BEHAVIORAL MECHANISMS OF DRUG ACTION: DOES COCAINE ALTER REINFORCER EFFICACY?

By

DAVID R. MAGUIRE

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For my parents, Dennis and Patricia Maguire

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David Richard Maguire

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The two main purposes of the present research were to examine (1) the role of drug-induced changes in reinforcer efficacy in modulating the effects of cocaine on operant responding and (2) the role that these changes might play in the development of tolerance.

Study 1 was designed to provide a within-subject comparison of sensitivity of an operant response (key-pecking in pigeons) to effects of cocaine with sensitivity of feeding. Pigeons responded for brief access to mixed grains under an intermittent schedule of reinforcement. The effects of a range of doses of cocaine were compared across two general response categories, key-pecking and feeding, during three dosing regimens, acute administration, chronic (i.e., daily) administration, and withdrawal. When administered acutely, cocaine produced dose-dependent disruption in all measures. After chronic administration, tolerance developed in the feeding measures but to a lesser degree in the key-pecking measures. During withdrawal, sensitivity of responding to cocaine did not return to pre-chronic levels. Generally, there were instances where doses that disrupted feeding also disrupted key-pecking suggesting a

role for cocaine-induced reinforcer devaluation in the rate-decreasing effects of cocaine on operant behavior. The effects of pre-session feeding were compared across key-pecking and feeding during two dosing regimens, chronic administration and withdrawal. Pre-feeding amount-dependently disrupted all measures to similar degrees; however, the effect of prefeeding was modulated by dosing condition. Responding was more sensitive to prefeeding while under chronic cocaine than during withdrawal.

Study 2 was designed to examine the extent to which the food-hopper mechanism might assume aversive properties following cocaine administration and whether these putative aversive properties will affect preference for the hopper-delivered food. Pigeons responded on two operanda, each of which provided intermittent access to different food types delivered by different food sources, a noisy grain hopper and a silent pellet dispenser. The effects of acute and chronic cocaine administration were tested across several phases. Generally, the effects of the cocaine whether administered acutely or chronically were similar for responding on both alternatives. The results, therefore, suggest that feeder type plays little role in the rate-decreasing effect of cocaine on operant behavior.

CHAPTER 1
GENERAL INTRODUCTION

According to a recent report (Substance Abuse and Mental Health Services Administration, 2010a), approximately 21.8 million Americans (8.7%), aged 12 years old and older are considered current illicit-drug users (i.e., they have used at least one illicit drug in the past 30 days), an increase from 8.0% in 2008. Ten percent of older children and adolescents (aged 12 to 17 years) and 21.2% of young adults (aged 18 to 25 years) are current illicit-drug users. Of current users, 1.6 million have recently used cocaine, and 1.3 million have recently used stimulant drugs other than cocaine. In 2009, 15% of Americans had tried cocaine by the time they were 30 years old; 7% had tried it by the time they were seniors in high school. 22.5 million (8.9%) of Americans fit the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) criteria for substance dependence or abuse of at least one illicit drug; of those, 1.1 million are dependent on cocaine. Incidence of cocaine use (i.e., first-time use) is estimated to be approximately 617,000 a year (1,700 per day) for Americans 12 years old and older; the mean age of initiation is 20 years old.

Despite recent downward trends in the prevalence of the use some drugs (e.g., Johnston, O'Malley, Bachman, & Schulenberg; 2010), illicit drug use and dependence remains a significant public health problem. The economic costs of substance abuse in the United States in 2002 were estimated to be $180.9 billion annually (Office of National Drug Control Policy, 2004). According to a recent report by the United States Department of Justice's National Drug Intelligence Center (2010), over 200,000 people are admitted to publically funded treatment facilities for substance abuse and dependence annually. In 2007, of the estimated 116 million visits to emergency rooms

across the country, approximately 1.9 million were associated with illicit drug use. Of those, cocaine was involved in the highest percentage (29%; approximately 180 visits out of every 100,000; Substance Abuse and Mental Health Services Administration, 2010b).

Short term physiological effects of cocaine use include constricted blood vessels, dilated pupils, and increased body temperature, heart rate, and blood pressure, as well as headaches and gastrointestinal complications. Short-term psychological effects include euphoria, feeling energetic, talkative, and alert, reduced need for food and sleep, and feelings of enhanced ability. Although abuse usually begins with short-term or intermittent use of the drug, use often results in binges or long-term patterns of use (e.g., Kalivas & Volkow, 2005). Long-term (chronic) use can lead to more severe outcomes such chronic anxiety, sleep deprivation, and paranoia. Indirect effects attributed to long-term patterns of use and routes of administration include malnourishment (due to the anorectic effects), loss of smell and nose bleeds (a common result of snorting the powdered form), and complications resulting from frequent injections. Binging can lead to irritability, restlessness, extreme anxiety, paranoia, and after intense bouts, acute cardiac emergencies (heart attack or stroke), respiratory arrest, seizures, or even death (Egred & Davis, 2005).

Given the prevalence of and dangers associated with drug abuse in general and cocaine abuse specifically, the United States government, among other organizations, has devoted substantial resources to both understanding the processes that give rise to drug abuse and developing effective treatments (e.g., the National Institute on Drug Abuse's annual budget request for the fiscal year 2011 was greater than $1 billion;

National Institute on Drug Abuse, 2011). Researchers in these domains recognize that, in addition to understanding the neurobiological processes associated with drug abuse, the relevant behavioral processes must also be considered. In an attempt to identify these processes, many have turned to the field of behavioral pharmacology to provide a more in-depth analysis of the interaction of drugs and behavior (Branch, 1984; Thompson & Schuster, 1968). Behavioral pharmacology is a field in the biological sciences, that has emerged from the integration of the experimental analysis of behavior and pharmacology, and which has facilitated an increase in understanding drug effects in terms of drug-behavior interactions.

A goal of research in behavioral pharmacology has been to identify relevant behavioral and environmental variables that contribute to the behavioral effects of drugs. This approach to understanding the behavioral effects of drugs is often referred to as an attempt to identify behavioral mechanisms of drug action (see Branch, 1984; 1991; Thompson & Schuster, 1968). Early research in the field focused on the role of the schedule of reinforcement in determining the effects of drugs on response rate and patterning (e.g., Clark & Steele, 1966; Dews, 1955; Herrnstein & Morse, 1957; Kelleher & Morse, 1968; C. Smith, 1964). The results of these studies demonstrated that the effects of some drugs on responding could not be predicted solely on the basis of known pharmacological properties of the drug; instead, environmental factors (both past and present) also had to be taken into account in order to account more fully for the behavioral effects of drugs.

An area of research has focused on the role of behavioral factors that modulate effects of cocaine on operant behavior. When administered acutely, psychomotor

stimulants, generally, have been shown to produce systematic, and often dose-dependent, changes in rates of operant behavior. Sensitivity of responding to cocaine's effects, however, has been shown to be related to behavioral variables such as reinforcement schedule type (e.g., Barrett, 1976; Kelleher & Morse, 1964; 1968; Gonzales & Goldberg, 1977), reinforcement-schedule parameter (e.g., Hoffman, Branch, Sizemore, 1987; Hughes & Branch, 1991; McMillan, 1969), degree of stimulus control (e.g., Thompson, 1977; Weiss & Laties, 1966), the subject's deprivation level (e.g., Hughes, Pitts, & Branch, 1996; Ross & Schaal, 2002; Schaal & Branch, 1992; Schaal, Miller, & Odum, 1995), and response effort (e.g., Makhay, Alling, & Poling, 1994) to name a few. One factor that has also received substantial attention is the effect of repeated administration of a drug on sensitivity of responding to that drug.

Repeated administration of a drug can often change the physiological and behavioral effects of the drug sometimes resulting in either an increased sensitivity to the drug's effects (i.e., sensitization) or a decreased sensitivity to the drug's effects (i.e., tolerance). Tolerance is a multifaceted phenomenon that has been implicated in problems of substance abuse and dependence (e.g., Johanson & Fischman, 1989; O'Brien, 2001; Schuster, 1978). Indeed, the development of tolerance to the physiological and psychological effects of a drug is one of the criteria often used to diagnose substance dependence. Although the behavioral factors that facilitate the progression from intermittent, short-term cocaine use to long-term dependence are not fully understood, research on the development of tolerance likely proves useful. The expansion of knowledge about the behavioral factors that contribute to the development of tolerance (in addition to the effects of the drug when administered acutely) likely has

implications for understanding the conditions that give rise to and sustain substance-abuse problems.

Research on effects of acute- and chronic- administration of cocaine and other psychomotor stimulants has been fruitful in terms of identifying behavioral mechanisms involved in the development of tolerance. The degree tolerance can be modulated by a number of behavioral factors (for reviews see Branch, 1993; Carlton, 1983; Goudie & Demellweek, 1986, Stewart & Badiani, 1993; Wolgin, 1989). These factors include whether the subject has the opportunity to respond under the influence of the drug (i.e., contingent tolerance; e.g., Carlton & Wolgin, 1971), reinforcement context (e.g., Schuster, Dockens, & Woods, 1966; J. Smith, 1986), repeated exposure to pharmacologically similar substances (i.e., cross-tolerance; e.g., Woolverton, Kandel, & Schuster, 1978b) and schedule of reinforcement (e.g., Branch, 1990; Hoffman, Branch, & Sizemore, 1987; Nickel, Alling, Kleiner, & Poling, 1993; Yoon & Branch, 2004). Although many questions remain unanswered, the forgoing research suggests that reinforcement processes, at the very least, can contribute to the development of behavioral tolerance to drug effects.

An experimental analysis of the behavioral effects of drugs requires systematic analysis of drug effects in terms of variables that control behavior under non-drug conditions. After considering the behavioral phenomenon of interest, researchers carefully arrange environmental conditions that produce and sustain stable baselines of behavior allowing for a systematic analysis of the effects of drugs on that behavior. These variables include, among others, establishing operations (EOs; i.e., manipulations that alter the momentary efficacy of the consequences of responding),

discriminative stimuli (i.e., contextual stimuli associated with particular environmental contingencies), and response-consequence relationships (e.g., schedules of reinforcement). To identify a behavioral mechanism of drug action is to be able to identify how a drug interacts with ongoing behavioral processes to produce specific effects. Although much research to date has been done with respect to identifying behavioral mechanisms of drug action of cocaine and other stimulants as well as myriad other behaviorally active substances (the research cited above is but a miniscule sample of this research), there is still work to be done. Indeed, identification of behavioral mechanisms is not a unilateral process and requires the integration of numerous lines of research (e.g., Pitts, 2010).

The two main purposes of the present research were to examine (1) the role of drug-induced changes in reinforcer efficacy in modulating the effects of cocaine on operant responding and (2) the role that these changes might play in the development of tolerance. Whereas research on operant behavior comprises a significant proportion of the research conducted in behavioral pharmacology (e.g., see Carlton, 1983; Harvey, 1971; Iverson & Iverson, 1981; Seiden & Dykstra, 1977), and whereas research on operant behavior involves arranging for behavior to be maintained by its consequences, a more in-depth understanding of the role of reinforcement efficacy in mediating the behavioral effects of cocaine will contribute to the rapidly expanding data base in this domain. Study 1 was designed to provide a within-subject comparison of sensitivity of an operant response (key-pecking) to effects of cocaine with sensitivity of feeding. Study 2 was designed to examine the extent to which the food-hopper mechanism

might assume aversive properties following cocaine administration and whether these putative aversive properties will affect preference for the hopper-delivered food.

CHAPTER 2
STUDY 1: EFFECTS OF COCAINE ON KEY-PECKING AND FEEDING

Study 1 Introduction

Many studies on effects of cocaine and other stimulant drugs on operant behavior (e.g., key-pecking or lever-pressing) have reported that these drugs produce dose-dependent disruption in responding maintained by food, water, milk or other consumable stimuli under a variety of experimental procedures (e.g., Branch & Dearning, 1982; Gonzalez & Goldberg, 1977; Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1991; Hughes, Pitts, & Branch, 1996; Jones, LeSage, Sundby, & Poling, 1995; Kleven & Woolverton, 1996; Makhay, Alling, & Poling, 1994; Moerschbaecher, Boren, Schrot, Simoes, & Fontes, 1979; Pinkston, Ginsburg, & Lamb, 2009; Ross & Schaal, 2002; Schama & Branch, 1989; C. Smith, 1964; J. Smith, 1986; Woolverton, Kandel, & Schuster, 1978a). Rate-decreasing effects have been attributed to a number of variables such as disruption of stimulus control (e.g., Dykstra & Genovese, 1987; Katz, 1990), motoric effects including drug-induced stereotypy (e.g., Wolgin, 1989; 2000; Wolgin & Hertz, 1995), schedule of reinforcement maintaining the behavior (e.g., Barrett, 1976; Kelleher & Morse, 1964), and have been shown to interact with effects of other motivational variables such as level of food deprivation (e.g., Hughes, Pitts, & Branch, 1996; Schaal & Branch, 1992).

The current experiments were designed to investigate the degree to which cocaine-induced changes in reinforcer efficacy, as indexed by consumption of the reinforcer, might contribute to rate-decreasing effects on operant behavior, and to investigate as well the extent to which such changes contribute to the development of tolerance. This was accomplished by conducting a within-subject comparison of

sensitivity of an operant (key-pecking) to cocaine's effects with sensitivity to its effects on feeding. We compared effects of cocaine on reinforcer (food presentation) production with effects on consummatory responses (eating the earned or freely presented food).

For the present study, consummatory behavior included engaging in commerce with the food hopper. Studies of drug effects on these types of behavior have been quite frequent with species such as rats (e.g., Wolgin, 1989; 2000; Woolverton, Kandel, & Schuster, 1978a). Typically, acute administration of stimulant drugs in rats dose-dependently suppresses feeding (e.g., see Balopolse, Hansult, & Dorph, 1979; Bane, McCoy, Stump, & Avery, 1993; Bedford et al., 1980; Foltin, Fischman, & Nautiyal, 1990; Foltin, 1989; Vee, Fink, & Constantine, 1983), and, after repeated administration of the drug, tolerance to the suppressive effects develops (Wolgin & Hertz, 1995; Woolverton, Kandel, & Schuster, 1978a). This type of research, however, has been infrequent in the avian behavioral pharmacology research.

The paucity of research on the effects of drugs on feeding in pigeons is surprising given the extensive use of pigeons as subjects in behavioral pharmacology research (cf. McMillan, 1990) and the relative ease of recording at least some behavior related to feeding in standard behavioral pharmacology experimental arrangements. Much of the research using pigeons has arranged for brief periods of access to grain to serve as the maintaining consequence of a target operant response. Therefore, in order to provide a more complete account of drug effects it is necessary to study any direct effects drugs may have on feeding. Such an analysis of the effects of drugs on

feeding in pigeons may contribute to the understanding of the behavioral mechanisms of drug action that operate when food is used to reinforce operant behavior.

Only in the past decade have studies emerged that report data about some effects of cocaine on feeding in pigeons under operant-conditioning procedures. Two studies have measured amount of grain consumed or hopper access under drug and non-drug conditions in order to conduct unit-price analyses (Hughes, Sigmon, Pitts, & Dykstra, 2005; Yoon & Branch, 2004). Hughes et al. measured the weight of a food hopper before and after selected sessions in order to obtain estimates of food eaten during different components of a multiple fixed-ratio (FR) schedule; Yoon and Branch used head-entry detectors (infrared beam detectors across the entrance of an aperture that provided access to a food hopper) to estimate amount of time the subject placed its head in close proximity to the hopper when it was made accessible. Both studies collected data from drug and nondrug conditions; however, in neither study were data presented in a way that would allow a derivation of dose-effect functions for feeding. Miller, Brodkorb, and Branch (2001) also used a head-entry detector to determine the amount of time spent in position to eat from a hopper during grain presentation under a behavior-correlated reinforcer magnitude procedure, but the data presented are from later phases of the experiment, and thus data indicating acute effects of cocaine on feeding were not available.

