiple schedule, we introduced two additional key colors—red and green. A 5-min blackout occurred at the beginning of all sessions. Each component was selected randomly without replacement and remained in effect until the pigeon earned four reinforcers. If a pigeon failed to earn all four programmed reinforcers within an allotted time limit, then components ended after 90 (white), 300 (red), or 810 (green) s elapsed. The white, red, and green key always signaled the small-, medium-, and large-ratio components, respectively. A sequence of all components comprised a block, and sessions ended after 3 blocks.

The FR response requirement in each component was increased gradually across sessions until the target FR in each component was achieved; the targeted terminal schedule was a multiple FR 5 FR 25 FR 125 schedule. Each FR increase (i.e., 2, 3, 5, 8 12, 20, 25, 30, 36, 47, 55, 65, 75, 85, 95, 105, 125) occurred only if visual inspection of the cumulative-response records and overall response-rate data revealed that within-session responding in all components appeared stable.

Baseline

During baseline our aim was to obtain consistent responding in all components with differentially longer post-reinforcement pause in the large-ratio component. In order to accomplish these outcomes, the details of the procedure were tailored to individual subjects. Pigeons 1082 and 1186 responded under FR 5 FR 25 FR 125 with 3-s access to grain. Pigeon 1166 responded under the same schedule, but his weight was increased from 85% to 98% of his free-feeding body weight, and his reinforcer access was increased to 4 s. Pigeon 1163 responded with 3-s access to grain, but his large-ratio performance deteriorated beyond FR 80, so this value ultimately was chosen for his large-ratio component. In order to maintain responding, pigeon 1859 required 6-s access to food and a reduction of the response requirements to FR 5, FR 15, and FR 45. The baseline conditions remained in effect until response rate and post-reinforcement pause were stable for at least 30 sessions.

General pharmacological procedure

Cocaine hydrochloride obtained from National Institute on Drug Abuse was dissolved in 0.9% saline solution. Doses were delivered in mg/kg, expressed in terms of the salt, and administered intramuscularly (pectoral muscle) immediately prior to a

session. Dose volume (in mL/kg) was determined by 0.1% of a subject's 85% weight. For example, Pigeon 1859 weighed 682 g and always received a 0.68-ml injection.

Acute administration and assessment

Doses were administered every fifth session in either an ascending (Pigeons 1166 and 1186) or descending (Pigeons 1082, 1163, and 1859) series. The series of doses for Pigeons 1082, 1163, and 1186 included 0.0 mg/kg (i.e., saline), 1.0 mg/kg, 3.0 mg/kg, 5.6 mg/kg, and 10.0 mg/kg. The effects of this series of doses on response rate and post-reinforcement pause were assessed twice. Pigeon 1859 received the same series of doses, but after the two determinations, we administered an abbreviated series of 0.0 mg/kg, 3.0 mg/kg, and 5.6 mg/kg for two additional determinations of each dose. We altered the series of doses for Pigeon 1166 such that the 1.0 mg/kg was excluded and a 17.0 mg/kg dose also was assessed. For each pigeon, the number of times a dose was administered is shown in Table 2-1.

Chronic administration

Based on visual analysis of the acute dose-response functions and corresponding cumulative-response records, we selected the largest dose that failed to suppress rates or elevate post-reinforcement pause during acute administration. We chose 1.0 mg/kg for Pigeon 1859, 3.0 mg/kg for Pigeons 1163, 1166, and 1186, and 5.6 mg/kg for Pigeon 1082. The dose then was administered immediately prior to 30 consecutive sessions. Rarely, during chronic administration, an apparatus failure prevented us from conducting a daily session. Under these circumstances, the pigeon still received administration of its chronic dose and was returned to its home cage.

During-chronic assessment

To determine whether and the extent to which tolerance developed, we reassessed the effect of the series of doses on rate and pause by administering a probe dose from the series every fifth session. On days intervening probes, pigeons received their chronic dose. After two determinations of each dose from the series, we replicated doses at the critical points in the curve and probed for tolerance to higher doses if necessary. For each pigeon, the number of the number of times a dose was administered is shown in Table 2-1.

Withdrawal and during-withdrawal assessment

Pigeons received saline immediately prior to 30 consecutive sessions. To determine whether tolerance was reversible or attenuated, we reassessed the effect of the series of doses a final time by administering a probe from the series every fifth session. On days intervening probes, pigeons received a saline injection. After two determinations of each dose from the series, we replicated doses at the critical points in the curve if necessary. For each pigeon, the number of the number of times a dose was administered is shown in Table 2-1.

Table 2-1. For all pigeons, the number of determinations for each probe dose across phases. See text for details.

Pigeon	Phase	Saline	1.0	3.0	5.6	10.0	13.0	17.0
1082	Acute	2	2	2	2	2	-	-
	Chronic	2	2	2	2	2	3	-
	Withdrawal	2	2	2	2	2	-	-
1163	Acute	2	2	2	2	2	-	-
	Chronic	2	2	2	2	2	-	-
	Withdrawal	3	3	6	6	3	-	-
1166	Acute	2	-	2	2	2	-	2
	Chronic	2	-	2	2	2	-	2
	Withdrawal	2	-	2	2	2	-	2
1186	Acute	2	2	2	2	2	-	-
	Chronic	2	2	2	4	4	2	-
	Withdrawal	2	2	2	2	2	2	-
1859	Acute	4	2	2	4	4	-	-
	Chronic	2	2	4	4	3	-	-
	Withdrawal	2	2	2	2	2	-	-

CHAPTER 3
RESULTS

Figures 3-1 through 3-5 show both of the primary dependent variables—overall response rate and post-reinforcement pause as a function of cocaine dose in each component of the multiple schedule for individual pigeons. The C and S on the x-axis represent Control and Saline, respectively. The control data points are an average of the effects from all sessions preceding a probe session in a given phase. All other data points are based on the average of at least 2 determinations per dose, but the exact number of doses that each pigeon received during each phase of probing can be seen in Table 2-1. The circles represent the acute probes, the squares represent the chronic probes, and the triangles represent the withdrawal probes. Error bars represent the range of effects.

Figure 3-1 shows data from Pigeon 1082. During acute dosing, 10.0 mg/kg of cocaine eliminated responding and maximized pausing in the medium- and large-ratio components. In the small-ratio component, 10.0 mg/kg of cocaine caused responding to be nearly eliminated and pausing to drastically increase relative to other doses. Following chronic administration, the effect of 10.0 mg/kg on both rate and pause was greatly attenuated. When 13.0 mg/kg was administered tolerance was evident in the small-ratio component for rate and pause, but less so in the medium- and large-ratio components. Interestingly, there must have been a small degree of tolerance to 13.0 mg/kg because some responding still occurred at this dose that was larger than the dose that had eliminated responding entirely during acute probing (i.e., 10.0 mg/kg). Following a period of withdrawal, the effects of cocaine appear to be more similar to the

effects during acute than chronic probing, indicating that tolerance mostly was reversible.

Figure 3-2 shows data from Pigeon 1163. During acute dosing, 10.0 mg/kg of cocaine eliminated responding and maximized pausing in all components. The range bars are wide at the 5.6 mg/kg dose because responding appeared to be bimodal. That is, for 3 of 6 determinations responding was eliminated, but for 3 of 6 determinations responding was comparable to that at lower doses. The order of the determinations was not predictive of the degree of responding that occurred. After chronic administration, tolerance occurred to the 5.6 mg/kg dose. The range bars at this dose during this phase also were wide, but mean responding shifted in a direction that indicates tolerance had developed. In other words, this pigeon was tolerant to the effects of 5.6 mg/kg more often following chronic administration than he was prior to chronic administration of 3.0 mg/kg. Following a period of withdrawal, however, Pigeon 1163 appeared to be more sensitive to cocaine's rate-suppressing and pause-increasing effects than he was during the acute (i.e., initial) phase.

Figure 3-3 shows data from Pigeon 1166. During acute dosing, some degree of responding was maintained in the small- and medium- ratio components even at the largest dose that the IACUC protocol permitted us to administer (i.e., 17.0 mg/kg). Towards this end of the curves, it is difficult to ascertain the degree to which tolerance developed in the small-ratio component due to the fact that the 17.0 mg/kg dose resulted in only a 50 % reduction in responding relative to control levels. (Note that in order to obtain even this reduction it was necessary to decrease the deprivation such that this pigeon was maintained at 98% of his free-feeding weight). All the mean values

from the probes during chronic administration, nevertheless, are above those from acute determinations. In the medium-ratio component tolerance developed to the effects of 17.0 mg/kg. That is, response rates were higher and pausing was shorter after chronic administration of 3.0 mg/kg. Some tolerance also is evident at the 10.0 mg/kg dose, but the ranges for the acute and chronic effects overlap somewhat. Relative to the medium-ratio component, tolerance to the 10.0 mg/kg dose is more evident in the large-ratio component. Though the effects on rate and pause sometimes fell in the range of the acute effects, the range also extended to levels comparable to responding under control conditions and smaller doses. Tolerance failed to develop at 17.0 mg/kg in the large-ratio component. After a withdrawal period, tolerance was not attenuated in the small-ratio component, but the effects of the 17.0 mg/kg dose in the medium-ratio component provided evidence that tolerance was reversed.

Figure 3-4 shows data from Pigeon 1186. For this pigeon, 5.6 mg/kg greatly reduced responding and elevated pausing in all components when administered acutely, but responding recovered entirely at this dose in all components following chronic administration of 3.0 mg/kg. Tolerance to 10.0 mg/kg was most evident in the small-ratio component. The range of effects was much smaller relative to the range of effects in the other two components. Tolerance still occurred during some sessions when 10.0 mg/kg was administered because the top of the range for response rate and bottom of the range for pause indicate that responding occasionally was indistinguishable from that under control conditions and smaller doses. When 13.0 mg/kg was administered (a dose that was larger than a dose that eliminated responding entirely during acute dosing), baseline-level, some, and no responding was observed in

the small-, medium-, and large- ratio components, respectively. After a period of withdrawal, tolerance was reversed only at the 13.0 mg/kg dose but not at smaller doses.