Recently, Yoon (2006) conducted two experiments examining effects of cocaine on feeding in pigeons under conditions similar to those in arranged during many behavioral pharmacological studies. After pigeons were trained to eat reliably from a grain hopper, food was presented intermittently and response-independently for brief

periods of time according to two schedule arrangements. The food-presentation schedules differed across experiments. In Experiment 1 food was presented according to a single variable-time (VT) 61-s schedule; that is, 2-s access to food was presented at irregular intervals averaging 61 s independent of the subject's behavior. In Experiment 2, food was presented according to a multiple fixed-time (FT) schedule, and components differed with respect to the arranged inter-food intervals and associated key colors. Two-second periods of access to grain were presented regularly at 10-s, 30-s, and 120-s intervals during the three different components. These schedules were implemented in order to mimic the pattern of food presentation typically observed under commonly used reinforcement-schedule arrangements. Three measurements of feeding were taken: head-entry latency was defined as the time from hopper presentation onset to entry of the food aperture; head-entry duration was defined as the total time that the pigeon kept its head in the aperture during hopper presentation; and proportion of food presentations with head entries was defined as the number of food presentations with at least one head entry divided by total number of presentations.

Once behavioral measures had become stable from session to session, the effects of a range of doses of cocaine were determined under conditions designed to assess both acute effects and effects in the context of daily administration of an effective dose. Generally, for both VT and FT food presentation, Yoon reported that when tested acutely cocaine dose-dependently disrupted feeding as indicated by significant changes in all three dependent measures. Both the probability of entering the food hopper and the duration of time spent in the hopper decreased and latency to enter the hopper increased. After daily (chronic) pre-session administration of an

intermediate dose of cocaine, tolerance to the drug's effects developed across all measures; that is, the initial effects of the doses tested were diminished and larger doses were required to produce the same level of disruption. Yoon noted that the pattern of drug effects, both acutely and chronically, closely resembled effects reported in the literature of the drug on other responses such as key-pecking. Like key-pecking, feeding was dose-dependently disrupted and ultimately eliminated with increasing doses of the drug, and, after chronic exposure, tolerance developed.

Inspection of the dose-effect curves for feeding from Yoon's study, however, reveals that during acute administration the doses required to produce substantial disruption in feeding were larger than those typically required to suppress key-pecking maintained under simple schedules of food presentation. Indeed, comparison of the ED_{50} (dose required to produce a 50% change) values, one estimate of behavioral sensitivity to the drug, reported by Yoon on feeding with those obtained from contemporaneous research on effects of cocaine on key pecking (e.g., under FR schedules) revealed that the ED_{50} values for feeding were generally higher than those for key-pecking. Across both experiments and all subjects in Yoon's study, the mean ED_{50} value for head-entry duration was 9.10 mg/kg (range: 8.25 to 9.96 mg/kg), for head-entry latency: 10.13 mg/kg (range: 9.61 to 10.78 mg/kg), and for proportion head entry: 10.68 mg/kg (range: 9.04 to 11.99 mg/kg). In comparison, Marusich and Branch (2009) reported on a series of studies investigating the effects of cocaine on key-pecking maintained by an FR 20 schedule of grain presentation and, based on the individual-subject ED_{50} values they reported, obtained a group-average ED_{50} of 4.89 mg/kg (range: 2.12 to 12.86 mg/kg), when administered acutely, which is substantially

lower than the values reported by Yoon. Based on these differences, it appears that feeding generally may be less sensitive to the effects of cocaine than key-pecking maintained by feeding. That is, larger doses are required to suppress feeding compared to those required to suppress key-pecking.

The contexts in which food was earned in the studies by Yoon and by Marusich and Branch are, nevertheless, different, and it would be premature to attribute the differences in ED_{50} values to a fundamental difference in sensitivity to the drug. To the extent, however, that the difference in cocaine's effects on these two types of behavior is robust and reliable, it may provide insight into a behavioral mechanism of action. Specifically, the difference may shed light on a possible mechanism responsible for the propensity of cocaine to suppress operant responding under a wide range of conditions. One possible explanation of the rate-decreasing effect of moderate to large doses of stimulant drugs implicates the well-established anorectic effects of stimulants such as cocaine (e.g., see Balopolse, Hansult, & Dorph, 1979; Bane, McCoy, Stump, & Avery, 1993; Bedford et al., 1980; Foltin, Fischman, & Nautiyal, 1990; Foltin, 1989; Rowland, Morien, & Li, 1996; Samson, 1986; Vee, Fink, & Constantine, 1983). According to an appetite-suppression explanation, cocaine reduces the appetite, and thus, the motivation to respond. That is, the drug suppresses response rates because it interacts with the effects of currently effective establishing operations (EO) such as food deprivation; thereby, reducing the efficacy of food as a reinforcer. Indeed, some researchers have interpreted rate-decreasing effects of drugs in terms of EO effects (e.g., see Laraway, Snycerski, Michael, & Poling, 2003's extensive discussion on establishing operations).

Several sources of evidence support a reduced-reinforcer-efficacy account. First, based on direct observation of subjects in the experimental chamber while under large doses of drug, there does not appear to be any significant motoric impairment that might render the subject unable to emit the target response. That is, the subjects do not appear to be incapacitated while under the drug and tend to move freely about the chamber. Second, other operations that alter the efficacy of the reinforcer tend to produce effects similar to those of cocaine. For example, when food presentation is used to maintain responding in operant-conditioning experiments, the subject is typically food-deprived to establish food as an effective consequence (cf. Ferster & Skinner, 1957; Skinner, 1938; 1953). A particular level of deprivation (e.g., when the subject is maintained at 80% of free-feeding body weight) is established prior to the experiment. If a subject is food-deprived and maintained at a constant level of deprivation, decreases in deprivation level will reliably reduce rates of operant responding maintained by food (e.g., Clark, 1958; Crocetti, 1962; Sidman & Stebbins, 1954). For example, when subjects are given free access to food prior to the session, thus reducing the level of deprivation, response rates are often decreased as a function of the amount prefed (e.g., Nevin, 1992), and pre-session access to food or water can produce selective decreases on responding maintained by that consequence without affecting responding maintained by the alternative consequence (e.g., Willis, Van Hartesveldt, Loken, & Hall, 1974). For these reasons (apparent lack of motoric effects and functional similarity to effects of other motivational manipulations), a reinforcer-efficacy account of stimulant drug effects seems plausible.

There are, however, a number of factors that mitigate the motivation-based explanation of these effects. First, the drug effects of psychoactive stimulants have been shown to depend on the schedule maintaining responding rather than the type of consequence. For example, Kelleher and Morse (1964), using monkeys, compared the effects of d-amphetamine on lever-pressing maintained by intermittent access to food with effects on responding maintained by shock avoidance across FI and FR schedules. One group of monkeys responded for food under each schedule in a multiple schedule of arrangement whereas another group responded for shock avoidance. They found that generally the largest dose tested (1.0 mg/kg) suppressed responding in both components; however, responding in the FI component, regardless of the type of consequence, tended to be less disrupted than responding in the FR component. In fact, at moderate doses (0.1 and 0.3 mg/kg) responding in the FI components was enhanced; whereas, responding in the FR component was suppressed. These results and others suggest the importance of schedule type rather than consequence type in determining the acute effects of a drug. These types of effects have led many to conclude that the effects of drugs are probably not best accounted for in terms of effects on any specific motivational variables. Indeed, such results led Mckearney (1972) to suggest that "…it can be summarized by saying that the notion cannot be supported that drugs have their effects on behavior because of effects on motivational states" and "if drug effects depended on the type of 'motivation' involved, then two things should be true: first, a drug's effects on similarly motivated behavior should be similar, and, second, a drug's effects on differently motivated behaviors should be different" (p. 4). Studies like those of Kelleher and Morse and others (e.g., see Cook & Catania, 1964;

Barrett, 1976; Barrett, Dworkin, & Zuccareli, 1977; see reviews by Barrett & Katz, 1981; McKearney, 1972; McMillan & Katz, 2002) highlight violations of such assumptions about a direct relationship between effects on behavior and the underlying motivational effects.

Second, effects like those reported by Yoon (2006) suggest that while key-pecking may appear less motivated while under cocaine, the tendency to eat when food is available remains less affected. These findings suggest a simple motivation-based account of cocaine's effects is insufficient. Indeed, other studies have reported similar differences between effects of anorectic drugs on responding to produce access to food and food consumption; that is, anorectic drugs reduced lever-pressing maintained by food at doses that had little effect on the amount of food eaten during periods of free access (e.g., LeSage, Stafford, & Glowa, 2004). If rate decreases result from the devaluing of food as a reinforcer, how is it possible that decreases in responding could occur at doses that ostensibly leave feeding unaffected? This comparison of effects of cocaine on feeding with those on key-pecking, between results reported by Marusich and Branch (2009) and Yoon (2006), however, is based on comparison of data across studies that employed different subjects with different experimental histories responding under different experimental conditions. In order to provide a more rigorous comparison of these effects, the experiments reported here aimed to employ a within-subject design to compare directly whether operant responding maintained by the opportunity to eat is affected at the same doses that decrease feeding in an operant-conditioning paradigm. In addition, this study further explored the development of tolerance to effects of cocaine as a result of repeated exposure. Yoon demonstrated that tolerance to effects

in feeding developed as it does in key-pecking. In the current experiment we compared the development of tolerance across key-pecking and feeding.

In addition to investigating effects of cocaine on key-pecking and feeding, this study also sought to investigate effects of pre-session feeding on key-pecking and feeding. As noted above, one possible behavioral mechanism involved in the effect of cocaine and other psychomotor stimulants on operant behavior is an effect on reinforcer efficacy. In the first part of the current experiment, we attempted to compare the effects of cocaine on key-pecking, the behavior that produces food, and feeding, consuming food. If the drug affects reinforcer efficacy, we expected to see similar sensitivities to the drug across behavioral measures. That is, if rate reductions owe largely to a reduction in reinforcer efficacy, then doses that disrupt key-pecking should also disrupt feeding as both are directly related to reinforcer efficacy.

In the second part of the current experiment, we attempted to investigate effects of changes in reinforcement efficacy by comparing effects of another operation that alters reinforcer efficacy (pre-session feeding) across key-pecking and feeding measures. Presumably, the amount of behavior that a consequence will maintain (i.e., reinforcement efficacy) is related to the extent to which the individual is deprived of that particular consequence. In operant conditioning experiments using reinforcers such as food or water, access to that item is restricted prior to the experimental session thus establishing food or water as an effective consequence. Pre-session access to the reinforcer is one method for reducing reinforcer efficacy and thus disrupting it reinforcing effects (e.g., (e.g., Clark, 1958; Crocetti, 1962; Nevin, 1992; Sidman & Stebbins, 1954). In addition, this manipulation serves a test of one of our assumptions: changes in

reinforcer efficacy should produce comparable disruptions in key-pecking and feeding. Presumably if an event serves as a reinforcer, the contingent delivery of which maintains responding, any devaluation of that reinforcer (e.g., by satiation) should disrupt all related behaviors, those related to producing the reinforcer and those related to consuming the reinforcer. The effects of prefeeding on operant response rate have been demonstrated reliably a number of times. The effects of prefeeding were analyzed to determine 1) if key-pecking and feeding are differentially affected by prefeeding and 2) whether effects of prefeeding are modulated by the prevailing drug-dosing phase.

Method

Subjects

Six male White Carneau pigeons (Columba livia) (numbered 283, 882, 893, 989, 997, and 9590) with prior experimental history served as subjects; all were approximately 12 to 15 months old at the beginning of the experiment. Prior to the beginning of the present experiment all pigeons were exposed to a series of conditions during which key-pecking was maintained under a multiple schedule of grain presentation; therefore, all pigeons had experience key pecking under a procedure similar to the one used in the current experiment. All pigeons were maintained at 85% of their free-feeding body weight (FFBW) via post-session access to a 50:50 mixture of mixed grain (Purina Pro-11®) and Purina Pigeon Checkers® and were housed individually in a colony room under a 16:8-hr light:dark cycle where water and health grit were continuously available.

Apparatus

An operant-conditioning chamber was used (BRS/LVE, Inc. model SEC-002) that had an internal space of 35.0 cm deep by 30.5 cm wide by 36.0 cm high. One wall of

the chamber was constructed of aluminum and contained three 2.5-cm (diameter) response keys arranged in a horizontal line, 26 cm above the chamber floor and 8.5 cm apart (center to center). Only the center key was used; the key could be transilluminated red, green, or yellow and required approximately 0.25 N of force to activate its corresponding switch. A 5.0 cm by 6.0 cm rectangular opening, through which mixed grain was presented, was located 11.0 cm directly below the center key and contained a light. A 1.1-W houselight was located 6.5 cm directly above the center key. Hopper entries were detected using a MED Associates® Single Channel I/R Source, Detector, and Control that generated an infrared beam across the opening of the food aperture. The chamber was also equipped with a Mallory Sonalert®, which generated a 30-ms feedback tone (2900 Hz) when activated, an exhaust fan for ventilation, and white noise was present in the room during the session to mask extraneous sounds. Experimental events were programmed and data recorded by a dedicated computer system (Palya & Walter, 1993). In addition, a Gerbrands® cumulative recorder (Model C-3) provided an online record of responding during each session.

Behavioral procedure

The baseline procedure used in the current study was a two-component multiple schedule (cf. Ferster and Skinner, 1957). Unless otherwise noted, the following behavioral procedure was in effect during every session of the study. Sessions were divided into six two-component blocks. Each component lasted for five grain presentations or 5 min, whichever occurred first. During one component of each block a fixed-interval (FI) 30-s schedule, signaled by illumination of the houselight and transillumination of the center key either a red or green (counterbalanced across

pigeons), was in effect; during the other component a fixed-time (FT) 30-s schedule, signaled by illumination of the houselight only (the center key remained dark), was in effect. The order of component types within each block was randomly determined with the constraint that across all six blocks of the session, one component type was presented first in three of the six blocks. Components were separated by a 10-s inter-component interval (ICI) during which the houselight and key light were extinguished and responses had no programmed consequences.

During the FI component, all key pecks on the lit key produced auditory feedback, a 30-ms beep from the Sonalert, and the hopper was presented immediately upon the first center-key peck 30 s after the beginning of the component or the end of the previous hopper cycle. During the FT component, key pecks ceased to produce the brief auditory feedback, and the hopper was presented response-independently 30 s following the beginning of the component or the end of the previous hopper cycle. Because some subjects initially pecked during the FT component at rates indistinguishable from those during the FI component, a 3-s differential reinforcement of other behavior (DRO) contingency was added to the FT schedule such that hopper presentations were postponed until 3 s had passed since the last key peck. For example, if the 30-s interval had timed out and a response had just occurred at 29 s, grain presentation was postponed until the 32-s mark, assuming no additional responses occurred. This added contingency was not explicitly signaled; thus, the schedule in place constituted a tandem FT DRO schedule. Fixed-time components lasted a maximum of 5 min. If key-pecking occurred throughout the FT component such that hopper presentations were postponed indefinitely (i.e., beyond the maximum

component length), the ICI was initiated at the 5-min mark, followed by transition to the next scheduled component. After the DRO contingency was implemented, responding during the FT component was completely suppressed in most subjects over the course of the following 1 to 3 sessions; Subject 997 continued to peck at very low rates. After rates were suppressed in the FT component, the DRO contingency was rarely contacted; however, it was active throughout the remainder of the experiment.

Reinforcement during both component types consisted of 2-s period of access to the food hopper, timed from the initial entry of the hopper. During food presentation, the houselight and key light (if it was lit) were extinguished, and the hopper light was turned on. At the end of food presentation, the hopper was lowered, hopper light extinguished and either the houselight and key light were turned back on (if the component continued) or the chamber remained dark, signaling the ICI. If head-entry did not occur, the hopper remained raised with the hopper light illuminated for 10 s. After 10 s, the food presentation was terminated (hopper light extinguished and hopper lowered) and the next interval or ICI was initiated. Sessions were conducted once daily seven days a week and lasted 35 to 45 min. Each session began with a 5-min blackout period. The pigeon was placed in the experimental chamber and 5 min later the houselight was illuminated signaling the beginning of the session. No data were collected during the pre-session blackout period and there were no programmed contingencies.