Figure 3-5 shows data from Pigeon 1859. When administered acutely, 10.0 mg/kg either markedly reduced or eliminated responding in all three components. The range of effects for 5.6 mg/kg was wide because the effects seemed to be bimodal. Several probe administrations allowed us to conclude that responding either was reduced greatly or not at all by this dose. After chronic administration of 1.0 mg/kg, the mean and the range of 5.6 mg/kg effects shifted up for response rate and shifted down for pause in both the small- and medium-ratio components, indicating that some degree of tolerance had developed. Tolerance to 10.0 mg/kg was not evident nor was tolerance observed at any dose in the large-ratio component. In the large-ratio component the chronic range of effects for both 3.0 mg/kg and 5.6 mg/kg did become narrower relative to the acute range, however. After a period of withdrawal, the effects of 5.6 mg/kg tended to shift towards the direction of acute effects, but did not reverse fully for rate and pause in the small-component ratio. Effects in the medium-ratio component remained at chronic levels following withdrawal, and no change across phases seemed to occur in the large-ratio component.

Figure 3-6 shows the mean response-rate data (shown in the left panels of Figures 3-1 through 3-5) fit to monotonic decreasing logistic dose-response functions. The following equation was used

$$Y = \frac{Bottom + (Top - Bottom)}{1 + 10^{(LogED_{50} - x)(HillSlope)}}$$

where *Top* and *Bottom* are the plateaus of the curve in the y-axis units. *Top* was allowed to vary and *Bottom* was constrained to zero because it is nonsensical for response rates to be negative.

ED_{50} is the concentration of the dose that yields responding halfway between *Bottom* and *Top*. In other words, ED_{50} estimates the dose that would reduce responding by 50%. *HillSlope*, which was allowed to vary, describes the steepness of the curve. A *HillSlope* of -1.0 is standard, and anything less (i.e., more negative) than -1.0 would be steeper (GraphPad Prism 5 ®).

Overall response rate in seconds is on the y-axis, and cocaine dose in mg/kg is on the x-axis (log scale). Each row of panels contains data for individual pigeons' small-, medium-, and large-ratio performance with the individually-tailored FR parameter displayed in each panel. The open circles and dashed curve represent the data from acute dosing. The closed squares and solid curve represent data from the during-chronic assessment, and the closed triangles and solid curve represent data from the during-withdrawal assessment. If the largest dose in the series failed to eliminate responding entirely in a component, we entered a zero as the response-rate data for the next largest dose (1/8 log unit larger) to complete the curve. The goodness of fit, or variance accounted for, was high with R^2 ranging from .93 to 1.0. The R^2 values for all curves are reported in Table 3-1. In these graphs, tolerance is indicated by the descending portions of the curve during chronic administration being to the right of that for the acute functions. That is the case in every panel except one (Pigeon 1859 in the large-ratio component) for the comparison between acute and chronic functions.

Overall, tolerance tended to develop to larger doses of cocaine after chronic administration of an initially (i.e., acutely) behaviorally inactive dose. For all pigeons except Pigeon 1166, the chronic dose-response function shifted to the right of the acute dose-response function in both the small- and medium- ratio components. Pigeon 1166's response rates in the small-ratio component were relatively insensitive to cocaine's rate-suppressing effects even at the largest dose that the IACUC permitted us to administer (i.e., 17.0 mg/kg). Tolerance (i.e., a shift in the chronic-dose response curve to the right of the acute dose-response curve) was observed in the large-ratio component for 4 of 5 pigeons with the exception being Pigeon 1859 whose chronic curve overlays his acute curve. For this pigeon, following a period of cocaine withdrawal, a left shift of the downward portion of the curve relative to the chronic curve indicates that tolerance either was erased entirely or at least attenuated in the small ratio component. In the medium-ratio component, the withdrawal curve more closely approximates the chronic curve, rather than the acute curve, indicating that tolerance was not attenuated. In the large-ratio component, despite the nonoccurrence of tolerance, the cocaine's rate-decreasing effects following a period of withdrawal were more pronounced than in either the acute or chronic phases.

To quantify and compare the degree to which tolerance developed across conditions and as a function of the FR parameter, Figure 3-7 shows the ED_{50} values obtained from the dose-response curves for each FR parameter across conditions. The white, dark, and shaded bars represent the acute, chronic, and withdrawal phases, respectively. For all pigeons, the chronic ED_{50} was greater than the acute ED_{50} in most components. For Pigeon 1166, we did not ascertain tolerance in the small-ratio

component because response rates were relatively insensitive to cocaine's rate-suppressing effects even at the largest dose that the IACUC protocol permitted us to administer (i.e., 17.0) across phases. For Pigeon 1859, the acute ED_{50} and chronic ED_{50} in the large-ratio component were equivalent, indicating that tolerance failed to develop.

The degree of tolerance, as indicated by the change in ED_{50} values, did not appear to be modulated by the FR-schedule parameter and seemed comparable across components for Pigeon 1163. For Pigeon 1082, the difference in ED_{50} values between the acute and chronic phases was slightly greater in the small-ratio component relative to the medium- and large-ratio component, in which comparable tolerance levels were observed. For 1166, 1186, and 1859, the magnitude of tolerance diminished as FR value increased. This effect was most evident for Pigeon 1186 (small-ratio tolerance compared to medium- and large- ratio tolerance), Pigeon 1166 (medium-ratio tolerance compared to large-ratio tolerance), and Pigeon 1859 (small- and medium-ratio tolerance compared to no tolerance in the large-ratio component).

The chronic ED_{50} values tended to be greater than the withdrawal ED_{50} values, indicating that the development of tolerance under these conditions appeared either to be reversible or attenuated. The FR-schedule parameter was not predictive of the degree of reversibility, and individual differences were observed. Interestingly, Pigeon 1163's acute ED_{50} values were larger than the withdrawal ED_{50} values, suggesting increased sensitivity to cocaine's rate-suppressing effects after chronic administration and a period of withdrawal. Tolerance was not reversed in only two cases: Pigeon 1166's large-ratio responding and Pigeon 1186's medium-ratio responding.

Figure 3-8 shows the mean pause data (shown in the right panels of Figures 1-5) fit to monotonic increasing logistic dose-response functions. The same equation that was used for response-rate curves in Figure 3-6 also was used for these pause curves. *Top* and *Bottom* are still the plateaus of the curve in the y-axis units, and *HillSlope*, which was allowed to vary, still describes the steepness of the curve. For the pause data *Bottom* was allowed to vary (but had to yield a value greater than 0), and *Top* was constrained to 300, 900, and 2430 for the small-, medium-, and large- ratio components, respectively. These values were chosen because they were the maximum time that a given component could be in effect each session if a pigeon failed to make any responses; no responses would reflect maximal pausing. If a dose failed to eliminate responding entirely (i.e., induce maximal pausing) in a component, we entered 300, 900, or 2430 as the pause data for the next largest dose (1/8 log unit larger) to complete the curve. ED_{50} is the concentration of the dose that yields responding halfway between *Bottom* and *Top*. In other words, ED_{50} estimates the dose that would increase pausing by 50%.

Post-reinforcement pause in seconds is on the y-axis, which extends beyond zero such that all data points are visible. Cocaine dose in log mg/kg is on the x-axis. Each row of panels contains data for individual pigeons' small-, medium-, and large-ratio performance with the individually-tailored FR parameter displayed in each panel. The open circles and dashed curve represent the data from acute dosing. The closed square and solid curve represent data from the during-chronic assessment, and the closed triangles and solid curve represent data from the during-withdrawal assessment.

The goodness of fit, or variance accounted for, was high with R^2 ranging from .87 to 1.0. The R^2 values for all curves are reported in Table 3-1.

A shift of the chronic curve down and to the right of the acute curve indicates that tolerance developed. This pattern of decreased sensitivity to cocaine's pause-increasing effects occurred for most pigeons in at least one of the three components, but there was much more individual variability in the pause data relative to the rate data.

Pigeon 1082 developed tolerance in all three components, with the degree of tolerance being greater as the FR requirement increased. For this pigeon, tolerance was reversible in the small- and large-ratio components, and it was diminished in the medium-ratio component after a period of withdrawal. Pigeon 1163 also developed tolerance in all three components, but the degree of tolerance in the large-ratio component was much smaller than that in the small- and medium- ratio components. Tolerance was not only reversed for this pigeon but also its pausing became more sensitive to cocaine's effects after withdrawal.

Pigeon 1166 was relatively insensitive to the pause-increasing effects in the small-ratio component. During acute administration the amount of time spent pausing during the small-ratio component of the session was already so low that we observed a floor effect—the chronic curve could not shift to the right given the dose range assessed. In the medium-ratio component, the curves fell on top of each other, which indicates that sensitivity to cocaine's effects remained unchanged across phases. A careful examination of pausing at 17.0 mg/kg, however, reveals that a small degree of tolerance developed and then was reversed: The chronic data point is below the acute data point, which in turn is below the withdrawal data point. Some tolerance also

developed in the large-ratio component. Despite a shift in sensitivity at lower doses, at higher doses pausing was not maximal after chronic administration. Pausing at 17.0 mg/kg then returned to the maximum level following withdrawal.

Pigeon 1186 developed marked and comparable tolerance across the components, but after withdrawal, tolerance was not reversible or even noticeably diminished in any component.

Pigeon 1859 developed the least amount of tolerance relative to the other pigeons. In fact, whether tolerance developed is, at worst, arguable and, at best, negligible. In the small- and medium- ratio components, the chronic curved appeared to shift slightly downward at lower doses, but overlapped the acute curve at higher doses. In these components the most convincing evidence for tolerance can be seen at 5.6 mg/kg where the chronic data point falls below the acute data point (note that the dose-effect equation underestimates the obtained acute data). In the large-ratio component there is a downward shift in the curve at higher doses, but again, the change in pausing is minimal. Evidence for tolerance seems to exist at 5.6 mg/kg (the chronic data point falls below the acute data point) and at 10.0 mg/kg. Acute administration of 10.0 mg/kg maximized pausing, but after chronic administration of 1.0 mg/kg, some responding occurred in the large-ratio component, resulting in somewhat decreased pausing. When the dose-effect functions were reassessed after a period of withdrawal, no changes in the functions occurred for either the small- or medium-ratio components; however, pausing in the large-ratio component, appeared to be more sensitive to cocaine's pause-increasing effects relative to pausing observed during the acute and chronic phases.

In addition to the visual analysis of the curve shifts, changes in pausing across phases can be quantified by obtaining ED_{50} values from the dose-response functions. Figure 3-9 shows individual pigeons' ED_{50} values based on the pause data for each FR parameter across conditions. The white, dark, and shaded bars represent the acute, chronic, and withdrawal phases, respectively. Three pigeons (1082, 1163, and 1186) had chronic ED_{50} values that were greater than acute ED_{50} values in all three components, meaning tolerance developed to cocaine's pause-increasing effects. For Pigeon 1082, the degree to which tolerance developed after chronic administration and the extent to which it was attenuated after withdrawal was similar across components. For Pigeons 1163 and 1186, the degree of tolerance was greater in the small- and medium- ratio components relative to the large-ratio component. For example, the difference between the acute and chronic ED_{50} in 1163's large-ratio component is much smaller than the difference between the acute and chronic ED_{50} in his small-ratio component. Another noteworthy detail in 1163's data is that the degree to which tolerance was reversed for this pigeon was inversely related to the degree to which tolerance was modulated by the FR parameter. That is, the difference between the withdrawal ED_{50} and both the acute ED_{50} and chronic ED_{50} was much greater in the small-ratio component relative to the other two components. Though tolerance also was related to the FR parameter for Pigeon 1186, its reversibility was not. In fact, tolerance was hardly reduced in the small- and medium- ratio components and not at all reduced in the large-ratio component.

For Pigeons 1166 and 1859, tolerance was not observed in either the small- or medium- ratio components, and the ED_{50} values across phases were approximately

equal. For both of these pigeons, a hint of tolerance in the large-ratio component was evident with the chronic ED_{50} being a bit greater than the acute ED_{50}. The small amount of tolerance that developed was not reversible, however, for Pigeon 1166 but was for Pigeon 1859.

Figure 3-10 displays an analysis that shows consumption, the number of reinforcers earned out of 12 available, as a function of cocaine dose. Cocaine's rate-decreasing and pause-increasing effects resulted in decreased consumption due to the time-limit contingency in each component. Data from individual pigeons are shown in each row, and the FR parameter displayed in each panel denotes the component. Closed circles, open squares, and closed triangles represent data obtained from the acute, chronic, and withdrawal phases, respectively. Each data point represents the mean number of reinforcers earned of at least two determinations at each dose. Some doses were probed more than twice, and the exact number of probes each pigeon received in each phase is reported in Table 2-1. Errors bars represent the range.

When administered acutely, 10.0 mg/kg was a large enough dose to either reduce markedly or eradicate consumption in all components for three pigeons (1082, 1163, and 1186). For these pigeons tolerance to cocaine after chronic administration is evidenced by increased consumption. The greatest degree of tolerance occurred at the smallest FR requirement. For Pigeons 1082 and 1186, tolerance in the small-ratio component was substantial—they never failed to earn an available reinforcer even at a dose that was higher than a dose that interrupted consumption acutely.

A ceiling effect occurred for Pigeon 1166 in the small-ratio component. Even the largest dose of cocaine did not interrupt consumption acutely; therefore we were unable

to examine any increases in consumption after chronic administration. Tolerance to 17.0 mg/kg in the medium-ratio component was extreme, and all 12 reinforcers were earned after chronic administration of 3.0 mg/kg compared to only 9 earned during acute administration. Some tolerance also is evident in the large-ratio component, but to a lesser extent than that observed in the medium-ratio component, therefore showing schedule parameter specificity similar to that of Pigeons 1082, 1163, and 1186.

For Pigeon 1859, tolerance occurred to effects of 5.6 mg/kg in the small- and medium- ratio components and to 3.0 mg/kg in the large ratio component. At these doses, the number of reinforcers earned was always high after chronic administration. During acute administration the range of consumption at these doses was much wider. Although mean consumption at chronic 10.0 mg/kg is lower than mean consumption at acute 10.0 mg/kg in the small- and medium- ratio components, the range of chronic effects extends beyond the mean of acute effects. In the large-ratio component both the acute and chronic range of effect at 5.6 mg/kg are wide. Acutely, the bottom of the range reaches zero, but Pigeon 1859 always earned at least some reinforcers and sometimes earned all reinforcers at 5.6 mg/kg after chronic administration of 1.0 mg/kg. Additionally, there seemed to be a hint of tolerance in the large-ratio component even at 10.0 mg/kg. Acutely 10.0 mg/kg caused Pigeon 1859's consumption to plummet, but after chronic administration he earned a reinforcer.

For Pigeon 1859, the combined analyses seem to suggest (albeit, weakly) that perhaps some tolerance developed to the 5.6 mg/kg dose. Figure 3-11, therefore, provides a more detailed, reinforcer-by-reinforcer analysis of the effects of 5.6 mg/kg following chronic administration of 1.0 mg/kg. Response rate and pause are shown on

the y-axes for the left panels and right panels, respectively, across successive ratios for the 5.6 mg/kg dose. Recall that each session consisted of 12 possible reinforcement opportunities for each component type, so points between the gaps in the data paths represent individual sessions prior to which a 5.6 mg/kg probe was administered. Also recall that if a pigeon failed to earn all of the programmed reinforcers within the designated time limit, a component ended. Thus, data paths with fewer than twelve data points indicate that not all of the possible ratios were completed. Phase-change lines separate acute dosing from during-chronic dosing as well as during-chronic dosing from during-withdrawal dosing. Additionally, the circle, square, and triangle data points represent acute, chronic, and withdrawal data, respectively. The FR parameter for each component is displayed in the upper left corner of the response-rate panels.

In the small-ratio component, the acute effects of 5.6 mg/kg cocaine decreased response rate in an individual ratio to 1 peck per second or less for more ratios (7 vs. 1) than did that dose after chronic administration. A similar, but less dramatic, pattern also occurred in the small-ratio component analysis of pausing. That is, there are more instances of long pausing in the acute phase relative to the chronic phase. Given that the withdrawal observations tend to be distributed between the range of acute and chronic effects, tolerance appeared to have been slightly attenuated following a period of drug withdrawal. In the medium-ratio component, though responding only sometimes was disrupted or eliminated in the acute phase, response rates never were eliminated by 5.6 mg/kg during chronic probing. Pause increases induced by 5.6 mg/kg also tended to be more variable and longer in duration in the acute phase relative to pausing observed in the chronic phase. After withdrawal, tolerance was attenuated for the rate

measure, yet not for the pause measure. In the large-ratio component, tolerance failed to develop to either rate-decreasing or pause-increasing effects of 5.6 mg/kg. Curiously, following withdrawal, rate and pausing were more sensitive to the effects of 5.6 mg/kg—relative to both the acute and chronic phases—during the first probe determination and less sensitive during the second probe determination. The overall impression from this analysis is that modest tolerance was evident in the two smaller-ratio components, but not in the large-ratio component.

Table 3-1. Variance accounted for (R2 values) for individual pigeons' response rate and pause dose-effect functions shown in Figures 3-6 and 3-8.

		R^2 Rate Curves Phase			R^2 Pause Curves Phase		
Pigeon	FR Component	Acute	Chronic	Withdrawal	Acute	Chronic	Withdrawal
1082	Small	1.00	0.96	0.99	1.00	1.00	1.00
	Medium	1.00	1.00	1.00	1.00	1.00	1.00
	Large	1.00	1.00	1.00	1.00	1.00	1.00
1163	Small	1.00	0.99	1.00	1.00	1.00	1.00
	Medium	1.00	1.00	0.99	1.00	1.00	1.00
	Large	1.00	0.99	1.00	1.00	1.00	0.99
1166	Small	0.93	0.95	0.94	1.00	1.00	1.00
	Medium	1.00	0.98	1.00	1.00	1.00	1.00
	Large	1.00	0.99	1.00	1.00	1.00	1.00
1186	Small	1.00	0.99	0.98	0.94	1.00	1.00
	Medium	1.00	1.00	1.00	1.00	0.87	1.00
	Large	1.00	1.00	0.99	1.00	1.00	1.00
1859	Small	0.99	1.00	0.99	0.97	1.00	0.99
	Medium	1.00	1.00	1.00	0.97	1.00	1.00
	Large	0.99	0.99	1.00	0.99	0.98	1.00

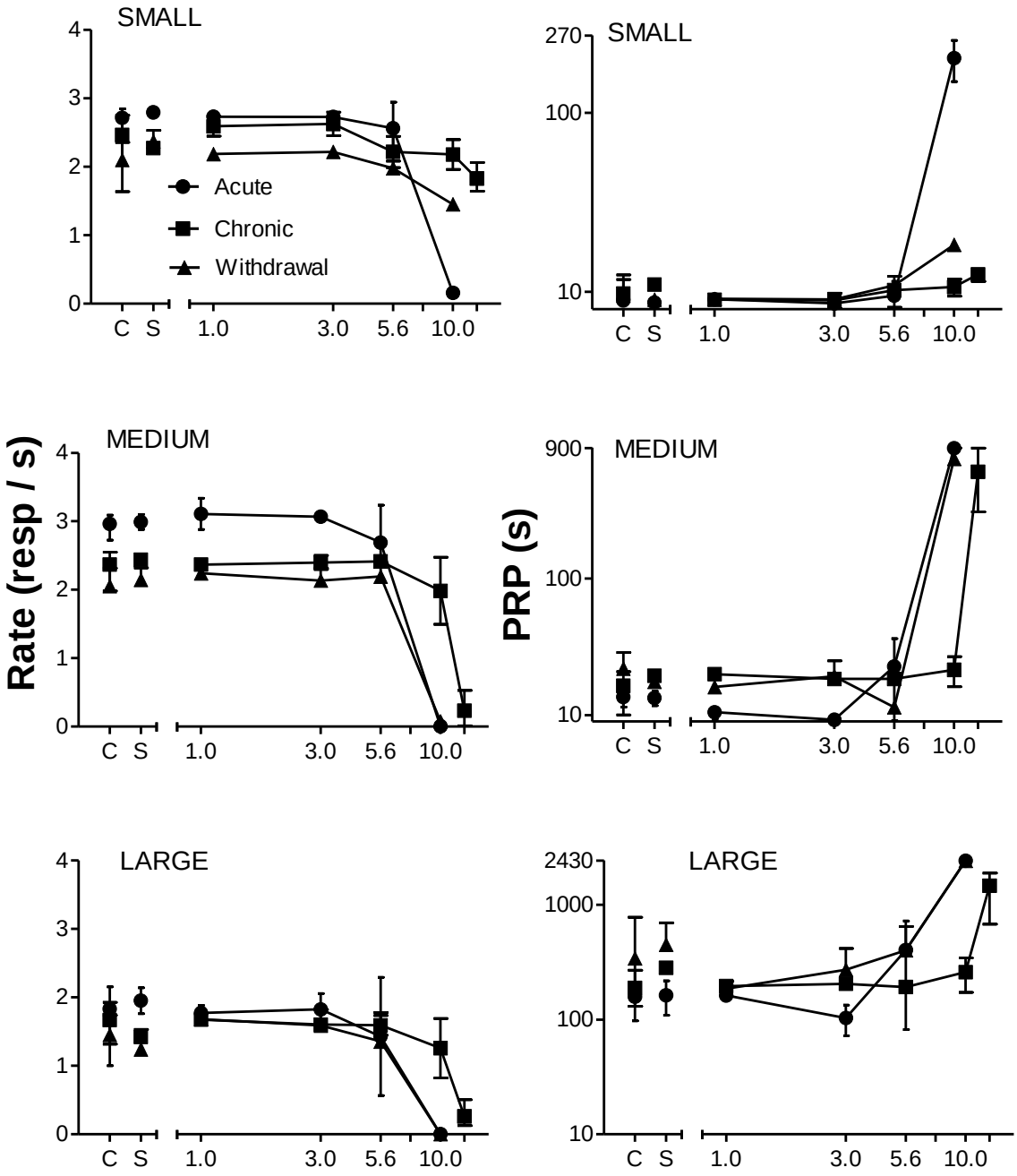

Figure 3-1. Response rate, expressed as pecks per second, and pause, expressed in seconds, as a function of cocaine dose for Pigeon 1082 for each FR parameter in the multiple schedule. The maximum value on the Y-axes for pause data indicate the arbitrary maximum possible average pause value for a component. Each data point is the mean of at least two probe determinations, and error bars denote the range of effects. Circles, squares, and triangles represent data obtained in the acute, chronic, and withdrawal phase, respectively.