Pharmacological procedure

Prior to selected sessions, either a dose of cocaine hydrochloride, dissolved in 0.9% sodium chloride (saline), or saline alone was administered via intramuscular injection immediately prior to the beginning of the session. The doses tested (expressed as total salt) were 0.3, 1.0, 3.0, 5.6, 7.4, and 10.0 mg/kg (13.0 mg/kg was

also tested in subject 283); injection volumes were 1 ml/kg. During all phases of the experiment, doses were tested in descending order with the constraint that each dose be given once before a second determination of any dose was made, and that at least four no-administration sessions (during acute administration) or chronic-dose sessions (see below) intervened between successive probe-dose administrations. All doses for all subjects were administered at least twice during each phase; in some cases (e.g., when the results from the first two determinations of a dose were discrepant) the effects of particular doses were determined more than twice. Saline was administered as the no-dose, administration control as part of the sequence regular dose-administration sequence, and no-administration control data were taken from the sessions immediately prior to probe sessions.

Experimental phases

Acute-dose determinations. The order of experimental phases is shown in Figure 2-1. After at least 20 baseline sessions (range: 21 to 39) and a determination that responding was stable, evidenced by the lack of trends in key-pecking and feeding measures over the last ten sessions, the acute-drug-administration phase began. Table 2-1 shows the number of baseline sessions conducted for each subject prior to initiating dose-effect curve determinations for the acute and all subsequent phases of the current study (other phases will be described below). The number of sessions conducted during dose-effect curve determinations is shown in parentheses. During acute testing doses were administered as described above. All probe-dose administration were separated by at least four no-administration baseline sessions. Table 2-2 shows the number of administrations of each dose during the acute phase and all subsequent phases of the experiment. When the results of two determinations of a dose were

discrepant, additional determinations were made in order to reassess the reliability of the effect of that particular dose. All doses administered were included in the analysis.

Chronic-dose determinations. After the acute dose-effect curves were determined, a single dose that produced substantial disruption in all measures was selected for each subject (the *chronic dose*; 5.6 mg/kg for Subjects 893 and 989; 7.4 mg/kg for Subjects 283, 882, 997, 9590) and was administered prior to the session daily for at least 30 sessions (range: 33 to 51). After responding stabilized, the effect of each dose of cocaine (and saline) was again determined as during the acute-administration phase, except that the chronic dose was administered prior to all intervening sessions. Probe doses were administered prior to selected sessions with the constraint that at least four chronic-dose sessions intervened.

Intervening phases. After dose-effect curve determinations were complete in the chronic-administration phase, two additional experimental phases were conducted prior to the beginning of the withdrawal phase (described below). These two phases were conducted to test whether the development of tolerance in key-pecking was related to the availability of response-independent food presentation in the FT component. Several studies have shown that the development of tolerance can be related to the reduction in reinforcement rate produced by the drug's effect on responding or by the availability of alternate sources of reinforcement (e.g., Schuster, Dockens, and Woods, 1968; J. Smith, 1986). Generally, if effects on responding do not produce a significant reduction in reinforcement (i.e., the drug effect does not produce a significant cost in terms of total food earned) or if other sources of reinforcement are

present, tolerance is less likely to develop (this is known as the reinforcement-loss hypothesis of behavioral tolerance).

Under the procedure employed in the current study, a complete suppression of key-pecking (i.e., the maximum effect of the drug) resulted in only a 50% decrease in rate of food presentation. Food continued to be available, response-independently, in the FT component; therefore, the development of tolerance in key-pecking under the FI schedule may depend upon the availability of other sources of reinforcement. Based on this logic, we attempted to test whether the removal of one source of food, the FT component, would promote the development of tolerance in key-pecking (and feeding) in the remaining FI component. The two subsequent phases consisted of the removal and the reinstatement of the FT component across phases that allowed an assessment of whether the removal of the FT component would promote tolerance and whether reinstatement of the FT component would reduce the degree of tolerance. Effects of cocaine on responding were re-determined during these phases as they had been during the previous chronic-administration phase. The data are not presented in this paper; however, details about the duration of each phase and the number of administrations are summarized in Tables 2-1 and 2-2.

Withdrawal determinations. The withdrawal phase began approximately 50 sessions after dose-effect curve determinations during the chronic FT-reinstatement phase. During the withdrawal phase, the chronic-dose administrations were replaced with daily saline administration; for Subject 9590, daily administrations were ceased altogether. All other procedural details are identical to the previous chronic phase (i.e., the mult FI FT schedule remained in effect) with the exception being the removal of the

daily administration of cocaine. A new baseline was established for at least 30 sessions (range: 30 to 37). After responding stabilized, the effects each dose of cocaine (and saline) on responding were again determined as during previous phases.

Pre-session feeding tests. Data for the prefeeding tests were collected during two of the phases described above: chronic-drug- administration and withdrawal (see Figure 2-1). Prefeeding tests occurred after dose-effect curve determination in the third chronic-cocaine phase (i.e., after reinstatement of the FT component, an intervening phase described above) and the withdrawal phase. Prefeeding tests in both phases began at least five sessions after the final probe-dose determination in the phase; thereafter, prefeeding tests occurred approximately every fifth session with the data from the immediately preceding session serving as a control. On prefeeding days, subjects were given access to a fixed amount of the 50:50 mixed grain and pigeon checkers (normally fed post-session) in their home cage between 30 and 60 min prior to beginning the session. Water and health grit remained available during the prefeeding period. The amounts prefed were based on the percentage of the subject's free-feeding body weight (FFBW). Five subjects (except 882) were fed amounts that corresponded to 3.5, 7.0, and 14.0% FFBW. Responding in subject 882 was unusually sensitive (relative to the other five subjects) to the prefeeding amount, so the range of values was altered to include 3.5, 5.25, 7.0, 8.75, and 10.5% FFBW. The amounts fed based on the FFBW calculated prior to the beginning of the entire experiment, and the same amounts were fed across both phases were the same despite any changes in daily running body weight across phases. Table 2-5 shows the mean daily running weight for each pigeon in each phase taken immediately prior to beginning control sessions.

If pre-session body weight on non-test days exceeded the typical running weight by more than 25 g, the experimental session for that day was cancelled; the daily administration (of the chronic dose or saline), however, was given. Sessions continued to be cancelled for that subject until body weight returned to normal (± 25g of normal running weight). Typically, this resulted in at most two consecutive cancelled sessions after larger amounts were tested.

Data analysis

All experimental events were time-stamped for data analysis. Unless otherwise noted, all data presented are based on session means. Two general types of dependent measures were obtained: key-pecking measures and feeding measures. Key-pecking measures consisted of overall response rates, run rates, and pause. These data were collected for both components, but, because no subjects responded consistently during the FT component, only key-pecking data obtained during the FI components were analyzed and are presented. Overall response rates were calculated for each FI inter-food interval by summing up the total number of responses and dividing by the duration of the inter-food interval. Inter-food intervals were defined as the total time between the end of a previous hopper cycle (or the beginning of the component) and the subsequent hopper presentation (or the beginning of the ICI if the component time limit was met). Run rates were calculated in the same manner as the overall rates with the pause time subtracted from the denominator; therefore, run rates indicate the rate of responding after the pause was terminated. The pause was calculated as the time between the initiation of the inter-food interval and the first key peck. To maintain progression through the component scheduling during the session, each component was presented for maximum duration of 300 s exclusive of food presentation. In the

event that responding was completely suppressed, by the drug or prefeeding, a component change would occur if this time limit was met in which case the pause value recorded (in the case that no responses occurred) was set at the maximum component duration of 300 s.

Feeding measures consisted of conditional head-in duration, head-entry latency, and proportion of hopper entries. Conditional head-in duration was the total amount of time per hopper cycle that the photo beam across the food aperture was broken. Hopper duration per hopper cycle was timed from the initial beam break and was set at a maximum of 2 s; therefore, the maximum head-in duration per cycle was 2 s. If the hopper was presented but a beam break did not occur, the hopper cycle was excluded from the head-in-duration calculation. Head-entry latency was the amount of time that passed from start of the hopper cycle to the initial beam break. Recall that, when presented, the hopper was available for a maximum of 10 s given that a head-entry did not occur, in which case the maximum head-entry latency of 10 s was recorded for that hopper cycle. Proportion of hopper entries was calculated by dividing the number of hopper cycles during which an entry occurred by the total number of hopper presentations. During the FT components, the total number of cycles was always 30 for each session (the total number of scheduled grain presentations during FT components) whereas during the FI components the total number of hopper cycles depended on the total number of hopper presentations produced. That is, the total number of hopper cycles could range from 30, if all hopper presentations were produced, to 0 if none were produced (e.g., in the case of complete suppression of key pecking by the drug).

Dose-effect analyses. Dose-effect curves for each phase and all measures were plotted to facilitate comparison of behavioral sensitivity to the drug. Curves were constructed by plotting the mean of all determinations of each dose within a phase as a function of dose. Normalized dose-effect curves were constructed by dividing the means from all determinations of each dose within a phase by the mean saline value for that phase and multiplying by 100, and thus expressing the effect of the drug relative to a control value. The percent-saline conversion allows for direct comparison of relative effects of the drug (against the no-drug administration control) within measure across phases (i.e., acute versus chronic) and across measures (e.g., overall rate versus run rate). Additional quantitative analyses were performed by fitting the following logistic function to each percent-saline dose-effect curve (Motulsky & Christopoulus, 2004):

$$Y = Min + \frac{Max - Min}{1 + 10^{(ED_{50} - Dose) * Slope}} \quad (2\text{-}1)$$

where *Y* is the dependent variable (expressed as percent saline), and *Dose* is the dose of cocaine (expressed in mg/kg). *Min, Max*, ED_{50}, and *Slope* are free parameters estimated via the least-squares method of nonlinear regression using the Solver function of Microsoft Excel®. Min and Max are the lowest and highest values of the dependent variable in the curve, respectively, which provide an estimate of the range of effect. ED_{50} indicates the dose that would produce a 50% change in responding, and Slope indicates the steepness of the curve. Both ED_{50} and Slope can be viewed as higher-order dependent measures that indicate sensitivity of responding to the drug. Smaller ED_{50} values indicate that the response measure is more sensitive to the effects of the drug; that is, smaller doses were required to produce the same proportional change when compared to responding represented by a larger ED_{50}. Smaller (flatter)

slopes indicate that larger changes in drug dose were required to produce proportionally similar changes in the measure than in measures represented by larger (steeper) slopes. Changes in these measures across other manipulations (e.g., after chronic exposure) indicate a change in sensitivity as a function of the manipulation.

Generally, the doses tested ranged from small doses that produced no measured behavioral effect to the largest doses that produced a substantial effect; consequently, when the drug produced only decreases in the behavioral measure, Min and Max were held constant at 0% and 100%, respectively, allowing only the free parameters ED_{50} and Slope free to vary. Alternatively, when the drug produced only increases in the behavioral measure, Min was held constant at 100% and Max was allowed to vary. In the case that the range of effect of the drug was not wide enough to provide a reasonable fit of the Equation 2-1 (e.g., no dose produced any substantial decreases in response rate), an additional dose was added for the purposes of fitting the curve. The additional dose was the next larger dose in the dosing sequence (17.0 for Subject 283; 13.0 for all other subjects), and it was assumed to produce the maximal effect. This allowed for a conservative estimate of ED_{50} values when larger doses were required to show the maximal effect but were not tested.

After normalized dose-effect curves were constructed and ED_{50}s were determined, individual-subject ED_{50} profiles (i.e., the collection of ED_{50}s across measures for a subject under a particular condition) were further analyzed using a binomial probability test. The tests were conducted for each subject and for the entire group under each condition to provide a quantitative estimate of whether ED_{50} values for feeding, generally, were higher than those for key-pecking. For each subject, the

ED_{50} for each key-pecking measure was subtracted from the ED_{50} for each feeding measure (from both components). This algorithm yielded 18 possible comparisons of all key-pecking and all feeding measures (3 key-pecking measures x 3 feeding measures x 2 component types). Positive differences (i.e., when the feeding ED_{50} was greater than the key-pecking ED_{50}) were treated as positive instances. A group-level aggregated test was conducted by summing up the total positive instances and total possible comparisons across subjects. If there was no significant difference across key-pecking and feeding measures, there should be approximately equal number of positive and negative instances. That is, differences between the two measures would be expected to be randomly distributed about modal probability of 50%. Tests were conducted with an alpha level of .05.

Prefeeding analyses. During pre-feed testing, weight gain prior to beginning of the session (as a result of pre-session access) was also collected. Subjects were weighed prior to pre-session feeding and again prior to beginning of the experimental session. The difference in weight was taken as a measure of actual weight gain.

In order to assess sensitivity to prefeeding quantitatively across the various dependent measures and across phases, normalized amount-effect curves were constructed by dividing all determinations of a single prefed amount within a phase by the mean control value for that phase and multiplying by 100. Additional quantitative analyses were conducted by modifying Equation 2-1 and fitting the function to individual normalized amount-effect curves using the same method described above. Equation 2-2 is shown below:

$$Y = Min + \frac{Max - Min}{1 + 10^{(EA_{50} - Amount) * Slope}} \quad (2\text{-}2)$$

where *Y* is the dependent variable (normalized), and *Amount* is the amount of food prefed (expressed in percentage FFBW). *Min*, *Max*, and *Slope* are identical parameters as in Equation 2-1, and EA_{50} indicates the prefed amount that would produce a 50% change in responding. Binomial probability tests were also conducted on EA_{50}s across measures and experimental phases to provide a quantitative estimate of differences in sensitivity.

Results

Baseline

Acute baseline. Mean overall response rates from the FI component across subjects ranged from 0.4 to 1.2 pecks/s, and mean run rates ranged from 1.2 to 2.3 pecks/s while mean pause ranged from 11.8 to 20.2 s. Feeding measures differed very little across component type. When pooled across component type, the head-entry latencies ranged from 0.52 to 0.94 s, head-in durations ranged from 1.78 to 1.99 s, and proportion of head entries averaged 1.0 in all subjects. Comparison of control data with data collected after saline administration reveals that saline administration had very little effect in all subjects.

Chronic baseline. Generally, across all subjects, by the end of the 30 sessions chronic-cocaine administration was associated with decreases in output (overall and run rates) to varying degrees across subjects ranging from slight (283 and 9590) to moderate (893, 989, and 997) to substantial (882). Mean overall response rates across subjects ranged from 0.2 to 0.6 pecks/s, and mean run rates ranged from 0.7 to 1.2 pecks/s. Mean pause ranged from 14.1 to 30.5 s. Feeding measures continued to differ very little across component type during the chronic-administration phase. When pooled across component type, the head-entry latencies increased slightly, ranging from

0.7 to 1.9 s, head-in durations decreased slightly ranging from 1.2 and 1.9 s, and proportion of head entries also decreased slightly, averaging .8 to 1.0 across subjects. The notable differences were in the head-in durations for subjects 283, 893 and 989 whose durations were moderately reduced by the chronic baseline.

Withdrawal baseline. During the withdrawal phase, mean overall response rates across subjects ranged from 0.2 to 1.0 pecks/s, and mean run rates ranged from 0.7 to 2.6 pecks/s while mean pause ranged from 14.9 to 22.0 s. Generally, compared to those observed during the chronic-administration sessions, rates during the dose-response assessments in the withdrawal phase were increased, while pauses were decreased and were more similar to those under the acute phase. Feeding measures continued to differ very little across component type during the withdrawal phase. Compared to values during the chronic-administration phase, when pooled across component type, the head-entry latencies decreased slightly, ranging from 0.7 to 1.1 s, head-in durations increased, ranging from 1.8 and 2.0 s, and proportion of head entries also increased, averaging .9 in one subject (893) to 1.0 in all other subjects.

Drug effects

Dose-effect curves for all primary dependent measures from all three phases of the experiment are plotted in Figures 2-2 through 2-10. Each panel shows the mean effects as a function of dose of cocaine and saline for individual subjects. Figures 2-2, 2-3, and 2-4 show overall rate, run rate, and pause curves, respectively. Figures 2-5, 2-6, and 2-7 show head-in duration, proportion head entry, and head entry latency curves, respectively, taken from the FI component, and Figures 2-8, 2-9, and 2-10 show head-in duration, proportion head entry, and head entry latency curves, respectively, taken from the FT component. Control data for the acute phase (located above the C) are means

of session means from sessions immediately preceding a probe administration. Data from sessions following saline administrations are shown above the S. All determinations for each dose are represented in the mean; error bars indicate the range of individual session values. Note the log transformation of the dependent measure (pause or head-in latency) in Figures 2-4, 2-7, and 2-10.