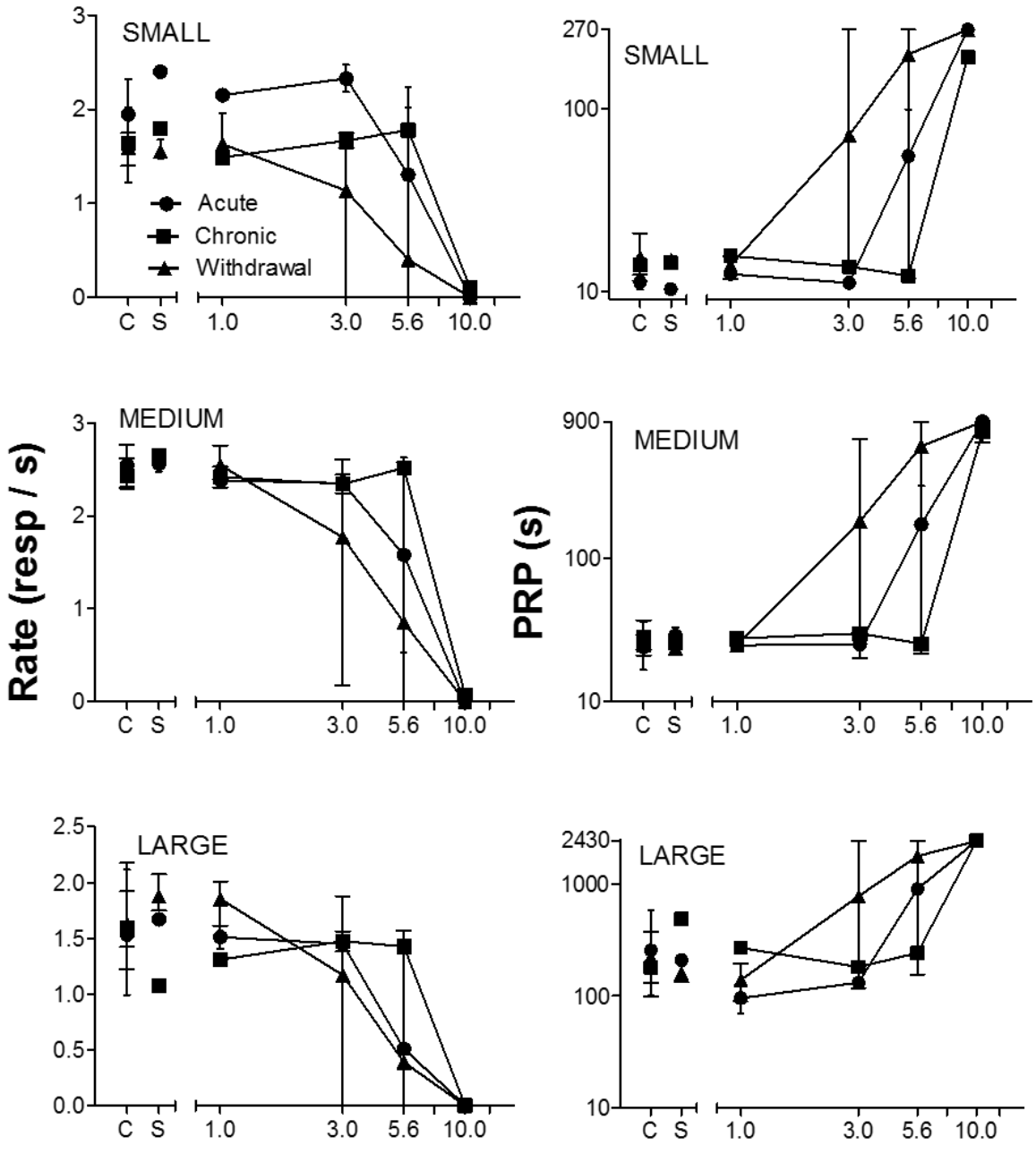

Figure 3-2. Response rate, expressed as pecks per second, and pause, expressed in seconds, as a function of cocaine dose for Pigeon 1163 for each FR parameter in the multiple schedule. Details are the same as those for Figure 3-1.

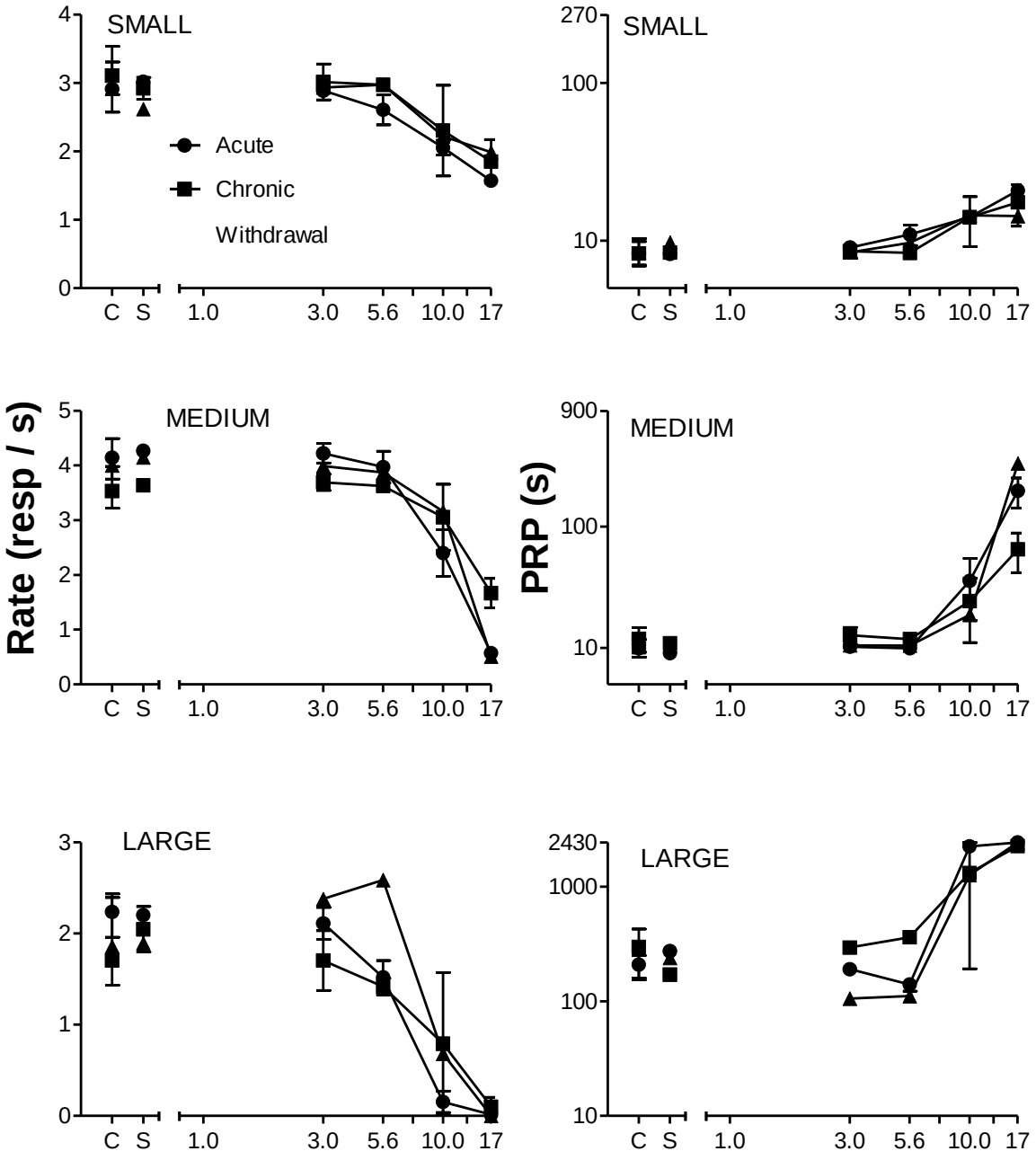

Figure 3-3. Response rate, expressed as pecks per second, and pause, expressed in seconds, as a function of cocaine dose for Pigeon 1166 for each FR parameter in the multiple schedule. Details are the same as those in Figure 3-1.