Acute administration. Data from the acute-administration phase are represented in each figure by filled circles. Generally, for the majority of subjects (except 283), cocaine produced monotonic, dose-dependent decreases in overall response rate (Figure 2-2) and run rate (Figure 2-3) and increases in the pause (Figure 2-4). At least one dose produced substantial decreases in responding (resulting occasionally in complete suppression), as indicated by rates near zero responses per second, for both overall and run rates, and pauses nearly 10 times those obtained under saline (refer to Data Analysis section for an explanation of the maximum pause value). For subject 283, intermediate doses of cocaine produced substantial increases in overall rate whereas larger doses had little effect. Note that of the six subjects, 283 responded at the lowest rates under baseline, and the increases at moderate doses, though proportionally significant, produced rates comparable to the baseline levels of most other subjects. Occasionally, the second largest dose tested, 10.0 mg/kg, suppressed responding completely. Run rate and pause, however, were less affected at moderate does; there was some disruption, reduced rates and longer pauses, at 10.0 mg/kg that resemble effects on overall rate.

For all subjects, cocaine dose-dependently disrupted feeding in both components indicated by decreases in head-in duration (Figures 2-5 and 2-8) and proportion of head

entries (Figures 2-6 and 2-9) and increases in head-entry latency (Figures 2-7 and 2-10). Across all feeding measures, the drug produced negligible effects at low doses, variable effects at moderate doses and, in most subjects (except 283), substantial disruption at the largest doses tested. For some subjects (893, 989, 997, and 9590) the variability in effects at moderate doses (5.6 and 7.4 mg/kg) ranged from slight disruption to complete suppression. For three subjects (989, 997, and 9590) the largest dose tested, 10.0 mg/kg, reliably suppressed feeding. Effects did not differ notably with respect to component type.

Acute ED_{50} analyses. Figures 2-11, 2-12, and 2-13 show representative fits of Equation 2-1 to the dose-effect curves for key-pecking, feeding during the FI component and feeding during the FT component, respectively, from the acute-administration phase. Rows show dose-effect curves for different measures; the left and right columns show the fits with the highest and lowest R^2 values for each measure, respectively. Table 2-3 is a summary of the ED_{50} values obtained for each dose-effect curve for all subjects, measures, and phases; R^2 values for each fit are shown in the parentheses. Note that the curve fits were generally very good with most R^2 values above .90. Because of the unusual bitonic shape of the dose-effect function for acute overall rate curve for subject 283 (see Figure 2-2; filled circles), Equation 2-1 was not fit, and those data were excluded from further ED_{50} analyses.

Figure 2-14 shows ED_{50} values (in mg/kg cocaine) plotted for each measure; data from individual subjects are shown in different panels. Darker bars represent data from the FI components (key-pecking values were not analyzed for the FT component), and the lighter bar represent data from the FT components. The vertical dashed line

separates key-pecking measures from feeding measures. Plotting ED_{50} values in this manner allows for direct, within-subject comparison of one measure of sensitivity across dependent variables. Differences in sensitivity to drug effects of different measures of responding are revealed by differences in ED_{50} values. Higher ED_{50}s indicate that larger doses were required to produce a 50% change in responding and, thus, indicate lower sensitivity of that aspect of behavior to the effects the drug. For most subjects (except 283), the ED_{50} for the pause was higher than for both overall and run rates suggesting that larger doses of the drug were required to disrupt pausing than to disrupt overall response output. Furthermore, across subjects, ED_{50}s for run rates were lower than for overall rates. These differences suggest that the drug disrupted overall response output at doses that left pausing less affected, and that run rate was the most sensitive of the key-pecking measures.

For feeding measures, dose-effect curves were similar across component type, indicated by the close approximation of ED_{50} values; that is, ED_{50} measures within measure, across component types are typically similar for all subjects. When there were differences across component types, the ED_{50} was higher in the FI component, and the difference was more pronounced for head-entry latency suggesting that head-latency required smaller doses to disrupt under the FT component.

Comparison across broad response categories, key-pecking versus feeding, reveals some notable patterns. For most subjects (except 893), the ED_{50}s for the pause were higher than for feeding measures. For three subjects (882, 893, and 989), ED_{50}s for feeding were generally larger than those for both overall and run rates; that is, larger doses were required to disrupt feeding measures. ED_{50} values for feeding across these

subjects were approximately 10 mg/kg whereas values for both response rates were closer to 5 mg/kg. Pausing under the FI schedule was least sensitive to the drug whereas overall and run rates were more sensitive. Feeding measures were moderately sensitive but generally less sensitive than output measures; that is, larger doses were required to disrupt feeding than were required to disrupt response output.

The results of the binomial probability tests for sensitivities across feeding and key-pecking are summarized in Table 2-4. For all subjects except 893, the binomial test failed to indicate a statistically significant number of positive differences across response categories; however, for 4 of those 5 subjects, the number of positive instances was greater than the number of negative instances (range: 11 to 12 out of 18 total) suggesting a tendency for feeding ED_{50}s to be higher than those for key-pecking. For subject 893, the sign test showed a statistically significant number of positive differences ($z = 3.06$, $p < .001$). For the group-aggregate data, the binomial test showed a statistically significant number of positive differences ($z = 2.67$, $p < .01$; 65 positive instances, 37 negative instances).

Chronic administration. Dose-effect curves for all measures from the chronic phase are represented by the open circles in Figures 2-2 through 2-10. For most subjects (except 997), the drug dose-dependently decreased both overall and run rates; however, the decreases were not always substantial. With the exception of the chronic dose in subject 893 (5.6 mg/kg), no chronically administered dose produced suppression of responding to the degree that it did during acute administration. For subject 997, there was no effect on response rates across the entire range of doses tested. For 5 subjects (except 283) the effects of the larger doses tested were

diminished, compared to acute effects, during the chronic phase as the curves appear to be shifted to the right. This effect is most pronounced in subjects 997 and 893, yet apparent in at least one dose for subjects 882 (10.0 mg/kg), 989 (5.6 and 7.4), and 9590 (10.0). For subject 283, the shape of dose-effect curve changed dramatically after chronic administration from a bitonic, inverted-U shape to a monotonic decreasing function, primarily due to the diminution of the rate-increasing effects of the moderate doses. The curve, however, was generally flattened with slight decreases in rate at the larger doses.

For three subjects (283, 893, and 989), following chronic administration the drug dose-dependently increased pause, whereas for the remaining three subjects (882, 997, 9590), pause was not affected across the range of doses tested. For 5 of 6 subjects (except 283), tolerance developed to the pause-increasing effects as evidenced by the flattening of the curve; that is, the effect at the larger doses was diminished or absent. For three subjects (283, 989, and 997), tolerance was apparent at moderate doses under which the drug had initially reduced pauses; the pause-decreasing effects appeared to be eliminated as indicated by the flattening of the curve.

For all subjects, tolerance developed across all three feeding measures (see Figures 2-5 through 2-10). When administered acutely, the drug produced dose-dependent, monotonic disruptions in all measures. These included reduced head-in durations and head-entry proportions as well as increased head-entry latencies. After chronic administration, the effects at the larger doses were diminished (see subjects 283, 893, 989, and 9590, all measures) or completely eliminated (see subjects 882 and

997, all measures). As with the acute effects of the drug, the effects after chronic administration were very similar across components.

Chronic ED_{50} analyses. For 3 of 6 subjects (893, 997, and 9590), the binomial probability test showed a statistically significant number of positive differences across broad response categories during the chronic-administration phase (see Table 2-4). For the remaining 3 subjects, the number of positive instances was not significantly significant; however, the number of positive instances was greater than the number of negative instances (11 to 12 out of 18 total). For the group-aggregate data, the sign test showed a statistically significant number of positive differences ($z = 4.72$, $p < .001$; 79 positive instances, 29 negative instances). For all subjects, the number of positive differences either increased or remained the same compared the numbers obtained during the acute-administration phase.

Figures 2-15 and 2-16 show ED_{50} values (in mg/kg cocaine) for key-pecking and feeding measures, respectively, from both the acute and chronic administration phases; data from individual subjects are shown in different panels. Darker bars show chronic-administration data. Differences across each acute-chronic pair indicate changes in ED_{50} as a result of the chronic administration. Tolerance is indicated by larger ED_{50} values during the chronic phase. In the key-pecking measures (Figure 2-15), tolerance developed to the greatest degree in run rate: five of six subjects (except 283) showed the effect as chronic ED_{50}s are consistently higher than acute ED_{50}s. Tolerance developed to a moderate degree in the pause in five of six subjects (except 882); however, the differences in ED_{50} values were variable and, for some subjects, not very substantial. Tolerance developed to a much smaller degree in overall rate: only one

subject showed the effect (997), and one subject (283) showed a much larger degree of sensitivity under chronic administration. The remaining four subjects showed little change in ED_{50} across key-pecking measures. In the feeding measures (Figure 2-16), tolerance developed in almost all subjects across all measures. Of the 36 possible comparisons (3 measures x 2 components x 6 subjects), the ED_{50} increased in 34 cases. The only exceptions were head-entry latency and proportion of head entry in the FI component for subject 283, both of which had high ED_{50} values during the acute-administration phase (approximately 15 mg/kg) that remained relatively unchanged during the chronic phase.

Figure 2-17 shows the $\log_2$-ratio of the chronic ED_{50} value to the acute ED_{50} value across measures for each subject. The ratio of ED_{50} values indicates the degree of change in the ED_{50} value across phases. The sign and absolute value indicate the direction and magnitude, respectively, of the shift in the dose-effect curve. Each whole-unit change in ratio represents a doubling of the ED_{50}. Taking the ratio rather than the absolute difference provides an estimate of the relative change and allows for comparison across measures that have different absolute sensitivities.

A significant degree of tolerance developed in run rate for all subjects for which a comparison was possible. Some degree of tolerance to effects on pause developed in 4 of 6 subjects, most notably in subject 893, and results for overall rates were varied. For subject 997, tolerance developed in overall rate to the same degree as other measures (run rate and all feeding). Of the possible 17 comparisons (3 measures x 6 subjects minus one for overall rate in 283), the ratios of 15 were positive.

For feeding, there were moderate to large shifts in the curves across most measures and subjects. Of the 36 possible feeding ratios, 35 were positive, suggesting that dose-effect curves shifted to the right. Overall, there was no relationship between component type and the development of tolerance except in head-entry latency. The shift in the curve for head latency was larger in the FT component for all subjects.

Withdrawal. Dose-effect curves for all measures from the withdrawal phase are represented by the closed squares in Figures 2-2 through 2-10. For 5 of 6 subjects (except 997), after the withdrawal period the drug dose-dependently decreased both overall and run rates, and for 4 of those 5 (except 882) decreases in rates were accompanied by dose-dependent increases in pause. For subject 997, low to moderate doses (0.3 and 1.0 mg/kg) produced slight increases in rate, and larger doses were ineffective. In the feeding measures, the drug produced moderate decreases in head-in duration at larger doses in 4 subjects (283, 893, 989, and 9590), no change in proportion head entry (means were close to 1.0 in all subjects across both components), and no change in head-entry latency except for a large increase in subject 989 at the 10.0 mg/kg.

The degree of recovery of the original, acute-administration drug effects (i.e., loss of tolerance following the cessation of the chronic-administration) was assessed by the extent to which withdrawal dose-effect curves shifted left away from the chronic dose-effect curves and toward the previously established acute dose-effect curves. Generally, across all measures the effect of the drug across the entire range tested remained at or near chronic-administration levels; that is, the initial effects of the drug were not recovered after the chronic administration was ceased. This is particularly

prevalent in the feeding measures; withdrawal and chronic curves consistently overlapped.

Withdrawal ED_{50} analyses. For 5 of 6 subjects (except 882), the binomial probability test showed a statistically significant number of positive differences (see Table 2-4). Recall that for each subject, the ED_{50} for each key-pecking measure was subtracted from the ED_{50} for each feeding measure (from both components). Positive differences were defined as instances in which the feeding ED_{50} was greater than the key-pecking ED_{50}. For subject 882, the number of positive differences was not significantly significant; however, 12 of 18 comparisons resulted in a positive difference indicating a higher tendency for feeding measures were less sensitive than key-pecking measures. For the group-aggregated data, the sign test showed a statistically significant number of positive differences ($z = 5.87$, $p < .001$; 85 positive instances, 23 negative instances). For all subjects (except 893), the number of positive differences either increased or remained the same compared the numbers obtained during the acute- and chronic-administration phases. For subject 893, the number of positive differences decreased from 18 (of 18, during the chronic-administration phase) to 16 (of 18, during withdrawal).

Figure 2-18 shows the $\log_2$-ratio of the withdrawal ED_{50} value to the acute ED_{50} value across measures for each subject. The ratio indicates the degree and direction of difference between effects of cocaine before and after a history of chronic administration. Positive ratio values indicate that the withdrawal ED_{50} value was higher than for the acute (i.e., the curve remained right of the acute curve). Across subjects, the majority of ED_{50} ratios (49 of 53 possible comparisons) were positive indicating a

consistent rightward shift during withdrawal. This effect was most consistent in the feeding measures; the log ratios of all measures were positive suggesting that effects of chronic administration on sensitivity to the range of doses tested was not altered substantially after at least 30 days of withdrawal.

Prefeeding effects

Figures 2-19 through 2-27 show amount-effect curves for all measures from the chronic-cocaine-administration and withdrawal phases represented by filled and open circles, respectively. Panels show data from individual subjects. All figures show the effect plotted as a function of percentage FFBW prefed. Recall that the absolute amount prefed differed across subjects, and the amount gained varied across individual pre-feed determinations. Table 2-5 shows the prefed amounts (center column) as well as the mean and range of the amount gained across both phases for all subjects (right two columns). The amount gained in most cases was higher than the amount prefed (in some cases substantially so) presumably owing to the availability of water and health grit during the prefeeding period.

Figures 2-19, 2-20 and 2-21 show data for overall rate, run rate, and pause, respectively. For five of six subjects (except 997), overall and run rates decreased and pauses increased as a function of amount. For subject 997, overall and run rates and pause were not affected across the entire range of amounts tested. For 4 subjects (except 893 and 997), overall rate and pause during withdrawal were generally less sensitive to prefeeding than during the chronic-cocaine-administration phase. Differences in sensitivity across drug-administration phases were indicated by differences in the effect of prefeeding amount relative to the control (i.e., 0% FFBW). The effect of drug-administration phase on sensitivity of responding to prefeeding was

particularly pronounced in subject 283 at 7.0 and 14.0% FFBW and in two subjects (989 and 9590) at particular amounts (see 14.0% for 989 and 7.0% for 9590). For Subject 882, the effect of prefeeding relative to control was similar up to the largest amount tested (7.0%); therefore, amounts that exceeded the initial range were tested which produced a shift of the amount-effect curve to the right. The phase differences were generally less pronounced in run rates (except for 283 at 14.0% and 882 at the larger amounts).

Figures 2-22, 2-23 and 2-24 show amount-effect curves for head-in duration, proportion head entry, and head-entry latency, respectively, from the FI component. Figures 2-25, 2-26, and 2-27 show amount-effects curves for the same measures from the FT component. Generally, effects were similar across component type. Effects of prefeeding on feeding were similar to those on key-pecking. That is, there was a prefed-amount drug-administration-phase interaction. Larger amounts tended to produce substantial decreases in both head-in duration (see subjects 882 and 893) and proportion head entry (see 882, 893, and 9590) as well as increases in head-entry latency (see 882, 893, 989, and 9590). Furthermore, in some subjects, disruptions were attenuated during the withdrawal phase. Head-in duration was decreased to below 50% of control at 14% FFBW during the chronic-administration phase, but less affected by the same amount during withdrawal (see also subject 882). Likewise, for subject 9590, the two smaller amounts (3.5 and 7.0% FFBW) produced decreases in proportion head entry under chronic-drug administration; the same amounts had no effect during withdrawal. The drug-administration-phase difference in sensitivity did not occur in 893 in head-entry latency suggesting that there was a selective effect across

feeding measures in some subjects. The phase difference, however, did occur in head-entry latency in other subjects (see 882, 989, and 9590).

EA_{50} analyses. Table 2-6 shows a summary of the fits of Equation 2-2 to all normalized amount-effect curves. The table shows EA_{50} curves obtained by the best fit nonlinear regression as well as the R^2 value for the fit; the majority of R^2 values were above .90. Figures 2-28 and 2-29 show EA_{50} values for each subject for all measures from both components for the chronic and withdrawal phases, respectively.

Under chronic drug, most EA_{50} values ranged from 5 to 15% FFBW. For some subjects (e.g., 283 and 989), EA_{50}s for feeding were higher than those for key-pecking, as feeding was generally less affected by prefeeding than key-pecking. For subjects 882, 893, and 9590, the degrees of disruption in all measures tended to be correlated, resulting in similar EA_{50} values across responses. The binomial probability test was conducted for each subject and for the group data to indicate whether sensitivity to prefeeding differed across broad response categories (i.e., key-pecking versus feeding). Positive instances were comparisons in which EA_{50}s for feeding were greater than those for key-pecking. The results of the test are summarized in Table 2-7 for both drug-administration phases. For three subjects (283, 882, and 989) under chronic-cocaine administration, the binomial test showed a higher number of positive differences (range: 14 to 16) across response categories suggesting that key-pecking was more sensitive to the effects of prefeeding than feeding. For one subject (9590), the number of positive differences, although not statistically significant; however, it was higher than the number of negative differences (12 out of 18). For the remaining two subjects (893 and 997) the number of negative instances was higher (12 and 18 out of 18), suggesting that for

these subjects, feeding was generally more sensitive than key-pecking to the effects of prefeeding. For the group-aggregated data from the chronic-cocaine-administration phase, the binomial test indicated that key-pecking was more sensitivity to the effects of prefeeding than feeding in the majority of cases (z = 1.64, p = .05; 63 positive instances, 45 negative instances).

During withdrawal, EA_{50} values appeared to be more similar across the two response categories in most subjects than during chronic-cocaine-administration, reflecting the diminution of the disruptive effects of prefeeding in the absence of the drug. For three subjects (882, 997, and 9590) during withdrawal, the binomial test showed a statistically significant number of positive differences (range: 13 to 14) across response categories. For the remaining subjects, the number of positive differences was not statistically significant; however, for two subjects (283 and 997) the number of positive differences was higher (12 and 10, respectively). For the group-aggregated data from the withdrawal phase, the binomial test indicated that the number of positive differences was statistically significant (z = 3.37, p < .001; 72 positive instances, 36 negative instances). The change in individual-subject sensitivity profiles across phases (from chronic-cocaine administration to withdrawal) was inconsistent. For three subjects, the number of positive differences increased; for two subjects, the number decreased; and for one subject, the number remained the same.

Figure 2-30 shows the $\log_2$-ratios of EA_{50} values during withdrawal to values from the chronic-administration phase. The ratio indicates the direction and magnitude of the change of the amount-effect curve after chronic administration was ceased. Positive values indicate a shift to the right of the amount-effect curve suggesting that larger

amounts were required to produce similar effects. Ratios were positive in 48 of 54 comparisons suggesting that the withdrawal curve generally shifted rightward relative to the chronic-cocaine-administration curve. The binomial test showed a significant, group-level shift in overall sensitivity of responding (in key-pecking and feeding) across phases ($z = 5.58$, $p < .001$).

Study 1 Discussion

In the current experiment, acute administration of cocaine produced dose-dependent disruption in all response measures. Small to moderate doses produced minimal disruptions in responding across both broad response categories in most subjects; larger doses tended to produce more significant disruptions. For these doses, response output (overall and run rates), as well as engagement with the food hopper (head-in duration and proportion of head entry) were decreased; pauses and head-entry latencies were increased. The effects on patterns of operant responding are quite similar to those reported in the literature. It has been widely reported that psychomotor stimulants such as cocaine can produce disruptions in patterns of operant behavior often resulting in lowered response rates and increased pauses (e.g., Gonzalez & Goldberg, 1977; Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1992; Hughes, Pitts, & Branch, 1996; Jones, LeSage, Sundby, & Poling, 1995; Kleven & Woolverton, 1996; Makhay, Alling, & Poling, 1994; Moerschbaecher, Boren, Schrot, Simoes, & Fontes, 1979; Pinkston, Ginsburg, & Lamb, 2009; Ross & Schaal, 2002; Schama & Branch, 1989; C. Smith, 1964; J. Smith, 1986), especially at larger doses. The data reported here are commensurate with such reports.

Moreover, acute administration produced dose-dependent increases in head-entry latency, and dose-dependent decreases in head-in duration and proportion of

head entries replicating and extending upon previous findings. Yoon (2006), for example, reported that cocaine dose-dependently decreased both head-in duration and proportion of head entries as well as increased head-entry latency. Furthermore, the results reported by Yoon suggested a high correlation among the effects of cocaine on each of the feeding measures; that is, the similar doses tended to produce similar degrees of disruption across measures during acute administration. Data from the current study replicate this result; ED_{50}s for all three measures were quite similar for all experimental phases. In addition, the lack of a consistent component-type effect suggests that effects of cocaine on feeding were not related to the conditions under which food was obtained (i.e., whether food was free or earned).

The current results are also commensurate with reports of the effect of psychomotor stimulants on feeding in a number of other species. For example, Foltin and Fischman (1988), using baboons, reported that pre-session administrations of amphetamine increased the latency to initial feeding, shortened feeding duration, and reduced the number of feeding bouts. These effects have also been demonstrated in rats (e.g., Cole, 1979, Cooper & van der Hoek, 1993, MacPhail & Gollub, 1974) and humans (e.g., Foltin, Kelly, & Fischman, 1989; Rogers & Blundell, 1979). The current results, therefore, expand upon an ever-increasing literature in a domain of research concentrating on the effect of drugs on feeding and replicate some of the anorectic effects of stimulant drugs.

After chronic-cocaine administration, tolerance to the initial effects of the drug developed across a majority of measures in all subjects. That is, after at least 30 sessions of daily exposure to a moderate-to-large dose, administered prior to the

session, the effects of the drug were diminished upon a redetermination of their effects. Response rates were no longer decreased and pauses were no longer increased as substantially as they had been during the acute-administration phase, larger doses were required to produce the same effect, and ED_{50}s were increased indicating that dose-effect curves had shifted to the right. This pattern of effect replicates a number of studies demonstrating tolerance to the effects of cocaine on operant behavior in pigeons (e.g., Branch, 1990; Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1991; Nickel, Alling, Kleiner, & Poling 1993; Pinkston & Branch, 2004; Weaver & Branch, 2008; Yoon & Branch, 2004). Tolerance also developed in most feeding measures as all subjects tended to enter the hopper more frequently, more quickly, and for longer durations, after chronic exposure replicating earlier results suggesting that feeding (from a food hopper, in pigeons) can become tolerant to the effects of cocaine given significant history with the drug (cf. Yoon 2006).

One interesting result was the development of differential tolerance across response categories. For all but one subject (997; see Figure 2-17), tolerance developed to a greater degree in feeding than in overall key-pecking rate and, in some subjects, pause, as indicated by higher log ratios of ED_{50}s for feeding measures than for key-pecking measures. Differential tolerance in this case may be the result of complex environment-behavior relationships and may be predictable given the nature of the arranged contingencies. According to the feedback functions relating reinforcement rate as a function of response rate under interval schedules, reinforcement rate is invariant across much of the range of response rates typically observed under FI schedules in pigeons (Nevin & Baum, 1980). That is, reinforcement rate is generally

unrelated to response rate except at very low response rates; reinforcement rate begins to decrease at response rates lower than the average inter-reinforcer interval. Under the procedure used in the current experiment, significant decreases in response rate (as a result of drug administration) were required to substantially decrease overall reinforcer rate, so it might be expected, given the reinforcement-loss hypothesis of behavioral tolerance (i.e., tolerance typically develops under conditions in which the drug effect reduces reinforcement rate; see Schuster, Dockens, & Woods, 1966) that tolerance might not necessarily develop under interval schedules. Tolerance, however, can develop under FI schedules despite this feedback function (see Schama & Branch, 1989), so it remains unclear as to why tolerance was less pronounced in key-pecking measures.

For feeding measures, however, the feedback functions are different. There is a direct relationship between head-in duration or proportion head entry and total reinforcement obtained (in grams of food). Assuming a constant rate of eating once the subject has entered the food hopper, disruptions in either aspect of feeding (shorter head-in durations or fewer entries) will likely result in immediate reductions in food consumption, and the effects will be directly related to the degree of disruption. Substantial disruptions in either aspect of behavior result in substantial decreases in food consumption. It's possible that each response category (key-pecking and feeding) was sensitive to the relevant feedback functions which, then, contributed to the development (or lack of development) of tolerance. A test of this theory may be to replicate the acute phase of the current experiment using schedules which also arrange

for a direct feedback function (e.g., ratio schedules) to determine if differential tolerance results.

During the withdrawal phase, the chronic dose was replaced with saline (or no daily administrations for subject 9590), and the effects of cocaine were reassessed. The effects of the drug on feeding after 30 days of withdrawal remained at or near during-chronic-administration levels; that is, tolerance to the initial effects of the cocaine persisted after the cessation of daily cocaine administration. Generally, dose-effect curves determined during the withdrawal phase remained shifted right compared to those determined during the acute phase. Yoon (2006) reported a similar phenomenon for feeding. In his experiment, a withdrawal phase was also included, during which daily cocaine administrations were replaced with daily saline administrations. Of the 18 possible comparisons in his study (6 subjects by 3 measures) only 9 comparisons indicated the persistence of tolerance. Interestingly, the 9 comparisons were consistent within subject; that is, three subjects showed the persistence of tolerance in all three measures. In two of the remaining three subjects, tolerance disappeared entirely, and in one subject, feeding was generally insensitive to the effects of the drug throughout the experiment.

The persistence of tolerance after the removal of daily cocaine administration could be the result of an irreversible change in responding that developed during chronic-drug exposure. Wolgin (1989), for example, conceptualized behavioral tolerance as the result of a conditioning process wherein compensatory responses emerge to counteract the initial effects of the drug. After chronic administration was ceased, the behavioral pattern that emerged under chronic drug may have remained at

strength such that subsequent challenges by the drug were less effective than they were prior to chronic administration. The compensatory-response account, however, suggests that tolerance will develop only when feeding takes place under the effect of the drug. Given that responding under the influence of the drug is not required for tolerance to develop in pigeons (i.e., tolerance can develop when the drug is administered post-session; see Marusich & Branch, 2009), it is unclear exactly what mechanism is responsible for the persistence of tolerance in the current experiment.

A primary purpose of this study was to compare the effects of cocaine on key-pecking, a reinforcer-production response, with feeding, a reinforcer-consumption response. In light of recent evidence (e.g., Yoon, 2006), we suspected that feeding might be less sensitive to the disruptive effects of cocaine than key-pecking. That is, larger doses of cocaine were required to disrupt feeding than were typically required to disrupt key-pecking. Yoon reported ED_{50} values for feeding that are higher than those generally reported in the literature for key-pecking under similar experimental arrangements (e.g., Marusich & Branch, 2009; see also Pinkston, Ginsburg, & Lamb, 2009). These differences, however, are based on comparison of data collected in different studies, using different subjects, and different procedures. If feeding is reliably less sensitive than key-pecking, further examination of this relationship might help to bolster (or reject) accounts of the oft-reported rate-reducing effects of psychomotor stimulants. For example, reductions in responding maintained by food reinforcement could be the result of a devaluation of food as a reinforcer; the motivation to respond for food may be reduced, which results in a reduction of response rates. This account is intuitively appealing: cocaine and other psychomotor stimulants have well-known

appetite-suppressive effects (e.g., e.g., see Balopolse, Hansult, & Dorph, 1979; Bane, McCoy, Stump, & Avery, 1993; Bedford et al., 1980; Cole, 1979; Foltin, Fischman, & Nautiyal, 1990; Foltin, 1989; Rowland, Morien, & Li, 1996; Samson, 1986; Vee, Fink, & Constantine, 1983); therefore, we expected effects of the drug on feeding to be closely related to effects on key-pecking.

In the current study, we attempted to compare these effects within subject, and the results expand upon the literature by providing a within-subject comparison of effects of cocaine on key-pecking and effects on feeding in a context where, not only were brief periods of access to food available intermittently, but they were presented both response-dependently and response-independently. Like Yoon's (2006) study, the effects of a range of doses of cocaine were assessed. A strength of this approach is the behavioral sensitivity of each response category was compared based on the effects of a range of doses of the drug on each response category, thus providing a more complete comparison. An additional strength of the current study is the measurement of additional responses (i.e., beside the operant response) in order to aid the analysis. Rather than inferring or assuming effects on feeding (e.g., that if the subject responds for food, it will inevitably consume it), more direct measurements of feeding were made. To conduct the comparison of relative sensitivity of each response category to the drug, the following steps were taken: (1) various measures of both key-pecking and feeding were taken prior to and after the administration of a range of doses of cocaine and across administration regimens, (2) estimates of the sensitivity of each measure were obtained through quantitative methods (i.e., curve fitting and ED_{50} estimation) to produce a sensitivity profile for each subject for each condition, and (3)

analyses of each subject's sensitivity profile were conducted to determine if and to what degree sensitivity to the effects of the drug differed across key-pecking and feeding.

Although differences in sensitivity of responding to the acute effects of cocaine across key-pecking and feeding did not appear to be substantial or reliable across subjects, sensitivity of key-pecking tended to be higher than for that of feeding in some subjects, in some measures. That is, in some cases, ED_{50}s for feeding were higher than those for key-pecking. For example, in two subjects (882 and 893), ED_{50} values for all key-pecking measures (except pause in 882) were lower than ED_{50} values for any of the feeding measures, suggesting that key-pecking was, in fact, more sensitive to the drug effects. Comparison across dose-effect curves for Subject 882 (see Figures 2-2 and 2-5) reveals this difference in sensitivity; moderate doses (1.0 and 3.0 mg/kg) had little effect on head-in duration but produced a 25% and 50% decrease, respectively, in overall key pecking rate. At the highest dose tested, pecking rates were almost completely suppressed, whereas, head-in duration was reduced to only 25% of baseline level. For Subject 893, the difference in the effect across measures is evident at the highest two doses given, 5.6 and 10.0 mg/kg. Each dose produced a greater-than-75% decrease in response rates but only a 50% decrease in head-in duration. These results suggests that, for at least two subjects, there was some differential effect across measures, and the pattern of differentiation reflects earlier observations that feeding was more robust than key-pecking; however, the effect was not very prevalent in the majority of subjects. For other subjects (283 and 997), differential sensitivities were not apparent.

Results of a group-level binomial test suggest that there were a significant number of positive differences between feeding and key-pecking ED_{50}s during the acute-administration phase. Of the 102 possible comparisons (based on total comparisons across subjects), 65 were positive instances (i.e., instances in which feeding ED_{50} values were higher than those for key-pecking), suggesting, overall, that feeding was less sensitive than key-pecking. This result, however, fails to inform fully on the outcome at the individual-subject level. According to individual-subject binomial tests for five of six subjects (except 893), the number of positive differences was not statistically significant; however, for four of those five subjects, the number of positive differences was greater than the number of negative instances. Taken together, these results suggest that, despite individual variability, there is an overall tendency for key-pecking to be more sensitive to the effects of cocaine than feeding.

Comparison of individual key-pecking measures with feeding measures may be more informative. Recall that sensitivity of feeding measures tended to be similar, whereas sensitivities across key-pecking measures for all subjects tended to vary systematically across measure. Sensitivity of key-pecking was generally ordered with pause being the least sensitive (highest ED_{50}s), overall rate being moderately sensitive, and run rate being most sensitive (lowest ED_{50}s); therefore, comparisons of all key-pecking measures together may not be appropriate. Across subjects, pause ED_{50}s were rarely lower than feeding values (8 of 36 comparisons), whereas run rate ED_{50}s were almost always lower than feeding values (32 of 36 possible comparisons) suggesting that, not only were pause and run rate differentially affected by the drug, so

too were run rate and feeding measures. Run rate was decreased at doses that left pause and feeding generally less affected.