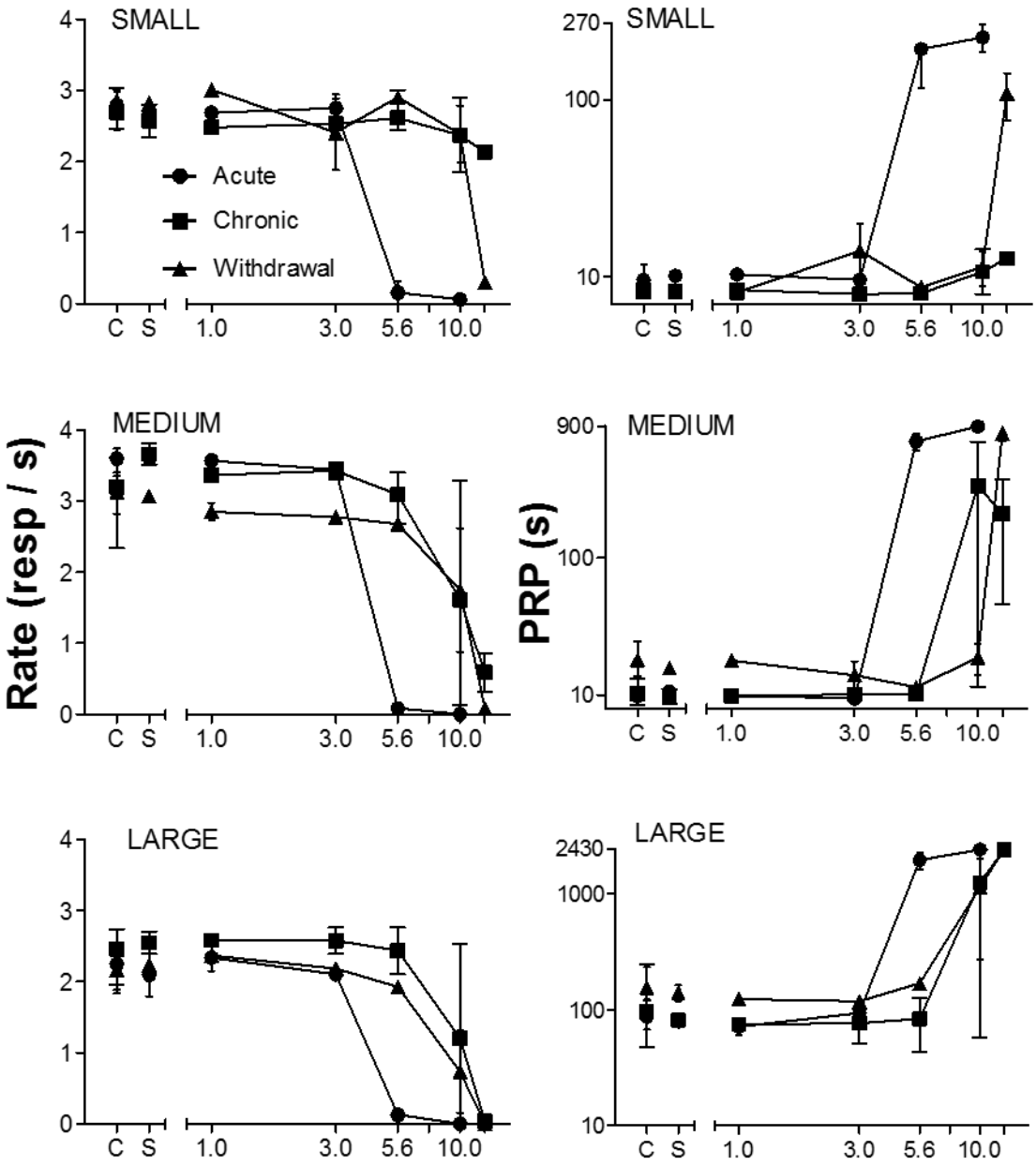

Figure 3-4. Response rate, expressed as pecks per second, and pause, expressed in seconds, as a function of cocaine dose for Pigeon 1186 for each FR parameter in the multiple schedule. Details are the same as those in Figure 3-1.

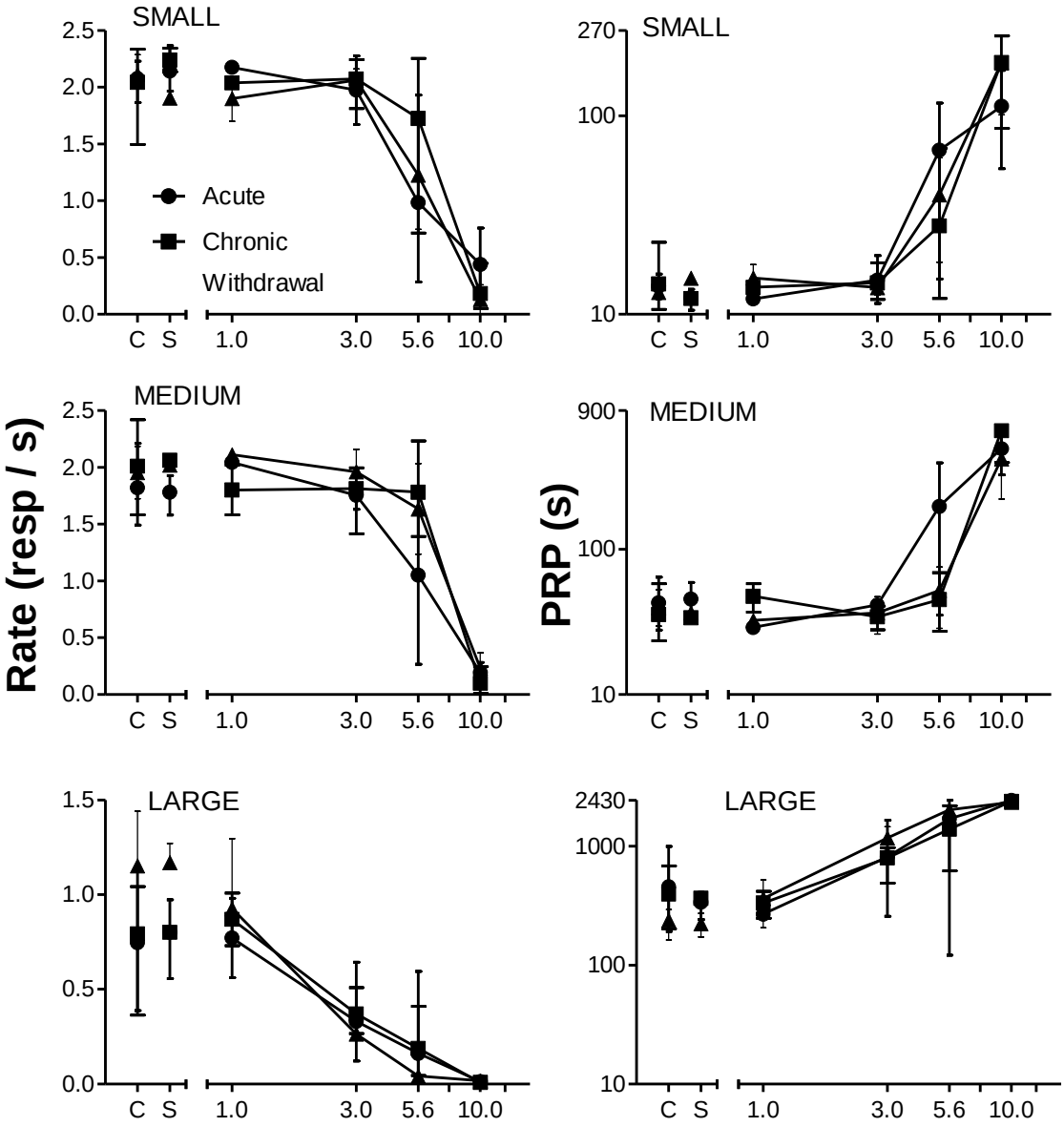

Figure 3-5. Response rate, expressed as pecks per second, and pause, expressed in seconds, as a function of cocaine dose for Pigeon 1859 for each FR parameter in the multiple schedule. Details are the same as those in Figure 3-1.

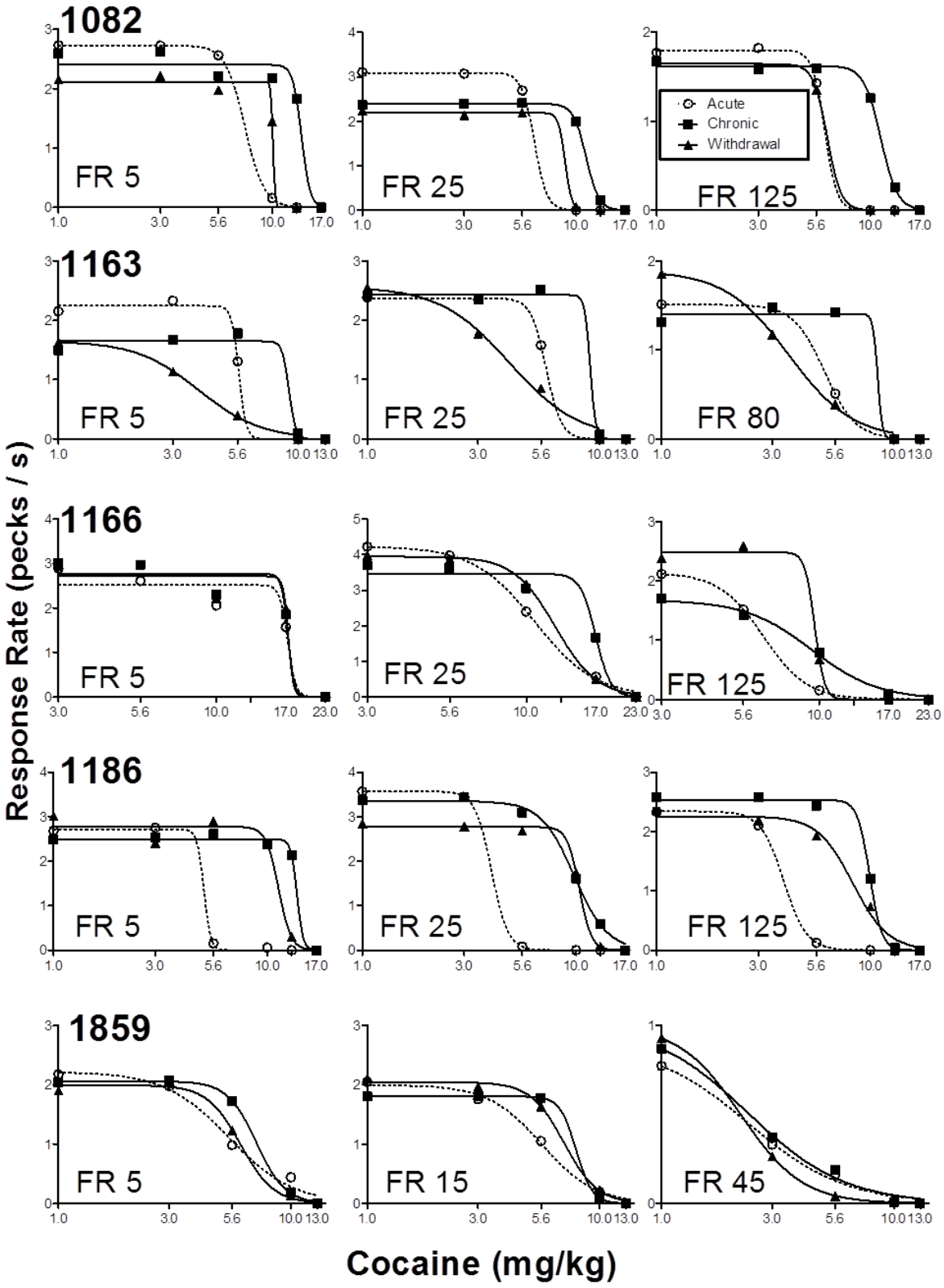

Figure 3-6. Dose-effect functions fit to the mean response-rate data for individual pigeons' (shown by row) FR parameters (shown by column). See text for details about fitting. Open circles and dashed curves represent acute data. Closed squares and solid curves represent chronic data. Closed triangles and solid curves represent withdrawal data.