Differences in sensitivity across response categories following chronic-cocaine administration and during withdrawal were more consistent across subjects than during the acute-administration phase. That is, the degree of differential sensitivity was more pronounced. A group-level binomial test comparing key-pecking and feeding ED_{50}s reveals that of 108 possible comparisons, feeding ED_{50}s were higher in 79 cases, suggesting that the number of cases of positive differences increased compared to the numbers obtained under acute administration (there were 65 positive instances during the acute-administration phase). Indeed, for every subject, the number of positive instances either increased or remained the same. The number of subjects for whom the number of positive differences reached statistical significance increased to three (compared to one during acute administration). The number of positive differences also increased during the withdrawal phase. At the group level, of 108 possible comparisons during the withdrawal phase, 85 were positive differences. The number of subjects for whom the number of positive differences reached statistical significance increased to five.

Increases in the degree of differential sensitivity across drug-administration phases likely owe to the differential development of tolerance after chronic administration and the differential loss of tolerance during withdrawal. Recall that although some tolerance developed in key-pecking after chronic-cocaine administration, the degree of tolerance was more substantial in the feeding measures indicated by larger rightward shifts in the dose-effect functions for feeding measures than for key-

pecking measures. Given the modest tendency for key-pecking to be more sensitive and the larger rightward shift in feeding dose-effect functions, the number of positive differences would either increase or remain the same. During withdrawal, the number of positive differences increased further during withdrawal as a result of the differential loss of tolerance. Recall that during withdrawal, a larger proportion of log ratios for feeding were higher than those for key-pecking (see Figure 2-18) indicating that ED_{50}s estimated during withdrawal were larger than those estimated during the acute-administration phase, suggesting that the curves for feeding remained shifted rightward, whereas key-pecking curves had generally shifted back (in some measures for some birds; see 283 and 9590). If feeding remained tolerant (i.e., ED_{50}s remained elevated) and key-pecking began to become less tolerance (i.e., ED_{50}s decreased), the number of positive differences would increase.

A purpose of the prefeeding tests was to assess whether pre-session access to mixed grain would produce selective effects on either of the general response categories (key-pecking or feeding) and whether sensitivity to prefeeding would be related to the prevailing drug-administration regimen. Pre-session feeding produced amount-dependent disruption in responding in most subjects. Effects were similar to those of cocaine: overall and run rates were decreased and pauses were increased. These effects were seen in all subjects but 997, whose responding was generally insensitive to the prefeeding regimen. Prefeeding also produced decreases in head-in duration and proportion head entries while increasing head-entry latency. Effects on feeding did not depend upon component type, nor did sensitivity differ consistently

across measures within broad response categories (e.g., across overall rate, run rate, and pause; see Figures 2-28 and 2-29).

Differences in sensitivity of responding to prefeeding were indicated by differences in EA_{50} values; if key-pecking was more sensitive to the effects of pre-session feeding than feeding, key-pecking EA_{50} values would be expected to be lower for feeding. During chronic-cocaine administration, slight differences in sensitivity to prefeeding were apparent in four of six subjects (283, 882, 989, and 9590) suggesting that for these subjects key-pecking was generally more sensitive to the effect of prefeeding than feeding. For the remaining two subjects (893 and 997) key-pecking tended to have higher EA_{50} values resulting in a majority of negative differences. Comparison of absolute differences between EA_{50}s (in Figure 2-28), however, suggests that the effect is less robust than the difference observed with cocaine. Indeed, at the group level, of 108 possible comparisons, only 63 resulted in positive differences. Although the absolute number of positive differences favors differential sensitivity, the degree of difference is not as substantial (e.g., compare differences across key-pecking and feeding measures with differences in Figure 2-14). During withdrawal, differences in sensitivity appeared to be more robust. For five of six subjects, the number of positive instances was higher than negative instances (range: 10 to 14). At the group level, 72 of 108 comparisons resulted in positive instances suggesting increased differential sensitivity. The increase resulted from unsystematic changes in individual subjects. For three subjects, the number of positive instances increased; for two, the number of positive instances decreased; and, for one subject, there was no change. It

seems, therefore, that the increase in differential sensitivity was not the result of a consistent increase at the individual-subject level.

Effects of prefeeding generally were modulated by the prevailing cocaine-administration condition. The first prefeeding tests occurred in the context of daily pre-session cocaine administration. The second series of tests occurred at least 50 sessions following the cessation of daily cocaine administration. Effects of prefeeding on key-pecking and feeding were more pronounced in the context of chronic-drug administration than during withdrawal. In some subjects, prefeeding produced substantial disruptions in key-pecking and feeding under chronic-cocaine administration at amounts that produced little effect during withdrawal. Chronic drug administration was associated with lower resistance of behavior to disruptive manipulations such as prefeeding. These effects, however, occurred across the last two phases of the current experiment after extended exposure to both the procedure and chronic drug, and a reversal phase (back to chronic-cocaine administration) was not included which would be necessary to assess the causal role of drug-administration regimen on modulating the effects of prefeeding. Additional research should be conducted to determine the reliability of the effect. Such an effect (the reduction of behavioral resistance to disruption by a chronic drug regimen) could have implications for drug abuse treatment programs that attempt to establish appropriate behaviors (e.g., maintaining a job) in the context of chronic-drug use. The current results suggest that behavior in that context may be more susceptible to disruption (e.g., any of the minor disruptions that occur in the context of job performance) than if drug use was ceased.

Comparison of the degree of differential sensitivity (i.e., sensitivity of key-pecking measures versus sensitivity of feeding measures) across disruptor type suggests that key-pecking was slightly more sensitive to the effects of behavioral disruptors than feeding. Although the degree of differential sensitivity was not very robust, there was a tendency for feeding to require larger magnitude disruptors (larger doses or larger prefed amounts) to produce the same degree of disruption compared to key-pecking. It's unclear at present what can account for this difference in sensitivity. One possible explanation might be that responses which are more closely associated with reinforcement, both in temporal and spatial proximity (e.g., approaching the hopper and picking up grains), are more resistant to disruption. This account accords with predictions of behavioral momentum theory (e.g., Nevin & Grace, 2000) which predicts that behaviors which occur in the context of higher reinforcement density, including shorter delays to reinforcement, will be more resistant to disruption.

In the present experiment, few responses were more closely associated with food reinforcement than approaching and engaging with the food hopper; therefore, the momentum of feeding may have been greater than that of key-pecking. Another, related, possibility is that amount of effort required to execute responses of each response category contributed to resistance to disruption. Approaching and entering the food hopper for pigeons appears to be a relatively low-effort response, akin to responding reinforced according to an FR1 schedule; that is, each feeding bout results in food. The ratio of key-pecks per reinforcer, however, was often much greater than one. Even though only one response was required to produce a reinforcer under the FI schedule, many responses typically occurred. Average baseline overall response rates

ranged from approximately 0.5 to 1.0 pecks/s which, given an average inter-reinforcer of 30 s, resulted in approximately 15 to 30 key pecks per reinforcement. It could be the case that more effortful responding is more sensitive to disruption.

Disentangling the contribution of these two factors (temporal proximity to food and response effort) would require that the experiment be replicated using schedule arrangements that test the independence of each factor. For example, in the current experiment, the ultimate act of consuming food can be conceptualized as result of the completion of a two-component chained schedule. Completion of the FI requirement constitutes the first link in the chain, and engaging in commerce with the hopper constitutes the second link. Engaging the food hopper thus required less effort and was more temporally contiguous with food consumption. A comparison condition might be arranged by adding a small ratio requirement prior to the FI component such that the subject would have to complete a signaled FR in order to gain entry into the FI link and ultimately food. A comparison of sensitivity of responding across all three components (FR, FI, and feeding) might reveal the source of the difference. If temporal proximity is a key factor, feeding would remain more resistant to disruption than responding in both the FR and FI components. If response effort was a primary determinant of sensitivity, sensitivity would be more similar between responding in the FR and feeding than between the FI and feeding.

Another purpose of the prefeeding test was to compare the pattern of effects of pre-session feeding (a variable assumed to affect reinforcer efficacy) with the pattern of effects of cocaine in order to glean some information about a potential behavioral mechanism. This approach—referred to as environmental mimicry—is by no means a

novel approach in behavioral pharmacology. Dews (1956), for example, reasoned that the first step in identifying a behavioral mechanism of drug action is to consider how the manipulation of other (non-pharmacological) variables affects responding under the same circumstances. When considering the rate-decreasing effects of methamphetamine and pentobarbital on key-pecking in pigeons reinforced with food under a multiple FI FR schedule, he noted that other manipulations such as pre-session feeding also typically produce rate decreases in operant behavior. In his study, after providing subjects with pre-session access to food he noted some similarities and some differences in the effects on performance leading him to conclude:

> The sudden changes in rate are strongly reminiscent of the effects of methamphetamine and quite different from the effects of pentobarbital. On the other hand, feeding did not lead to a reduction in the initial pause, nor did it lead to an increase in the total output of pecks…Hence, part, but only part, of the effects of methamphetamine are like the effects of sudden reduction in deprivation. This is an interesting view of the well-known "appetite-reducing" effect of methamphetamine in humans. (p. 274-275)

He then continued, noting that the analogy drawn between effects of the two variables could not be sustained due to inconsistencies in the pattern of effects, and suggested that classifying behavioral effects of methamphetamine as anorectic was, at best, tenuous. In his study, therefore, the environmental manipulation failed to produce clear evidence as to a mechanism of action. Nevertheless, identification of effects of drugs with effects of other variables is an important step toward identifying behavioral mechanism of a drug as well as teasing apart mechanisms of action of different drugs.

Dews (1962) later employed the same general strategy to support the conclusion that chlorpromazine altered operant behavior reinforced under multiple schedules by disrupting stimulus control.

Given the similar patterns of effects of cocaine and pre-session feeding in the current experiment, is it reasonable to conclude that the effects of these two independent variables were mediated by a common process, that is, by reducing the reinforcing efficacy of food? Based on the current results, the answer is a resounding "maybe." Cocaine and pre-session feeding both disrupted key-pecking maintained by food. The similarities in the drug- and amount-behavior relationships were strikingly similar at different levels of analysis. Formal similarity in empirical relationships, however, does not necessarily entail functional similarity. To make such an argument is to commit what Skinner (1969) referred to as the formalistic fallacy. That is, by ascribing common causes to events that are formally similar, one might overlook the possibility that similar behavioral effects can be produced by multiple independent variables. The systematic effects of cocaine and pre-session feeding, though similar in form, may not be the result of the same processes.

How then are we to determine whether the effects of cocaine on responding in the current study were mediated through changes in reinforcing efficacy? According to Katz (1990; see also Witkin and Katz, 1990), at least one additional criterion must be met before a behavioral mechanism can be identified. Katz agreed with Dews' (1956) initial recommendation that if a behavioral mechanism of drug action is to be identified with a particular behavioral process, other variables that modify that process should

also produce similar changes. Katz argued, however, that in addition to demonstrating formal similarities in the relationships, functional equivalences must also be established.

One method for demonstrating functional equivalence proposed, by Katz (1990), is the method of environmental antagonism. That is, after demonstrating that two variables, when manipulated independently, produce formally similar effects, the effects of the interaction among them must also be studied. The outcomes of interactions among multiple independent variables should be predictable given knowledge the mechanism of action. Given that a single process is involved, the results could point to either an antagonistic relationship (i.e., the effects of both variables counteract one another) or an additive relationship (i.e., the effects of one variable enhances the effects of the other). If the results of the interaction comport with predictions, then the evidence for a behavioral mechanism is stronger.

In the current experiment, two variables (cocaine and pre-session feeding) produced systematic effects on responding when assessed independently. Disruptions of responding by both variables were magnitude related; larger doses or larger amounts produced more substantial disruption. The first criterion offered by Dews (1956) was, thus, satisfied. Assuming a common mechanism of action, we would predict that, under the current circumstances, prefeeding combined with the cocaine administration would produce disruptions of a larger magnitude than either variable alone. That is, the reinforcer-devaluing effect of each variable would combine to produce substantial disruptions, perhaps at magnitudes of each variable that produced very little effect when presented independently (e.g., 1.0 mg/kg cocaine or 3.5% FFBW prefed).

Although the current experiment was not designed to assess the results of all interactions between the two variables, the results from two phases may provide a hint as to whether such an interaction occurred. Recall that prefeeding tests occurred across two phases that differed with respect to the chronic-administration regimen. In one phase, the chronic dose for each subject was administered prior to every session including prefed sessions; in the other, the administration of the chronic dose was ceased and only saline was administered. A prediction based on the environmental-antagonism approach is that cocaine would interact with the prefeeding regimen by enhancing the effect of pre-session feeding. Indeed, that was the general effect. For the subjects in which there was an effect of prefeeding (except 997), the effect of prefeeding was enhanced, to some degree in most measures, under chronic-cocaine administration demonstrating an additive effect of the drug on the effect of prefeeding. This is but one of the possible interactions that could be studied. Unfortunately, other interactions were not studied in the current experiment; however, previous research may inform on this question. For example, Schaal and Branch (1992) found that in pigeons that sensitivity of key-pecking to cocaine varied systematically as a function of food-deprivation level. During the baseline phase, when deprivation was maintained at 80% FFBW, cocaine produced dose-dependent decreases in overall response rates. Sensitivity of responding to the effects of cocaine was enhanced when deprivation was changed to 90 and 100% FFBW (i.e., the dose-effect curve was shifted left) and attenuated when deprivation was changed to 70% FFBW (i.e., the dose-effect curve was shifted right). That is, the rate-decreasing effect of cocaine on response rate was modulated by deprivation level in predictable ways. When the reinforcing efficacy of the

food was enhanced (i.e., deprivation increased) the drug effect was antagonized, and when the efficacy of food was reduced (i.e., deprivation reduced) the drug effect was enhanced. Similar effects have been reported in other studies with pigeons with cocaine (e.g., Hughes, Pitts, & Branch, 1996; Schaal, Miller, & Odum, 1995) and rats with amphetamine (e.g., see Gollub and Mann, 1969). Moreover, research has shown that disruptive effects of amphetamine on feeding in rats are also modulated by deprivation level (MacPhail & Gollub, 1974). Although these interactions can be interpreted in other ways (e.g., deprivation level may simply modulate the efficacy of all behavioral disruptors, not just those whose effects are mediated through reinforcer efficacy), the convergence of evidence offered by the current experiment taken together with previous research strengthens the case for drug-induced changes in reinforcer efficacy as a behavioral mechanism of action (Pitts, 2010).

If the rate-decreasing effects of cocaine are the result of a drug-induced modulation of the reinforcing efficacy of food, it stands to reason that the drug would reduce the efficacy of food in other contexts beyond the experimental chamber. For example, one would predict that if food consumption was substantially depressed in the operant chamber, it would also be depressed in another feeding context such as the home cage. Recall that each subject's daily running body weight was maintained by post-session feeding in their home cage in the case that feeding was required. Post-session feeding was required most often following sessions in which a large dose of the drug suppressed key-pecking and feeding. Anecdotal evidence, however, suggests that the generalized suppression of feeding did not occur. Although no systematic observations occurred and no data have been collected, we have often observed that

when the experimental session ends and subjects are returned to the home cage, they often readily consume food provided in the home cage. On the basis of these observations, taken together with the results of the current experiment, we hypothesized that the rate-decreasing effects of cocaine may owe partly to a reduction of the reinforcer efficacy of food, and that the reduction in efficacy may be mediated through some feature of the experimental chamber. This mediating factor, therefore, might be responsible for the selective disruptions of food consumption (i.e., disruptions of feeding the operant chamber but not on the home cage). The experiment described in Study 2 was designed to test this hypothesis.

Table 2-1. Number of Baseline Sessions in Each Phase

	Phase				
Subject	Acute	Chronic	Chronic (Ext)	Chronic (Rev)	Withdrawal
283	39 (162)	37 (72)	20 (108)	30 (103)	32 (71)
882	35 (154)	33 (56)	33 (81)	30 (50)	35 (61)
893	36 (155)	42 (46)	33 (46)	30 (50)	35 (53)
989	36 (155)	51 (57)	28 (104)	30 (53)	30 (61)
997	36 (162)	47 (55)	20 (56)	30 (51)	31 (56)
9590	21 (141)	41 (76)	22 (84)	30 (50)	37 (63)

The duration of the drug-dose determination phase is shown in parentheses.