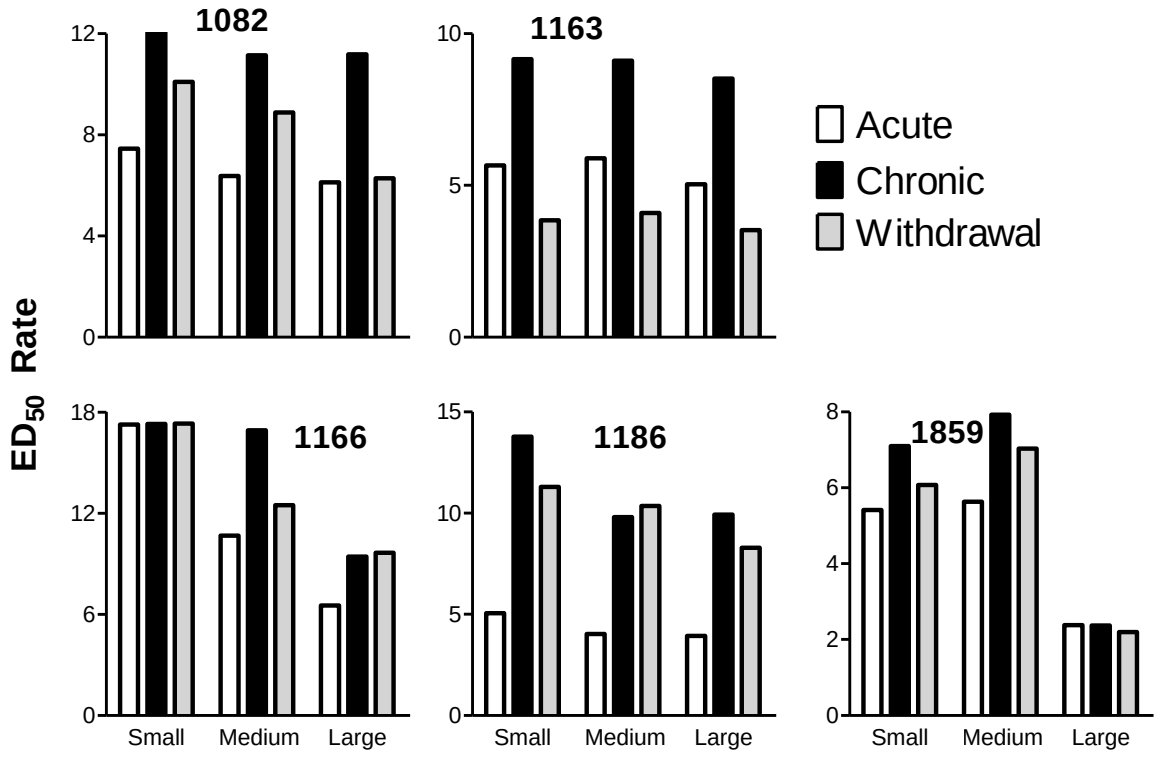

Figure 3-7. *ED_{50}* values obtained from the fitted dose-effect functions for response rate. Each panel represents an individual pigeon. White, black, and grey bars represent acute, chronic, and withdrawal phases, respectively.

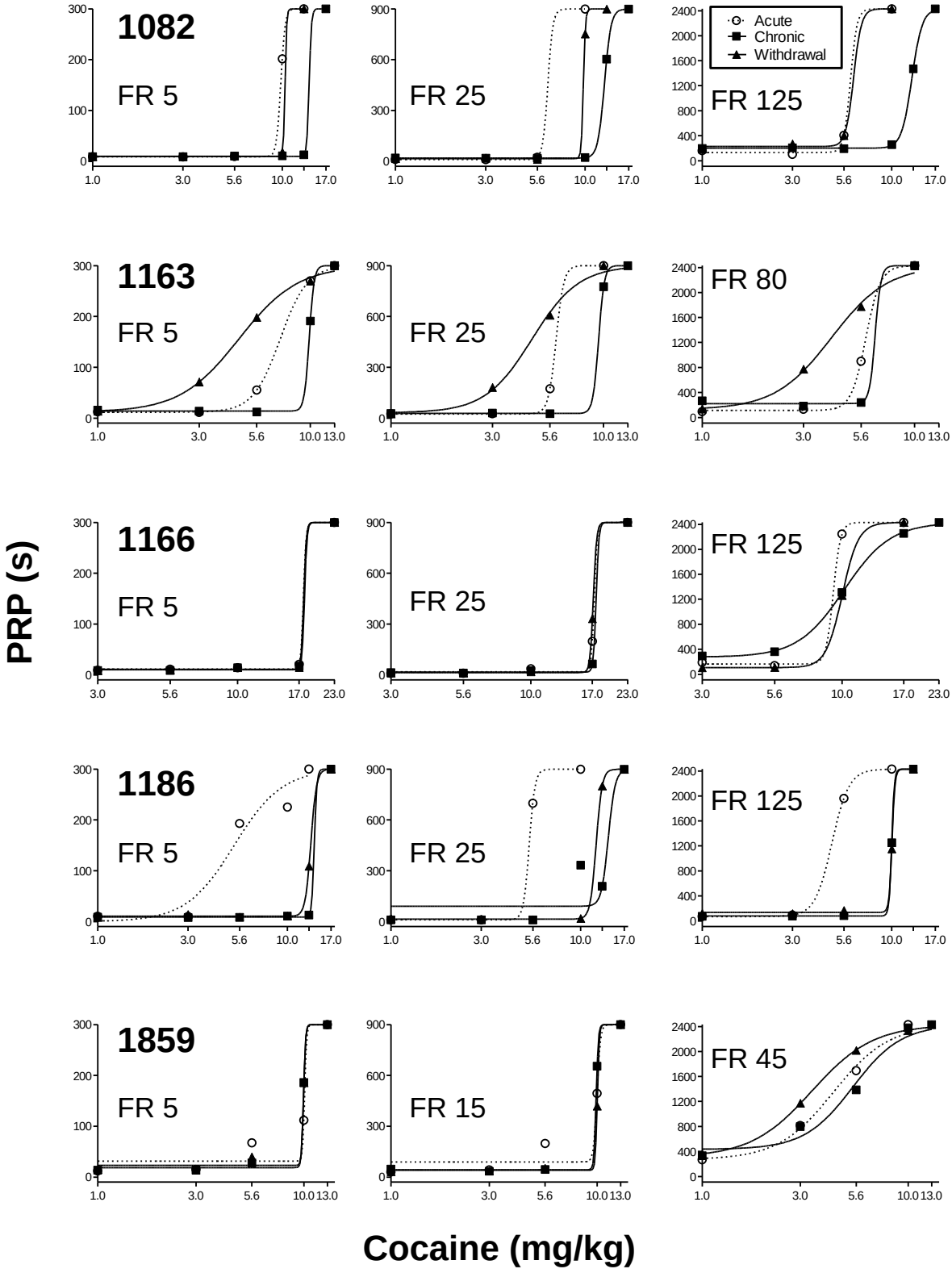

Figure 3-8. Dose-effect functions fit to the mean post-reinforcement pause data for individual pigeons' (shown by row) FR parameters (shown by column). Open circles and dashed curves represent acute data. Closed squares and solid curves represent chronic data. Closed triangles and solid curves represent withdrawal data.

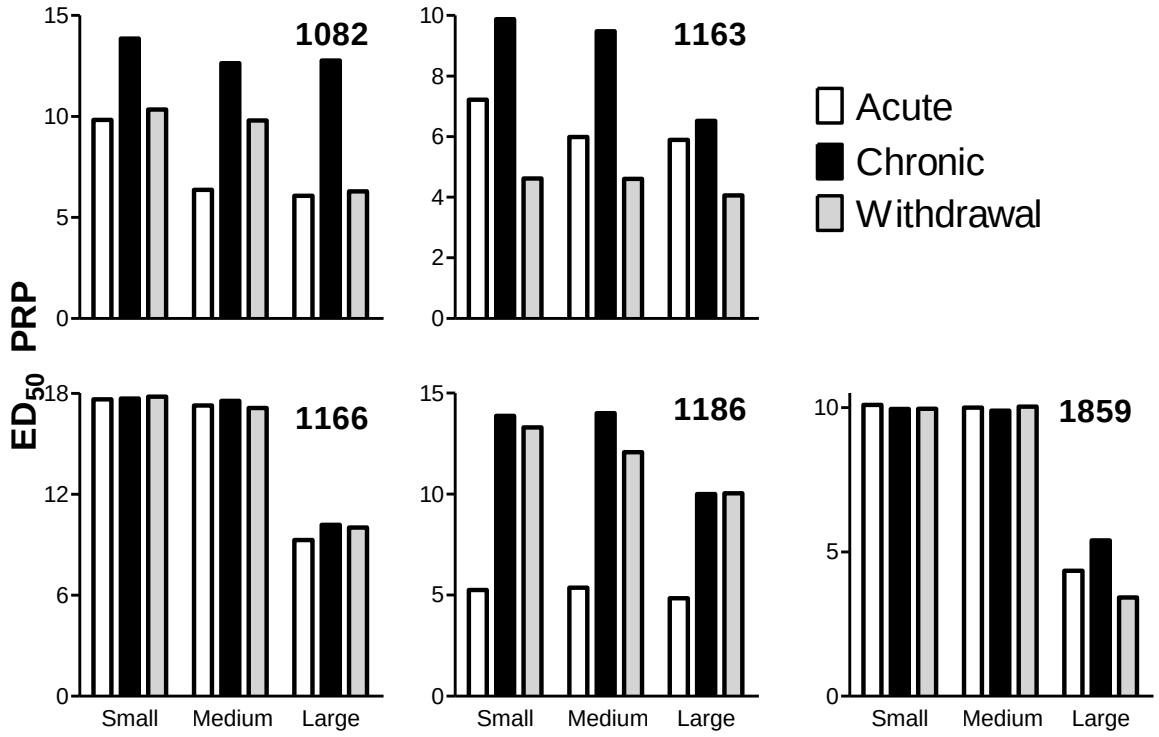

Figure 3-9. *ED_{50}* values obtained from the fitted dose-effect functions for pausing. Each panel represents an individual pigeon. White, black, and grey bars represent acute, chronic, and withdrawal phases, respectively.

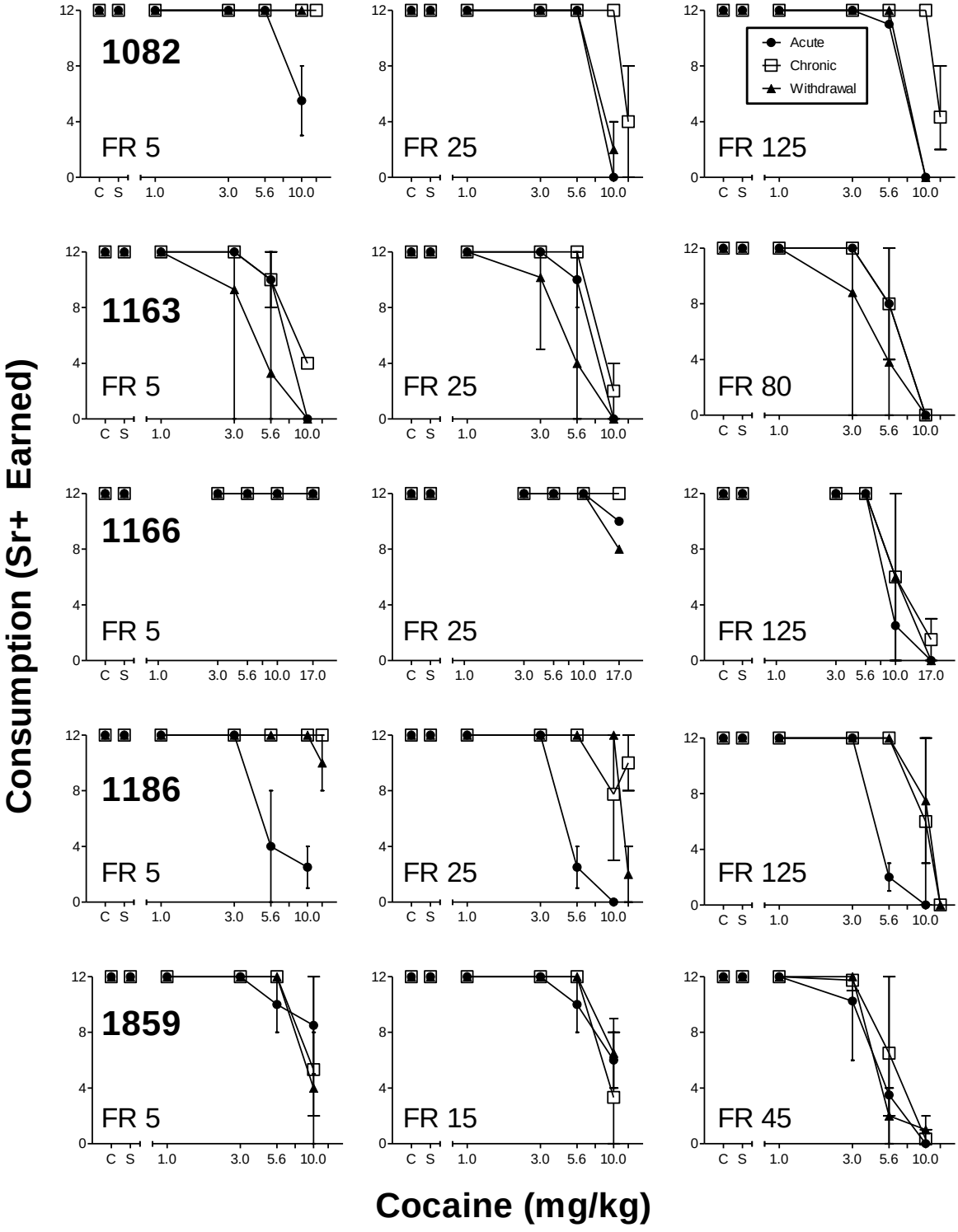

Figure 3-10. The number reinforcers earned out of the 12 possible as a function of cocaine dose for individual pigeons' (shown by row) FR parameters (shown by column). Each data point is the mean of at least two probe determinations, and error bars denote the range of effects. Filled circles represent data obtained in the acute phase, open squares represent data obtained in the chronic phase, and filled triangles represent data obtained in the withdrawal phase.

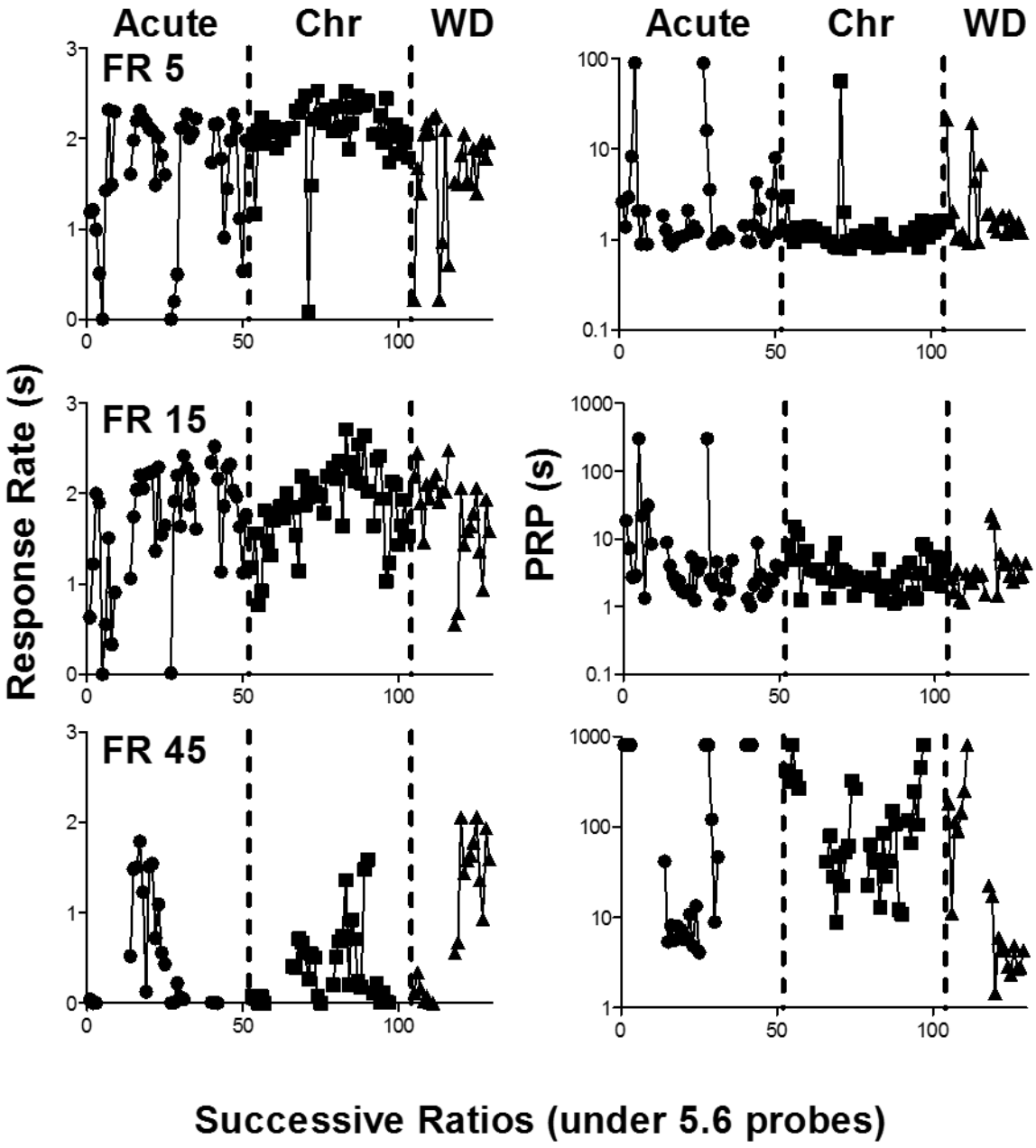

Figure 3-11. Response rate, expressed in pecks per second, and post-reinforcement pause, expressed in seconds, as a function of successive ratios under 5.6 mg/kg probes for Pigeon 1859. FR parameters for each component are displayed by row. Phase-change lines separate the acute (circle data points), chronic (square data points), and withdrawal (triangle data points) conditions. Gaps in the data path represent sessions intervening between 5.6 mg/kg probe administrations.

CHAPTER 4
DISCUSSION

The purpose of the present experiment was to determine whether tolerance developed to cocaine's rate-decreasing and pause-increasing effects and, if it did, whether the degree of tolerance developed differentially across FR parameters. To do so, we arranged a three-component multiple FR schedule of food reinforcement, and the effects of a series of doses of cocaine (i.e., response rate and pause) were assessed before, during, and after chronic pre-session administration of a low dose that produced no changes in rate or pausing, hereafter called "behaviorally inactive." Following chronic administration, 4 of 5 pigeons demonstrated decreased sensitivity to doses of cocaine that acutely produced diminution, and even elimination, of responding, and following a withdrawal period, tolerance was reversed entirely or attenuated. For 1 pigeon the extent to which tolerance developed was markedly less pronounced relative to the other pigeons. Nonetheless, an overall pattern revealed the degree of tolerance was inversely related to the FR requirement, with tolerance generally being greater as the FR requirement decreased for all pigeons.