Table 2-2. Number of Determinations of Each Dose by Phase

	Dose (mg/kg)							
Subject	Saline	0.3	1.0	3.0	5.6	7.4	10.0	13.0
283	4,2,5,4,-	2,2,2,4,2	2,2,2,3,2	4,2,2,2,2	4,2,2,2,2	5,-,-,-,2	5,2,2,2,2	2,3,4,2,2
882	3,2,3,2,-	2,2,3,2,3	2,2,3,2,3	3,2,3,2,2	4,2,3,2,2	4,-,-,-,2	4,2,2,2,2	--
893	3,2,2,3,-	2,2,2,2,2	2,2,2,2,2	2,2,2,2,2	6,-,-,-,2	--	6,2,2,3,2	--
989	3,2,4,3,-	2,2,6,2,3	2,2,2,2,2	3,2,2,2,2	6,-,-,-,2	4,2,3,2,2	3,2,4,2,2	--
997	4,2,2,2,-	2,2,2,2,2	2,2,2,2,2	2,2,2,2,2	4,2,2,2,2	5,-,-,-,2	2,2,2,2,2	--
9590	5,2,4,2,2	2,4,5,2,2	2,4,2,2,2	2,2,2,2,2	5,2,2,2,2	2,-,-,-,2	2,2,2,2,2	--

Phases are listed in the following order: Acute, Chronic, Chronic (EXT), Chronic FT-Rev, Withdrawal. Single dashes indicate the dose for that phase. Double dashes indicate that the subject did not receive that dose.

Table 2-3. Summary of ED_{50} Values Across Subjects and Phases and Components

Subject	Phase	Overall Rate (pecks/s)	Run Rate (pecks/s)	Pause (s)
283	Acute	*	11.8 (0.88)	13.8 (0.88)
	Chronic	7.1 (0.8)	12.6 (0.86)	14.3 (0.99)
	Withdrawal	10.8 (0.92)	11.7 (0.81)	11.8 (1)
882	Acute	4.3 (0.9)	2.5 (0.93)	12.1 (1)
	Chronic	4 (0.8)	5.3 (0.85)	11.4 (1)
	Withdrawal	7.1 (0.91)	5.9 (0.93)	11.7 (1)
893	Acute	5.6 (0.99)	4.4 (0.97)	5.8 (0.99)
	Chronic	6 (0.93)	7.1 (0.96)	10 (1)
	Withdrawal	5.6 (0.95)	6.8 (0.96)	10.5 (1)
989	Acute	5.3 (0.89)	3.5 (0.98)	7.7 (0.98)
	Chronic	5.6 (0.96)	7 (0.9)	10.9 (1)
	Withdrawal	6.7 (0.97)	6.3 (0.93)	9.9 (1)
997	Acute	7.7 (0.91)	7.1 (0.99)	9.5 (1)
	Chronic	10.7 (0.94)	9.8 (0.84)	11.1 (1)
	Withdrawal	10.5 (0.8)	10.2 (0.83)	11.1 (1)
9590	Acute	7.6 (0.97)	5.5 (0.95)	10 (1)
	Chronic	7.7 (0.83)	8.4 (0.93)	11.1 (1)
	Withdrawal	7.8 (0.89)	7.4 (0.95)	10.8 (1)

Table 2-3. Continued.

		Head-in Duration (s)		Proportion Head Entry (s)		Head-entry Latency (s)	
Subject	Phase	FI	FT	FI	FT	FI	FT
283	Acute	10.5 (0.9)	10.4 (0.86)	14.5 (0.76)	11.1 (0.92)	14.3 (0.9)	8.4 (0.94)
	Chronic	12 (0.87)	11.8 (0.85)	14 (1)	13.4 (0.97)	14.6 (1)	13 (0.97)
	Withdrawal	14.1 (0.95)	12.9 (0.85)	15 (1)	11.8 (1)	14.4 (1)	10.3 (0.99)
882	Acute	9.3 (1)	8.7 (0.98)	9.6 (0.97)	8.8 (0.99)	9 (0.96)	8.1 (0.98)
	Chronic	11.1 (0.99)	10.8 (0.97)	10.9 (1)	10.9 (1)	10.7 (1)	11 (1)
	Withdrawal	11.1 (0.98)	10.9 (0.75)	11.5 (1)	11.4 (1)	10.5 (1)	10.3 (1)
893	Acute	7.5 (0.94)	8.7 (0.93)	9.4 (0.91)	8.5 (0.88)	9.3 (1)	4.9 (0.96)
	Chronic	10.5 (0.96)	10.7 (0.96)	10.9 (0.99)	12 (0.99)	10.8 (1)	10.6 (1)
	Withdrawal	10.4 (0.94)	10.4 (0.96)	11.5 (1)	12 (0.99)	12.4 (0.99)	11.8 (0.99)
989	Acute	6.8 (1)	6.9 (0.99)	6.9 (1)	5.9 (0.99)	8 (0.93)	5.3 (0.99)
	Chronic	9.7 (0.96)	9.6 (0.97)	10.7 (1)	8.8 (1)	10.3 (0.98)	9.1 (1)
	Withdrawal	10.2 (0.98)	8.7 (1)	10.5 (1)	8.7 (1)	9.9 (1)	8.1 (1)
997	Acute	8 (1)	8.4 (1)	7.7 (0.99)	8 (1)	8.6 (0.96)	7.6 (1)
	Chronic	10.9 (1)	10.4 (0.98)	11 (0.99)	12 (1)	11.9 (1)	11.1 (1)
	Withdrawal	12 (1)	10.8 (1)	11.9 (1)	12 (1)	10.3 (1)	11 (1)
9590	Acute	8.2 (0.97)	8.3 (0.99)	8.3 (1)	8.7 (0.96)	9.1 (0.98)	7 (0.88)
	Chronic	10.8 (0.98)	10.5 (0.96)	12.5 (1)	11 (1)	11 (1)	10.8 (0.93)
	Withdrawal	9.3 (0.89)	9.4 (0.92)	10.3 (1)	11.1 (1)	11.1 (0.99)	10.9 (0.98)

ED_{50} values are expressed in mg/kg. R^2 values for the best-fit curve (see Equation 2-1) are shown in parentheses.
*Due to the shape of the dose-effect function an ED_{50} value was not estimated for subject 283 for overall rate.

Table 2-4. Results of Binomial Sign Test Dose-effect Curves

Subject	Acute	Chronic	Withdrawal
283	4/12[#]	11/18	14/18*
882	12/18	12/18	12/18
893	16/18*	18/18*	16/18*
989	12/18	12/18	14/18*
997	10/18	13/18*	14/18*
9590	11/18	13/18*	15/18*
Total positive instances	65/102	79/108	85/108
Binomial *z* approximation	2.67	4.72	5.87
p value	.0037	< .001	< .001

Values indicate the number of comparisons from each phase for which a measure of feeding sensitivity was greater than a measure of key-pecking sensitivity. The second number indicates that total number of possible comparisons.

* Denotes statistically significant differences at the $p < .05$ level. Given 18 comparisons, 13 or more must be positive instances (feeding greater than key-pecking) to achieve statistical significance.

[#] For subject 283, overall rate was excluded from the comparison; therefore, only 12 comparisons were possible. Given 12 possible comparisons, 10 positive instances are required to achieve statistical significance at the $p < .05$ level.

Table 2-5. Summary of Free-feed Body Weights, Amounts Fed, and Weight Gain

	Daily Running Weight			Weight Gain	
Subject	Chronic	Withdrawal	Amount Fed	Chronic	Withdrawal
283	545	542	23	28.5	36.5
	546-555	*538-547*		*28-29*	*35-29*
			46	67	61.5
				54.8	*44.79*
			92	124.5	87
				123-126	*84-89*
882	600	603	26	47	88
	591-604	*594-601*		*42-52*	*88*
			39	69	71.5
				67-71	*64-71*
			52	94.5	75
				89-100	*72-78*
			65		86
					75-97
			78		92.5
					85-100
893	488	513	20	21.5	25
	478-500	*494-527*		*20-23*	*18-32*
			40	42.5	58
				42-43	*54-62*
			80	94.3	83.5
				88-101	*77-90*
989	563	561	24	37	55
	558-568	*559-564*		*24-50*	*51-59*
			48	58	72.5
				50-71	*66-79*
			96	68.5	87.5
				63-74	*79-96*
997	450	452	19	38.5	33
	440-462	*448-456*		*37-40*	*30-36*
			38	57.5	57.5
				57-58	*53-62*
			76	73	67.5
				67-81	*61-74*
9590	609	616	26	43.5	81
	606-612	*609-621*		*28-59*	*60-102*
			52	95	112.5
				94-96	*107-118*
			104	155	129.5
				155	*125-134*

All values are in g. The amount of grain prefed is shown in the center column. The mean actual weight gain (from prior to prefeeding to immediately following) is shown in the two right columns for each phase. Ranges are shown below the mean in italics.

Table 2-6. Summary of EA_{50} Values Across Subjects, Phases and Components

Subject	Phase	Overall Rate (pecks/s)	Run Rate (pecks/s)	Pause (s)
283	Chronic	7 (1)	7.3 (0.98)	13.6 (1)
	Withdrawal	14 (0.89)	19.5 (0.96)	14.1 (1)
882	Chronic	5.1 (0.99)	6.9 (1)	7.2 (1)
	Withdrawal	8.9 (0.77)	9.9 (0.57)	11 (1)
893	Chronic	8.2 (1)	11.9 (1)	11.2 (1)
	Withdrawal	10.4 (0.84)	11.4 (0.98)	10.9 (1)
989	Chronic	7.5 (1)	8.8 (0.99)	11.2 (1)
	Withdrawal	10 (0.96)	10.4 (0.94)	12.6 (1)
997	Chronic	12.7 (0.9)	18.3 (1)	12.9 (1)
	Withdrawal	11.4 (0.96)	19.4 (0.97)	11.5 (1)
9590	Chronic	4.5 (0.97)	5.3 (0.97)	8.2 (1)
	Withdrawal	10.1 (0.89)	7.2 (0.96)	10.3 (1)

Table 2-6. Continued.

		Head-in Duration (s)		Proportion Head Entry (s)		Head-entry Latency (s)	
Subject	Phase	FI	FT	FI	FT	FI	FT
283	Chronic	14 (1)	14.1 (0.97)	14 (0.99)	12.5 (0.98)	14.4 (1)	12.5 (0.98)
	Withdrawal	14.7 (0.96)	14.8 (0.95)	14.5 (0.86)	14.3 (1)	14.4 (0.99)	14.3 (1)
882	Chronic	7 (1)	6.9 (1)	7 (1)	7.3 (0.99)	8.2 (1)	7.3 (0.99)
	Withdrawal	11.7 (1)	11.2 (0.99)	11 (0.93)	10.6 (1)	11 (1)	10.6 (1)
893	Chronic	10.4 (1)	9.9 (1)	10.8 (1)	8.9 (0.97)	10.1 (1)	8.9 (0.97)
	Withdrawal	11.7 (1)	11.6 (0.99)	11.1 (1)	10 (1)	10.5 (1)	10 (1)
989	Chronic	12.5 (0.98)	12.7 (0.93)	11.4 (0.9)	10.6 (0.96)	10.3 (0.83)	10.6 (0.96)
	Withdrawal	12.7 (1)	11.8 (1)	12.2 (1)	12 (1)	11.9 (1)	12 (1)
997	Chronic	11.6 (1)	12.1 (1)	11.6 (1)	11 (1)	11.3 (1)	11 (1)
	Withdrawal	12.7 (1)	11.1 (1)	12.1 (1)	11.6 (1)	11.6 (1)	11.6 (1)
9590	Chronic	7.1 (1)	7.9 (0.98)	6.6 (0.98)	7.1 (0.99)	6.1 (0.99)	7.1 (0.99)
	Withdrawal	11.2 (1)	11.1 (1)	11 (1)	9.8 (1)	10.8 (1)	9.8 (1)

EA_{50} values are expressed in percentage FFBW. R^2 values for the best-fit curve (see Equation 2-2) are shown in parentheses.

Table 2-7. Results of Binomial Sign Test for Amount-effect Curves

Subject	Chronic	Withdrawal
283	16/18*	12/18
882	14/18*	14/18*
893	6/18	9/18
989	15/18*	13/18*
997	0/18	10/18
9590	12/18	14/18*
Total positive instances	63/108	72/108
Binomial *z* approximation	1.64	3.37
p value	.05	< .001

Details are the same as in Table 2-4.

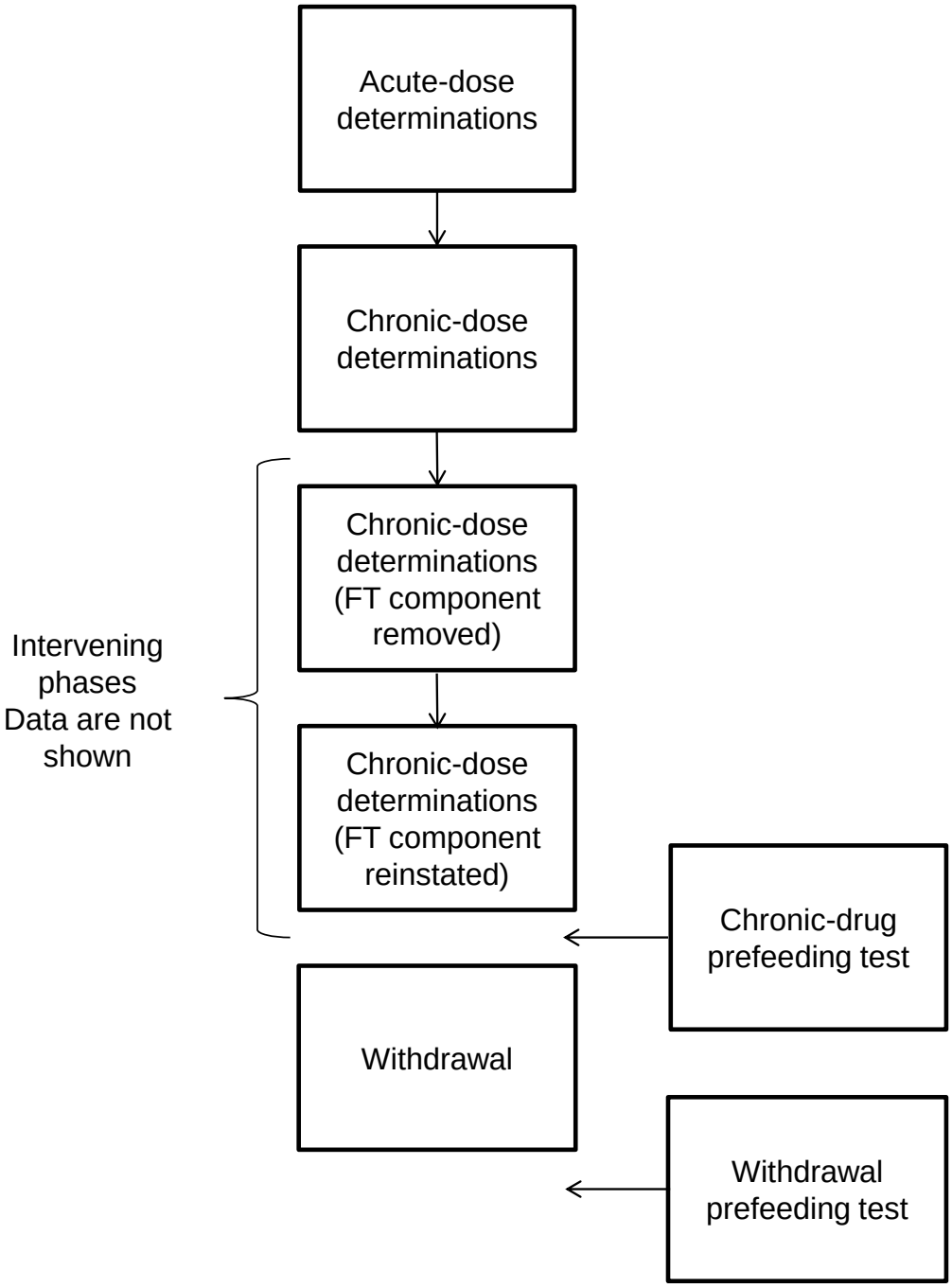

Figure 2-1. The order of experimental phases. Drug-administration phases are shown on the left; prefeeding phases are shown on the right. Prefeeding tests occurred after dose-effect-curve determination in each of the last two phases.