Acute cocaine administration produced dose-dependent decreases in responding across all three components of the multiple schedule, a finding that is consistent with those obtained in other studies employing FR arrangements either as a multiple schedule or a single schedule (e.g., Hoffman et al., 1987; Hughes & Branch, 1991; Pinkston & Branch, 2004; Schaal, Miller, & Odum, 1995; Stafford & Branch, 1996). Follow acute cocaine administration, within and across session responding remained stable throughout chronic cocaine administration of the behaviorally inactive dose, which further supported the declaration made during acute probing (consisting of just

two determinations of this dose) that it was “behaviorally inactive” (1.0 mg/kg for Pigeon 1859, 3.0 for Pigeons 1163, 1166, and 1186, and 5.6 mg/kg for Pigeon 1082). Had we assessed the effects of doses between 1.0 and 3.0 mg/kg for Pigeon 1859 during acute probing, we may have been able to identify a behaviorally inactive dose greater than 1.0 mg/kg. Chronic administration of said hypothetical dose may have occasioned more apparent and convincing tolerance comparable to that observed with the other 4 pigeons. Thus, parametric assessment of the behaviorally inactive dose (and, relatedly, duration of the chronic administration phase) certainly is worthy of future investigation.

To our knowledge, this is the first demonstration of tolerance to behavioral effects of larger doses of cocaine following chronic pre-session administration of a behaviorally inactive dose. Bowen et al. (1993) assessed tolerance to the suppressive effect of cocaine on a milk-drinking task in rats using a low, moderate, or high dose. They found that dose-specific tolerance developed to effects of the low dose, but it failed to generalize during administration of higher probe doses. Note that because tolerance developed with the low dose, it could not have been behaviorally inactive. Furthermore, the tolerance observed in our experiment compellingly was not dose-specific. Rather, when we probed for tolerance by occasionally substituting higher doses for the chronic dose, tolerance was evident at a range of higher doses, inconsistent with findings reported by Bowen et al.

Our findings confirm and extend the results reported by both Stafford and Branch (1996) and Pinkston and Branch (2004). Whereas Stafford and Branch demonstrated that chronic pre-session administration of a low dose engendered tolerance to cocaine’s disruptive effects on responding maintained by an FR 30 schedule of reinforcement,

Pinkston and Branch arranged a multiple FR 5 FR 100 schedule and demonstrated that tolerance developed following chronic pre-session administration of a low dose. The effect reported by Pinkston and Branch occurred only for 3 of 6 pigeons, all of which previous had been exposed to a chronic post-session administration condition. Their pigeons not only had a history of drug administration, but also the low dose was selected for pre-session administration because it had no effect on within-session response when post-session administrations were administered acutely. By the end of chronic post-session administration of the low dose, within- and across- session response rates no longer were identical to control response rates. Response rates had decreased in either the small- or large- ratio component for 4 of 7 pigeons. Thus, the changes observed as a result of chronic post-session administration indicate that the dose may have had some behavioral action that became apparent only during repeated administration. In our experiment we were able to demonstrate that pre-session administration of a behaviorally inactive dose did not affect response rates across chronic-administration sessions. When administration of the chronic dose was withdrawn, and saline was administered chronically, response rates persisted at relatively stable levels (i.e., did not change).

Additionally, we found that the degree of tolerance often depended on the FR parameter, consistent with previous studies showing that the response requirement is a key determinant of the development of tolerance. That is, tolerance generally is limited to responding under small-ratio components, and not under large-ratio components, of a multiple schedule (Branch, 1990; Hoffman et al., 1987; Hughes & Branch, 1991; Nickel & Poling, 1990; Nickel et al., 1993; Pinkston & Branch, 2004; Van Haaren & Anderson,

1994; Yoon & Branch, 2004). A noteworthy feature of the present data was that for 4 of 5 pigeons, some degree of tolerance developed in the large-ratio component. For example, for Pigeons 1082, 1163, 1186 moderate tolerance developed in that component to the effects 10.0 mg/kg—evidenced by response rate means, upper ranges, or both that are comparable to control and saline levels of responding. Tolerance failed to develop to the effects of 13.0 mg/kg (1082 and 1186) or 17.0 mg/kg (1163) in the large-ratio component; the same was not true in the small-ratio component, however. Similarly, for Pigeon 1163 some tolerance to the effects of 5.6 mg/kg but not 10.0 mg/kg was evident in the large-ratio component, even though tolerance occurred to the effects of 10.0 mg/kg in the small-ratio component.

It would be premature to conclude that lesser tolerance observed in the large-ratio components implicates FR 125 (for Pigeons 1082, 1166, and 1186), FR 80 (for Pigeon 1163), and FR 45 (for Pigeon 1859) as upper limits of response requirements beyond which tolerance becomes increasingly unlikely to occur. Rather, it is more probable that tolerance was least evident in the large-ratio components due the context of the multiple schedule. For instance, it is unknown whether and the degree to which tolerance would occur to cocaine's rate-decreasing effects on responding under a single FR 125, FR 80, or FR 45 schedule following chronic administration of a behaviorally inactive dose.

Smith (1986) clearly demonstrated the effect of context on tolerance. In his study, rats pressed a lever under a multiple differential-reinforcement-of-low-rates (DRL) random-ratio (RR) schedule. Administration of amphetamine increased rates under the DRL component and decreased rates under the RR component, resulting in a decreased rate of reinforcement in both components. During chronic administration

tolerance occurred in the RR component but not in the DRL component. Chronic amphetamine administration under a DRL schedule alone, after the RR component was removed from the procedure, however, did engender tolerance to the rate-increasing effects of amphetamine. Smith noted that in the multiple-schedule context, when both schedules alternated, the drug-induced loss of reinforcement was proportionally much greater in the RR component relative to that in the DRL component, and he concluded that is why tolerance developed only in the RR component. That is, little to no tolerance occurred in the DRL component because the rats were adjusting and allocating their behavior to compensate for the proportionally greater reinforcement loss in the RR component. When the DRL component was presented independently from the RR context, tolerance did develop in the DRL schedule. Presumably the dissociation between DRL-responding tolerance in a single but not multiple schedule materialized because the loss of reinforcement no longer was relative to an additional context. Under the DRL alone condition, the rats behaved efficiently by adjusting response rates and recouping the drug-induced reinforcement loss.

Perhaps the most striking feature of the present findings is that tolerance developed despite no apparent loss, or even reduction, of reinforcement rate in any of the FR components during chronic administration of the small dose. Such a finding cannot be accounted for by the long-standing, widely supported explanation for behavioral tolerance known as the reinforcement-loss hypothesis (Schuster et al., 1966), which asserts that tolerance is an adaptive mechanism allowing an organism to adjust its behavior to compensate for the decreased rate of reinforcement in the presence of drug effects. The reinforcement-loss hypothesis is silent with respect to

the development of tolerance when there is no evidence of disruption during chronic administration.

One could argue the pigeons in the present experiment rapidly adjusted to the loss of reinforcement during acute administration of larger doses. Such a position would suggest that upon repeated tests with a particular dose during acute administration, second and subsequent administrations should reveal effects consistent with the development of tolerance. No such effects were observed.

Although the chronic dose never disrupted behavior such that rate of reinforcement was altered (i.e., responding under the chronic dose was indistinguishable from control responding), we cannot dismiss entirely the role of reinforcement rate. At least in some senses, reinforcement rate still may be relevant in an interpretation of the present data. Because FR schedules were employed, reinforcement rate in a given component depended on response rates: increased responses rates proportionally increase the reinforcement rate. Across components, even if response rates were equivalent, reinforcement rates differed because of the differences in response requirement (e.g., completing an FR 125 requires more time than does completing an FR 5). Under baseline conditions, response rate was highest in the medium-ratio component and lowest in the large-ratio component. Responding under ratio schedules is known to increase and then decrease with increases in response requirement (e.g., Baum, 1993). If baseline response rates are conceptualized as strength of the response, and acute cocaine administration disrupts responding, then we should have observed the greatest and least relative reduction in rates to occur in the large- and medium-ratio components, respectively. Behavioral

momentum theory (Nevin, 1974), however, asserts that behavior in the context of higher reinforcement rates, by virtue of stimulus-reinforcer pairings, will be more resistant to change upon subsequent presentation of disruptor variables, independent of baseline response rates (i.e., response-reinforcer pairings). This perspective seems to provide a better account for the present data in that the obtained reinforcement rate was greatest in the small-ratio component and responding under this component also was least sensitive to cocaine's acute effects for most (3 of 5) pigeons. Perhaps it is the case that the greatest degree of tolerance will occur in contexts that engender the least initial disruption of responding. That is, behavioral momentum may be predictive of subsequent tolerance. Nevertheless, two caveats are noteworthy here. First, both Branch (1990) and Schama and Branch (1989) did not find a systematic relationship between differential reinforcement rates and the degree to which tolerance developed across components of multiple schedules. Second, response strength indexed using pharmacological disruptors often produces different effects than when traditional disruptors, such as extinction and prefeeding, are employed (Cohen, 1986).

Overall, tolerance generally was greatest in the components with smaller ratios, and following a withdrawal phase, tolerance was usually diminished. These results confirmed those obtained in previous studies suggesting tolerance to cocaine's effects could occur by chronic low-dose administration. Moreover, our results demonstrate that under these conditions, repeated exposure to the deleterious effects of cocaine on food-maintained responding is not a necessary factor in the development of tolerance. At first glance, it is tempting to explain the tolerance obtained in the present study by pointing to physiological and pharmacological mechanisms given that we were unable

to track the emergence of tolerance across sessions during chronic administration. The use of a behaviorally inactive dose obstructed observable changes in behavior during chronic administration, and we only were able to determine that tolerance had occurred via occasional probing with higher doses. The use of the multiple schedule allowed us to demonstrate that tolerance was not equal across components, therefore, metabolic or physiological changes alone cannot explain our results. Identification and parametric assessment of other conditions under which the reinforcement-loss hypothesis fails to account for behavioral tolerance should be the focus of future research. A question that was not addressed by the present data was whether an injection of the behaviorally inactive dose was discriminable from an injection of saline. Empirically addressing questions of this nature could prove fruitful in contributing to and enhancing the understanding of potential interactions between physiological and behavioral mechanisms of drug tolerance.

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BIOGRAPHICAL SKETCH

Vanessa Minervini grew up in Pawleys Island, SC where she attended Waccamaw High School and graduated in the top 5 of her class. Upon graduation, she was admitted to the College of Charleston Honors College where she completed her undergraduate studies supported by the Palmetto Fellows and South Carolina Life scholarships. She graduated in 2010 with a Bachelor of Science in psychology and a minor in health. The focus of her bachelor's thesis was food-demand elasticity as a function of session duration in rats. Vanessa pursued her interested in the experimental analysis of behavior by entering a doctoral program in psychology at the University of Florida. Vanessa earned her master's degree in May 2013 from the University of Florida and plans to continue her career in academia by finishing her doctorate, completing post-doctoral training, and obtaining a faculty position at a research institution.