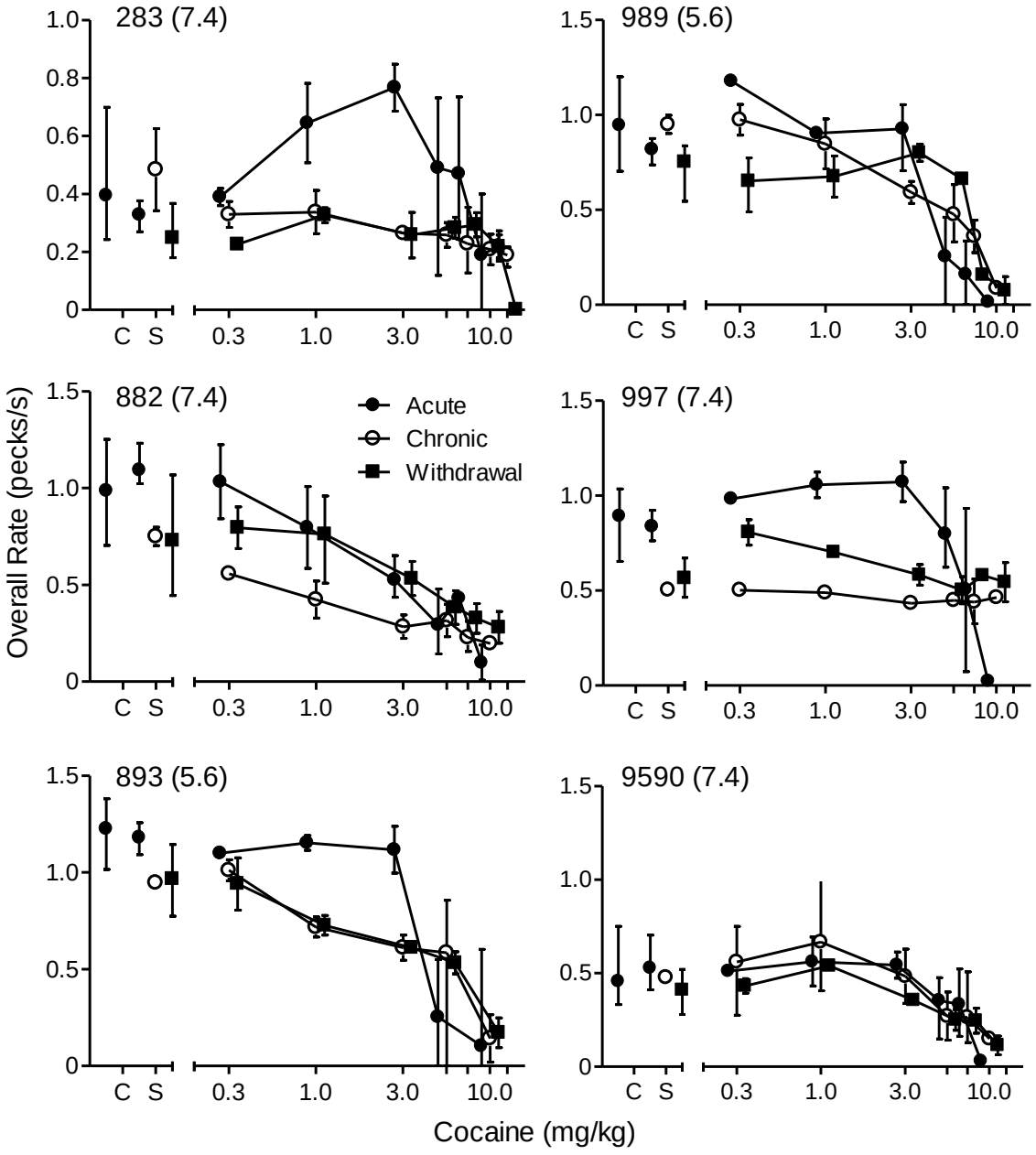

Figure 2-2. Dose-effect curves for overall response rates. Data points over the C represent control data; data points over the S represent saline data. Filled circles, open circles, and squares represent session means obtained during the acute, chronic, and withdrawal phases, respectively. Error bars indicate the range. The chronic dose for each subject is indicated in the parentheses next to the subject number. Note the different *y*-axis scale for 283 (upper-left panel).

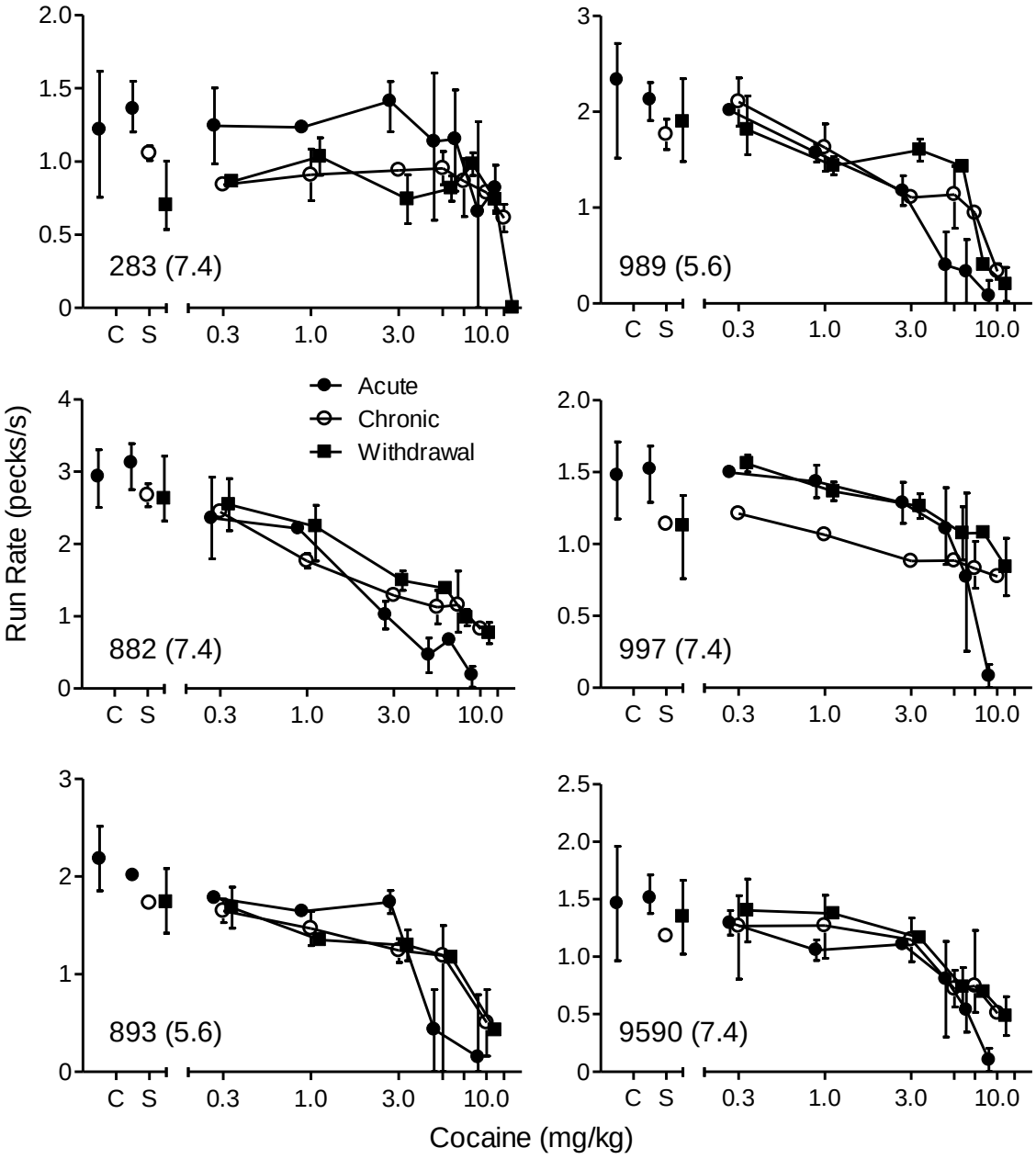

Figure 2-3. Dose-effect curves for run rate. All details of are the same as in Figure 2-2. Note the different *y*-axis scales across panels.

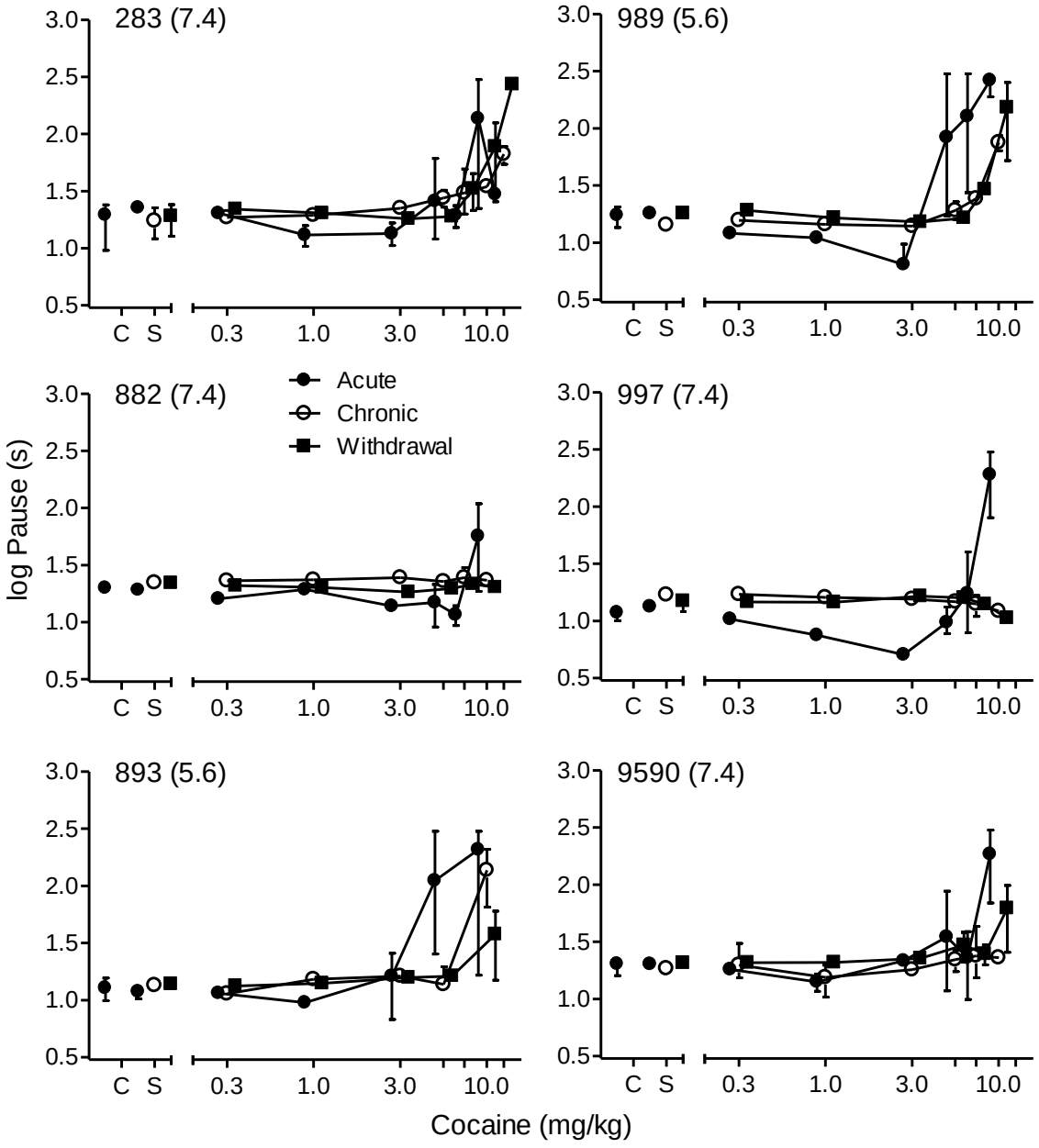

Figure 2-4. Dose-effect curves for pause. All details of are the same as Figure 2-2.

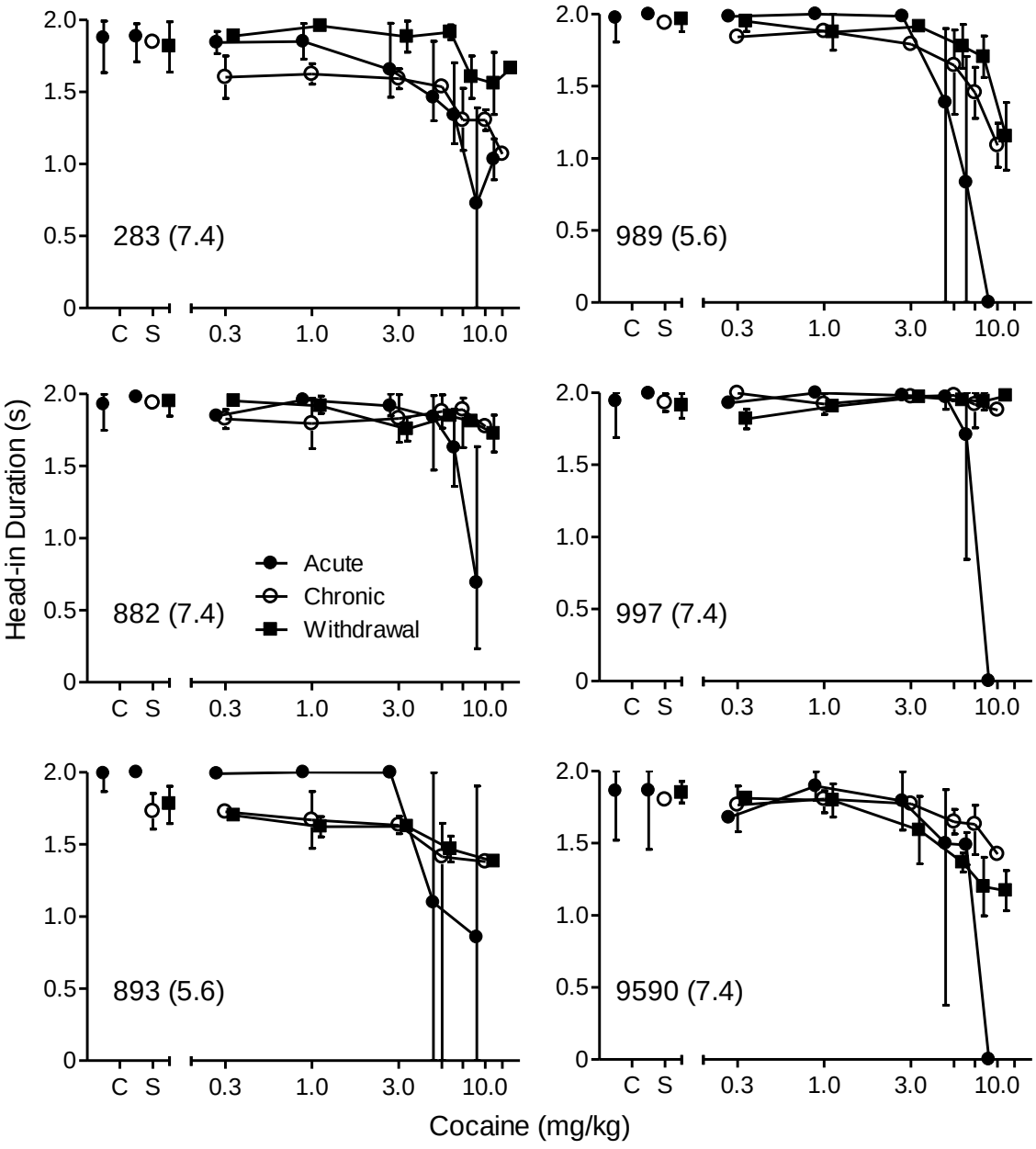

Figure 2-5. Dose-effect curves for head-in duration. Data are taken from the FI component. All details of are the same as Figure 2-2.

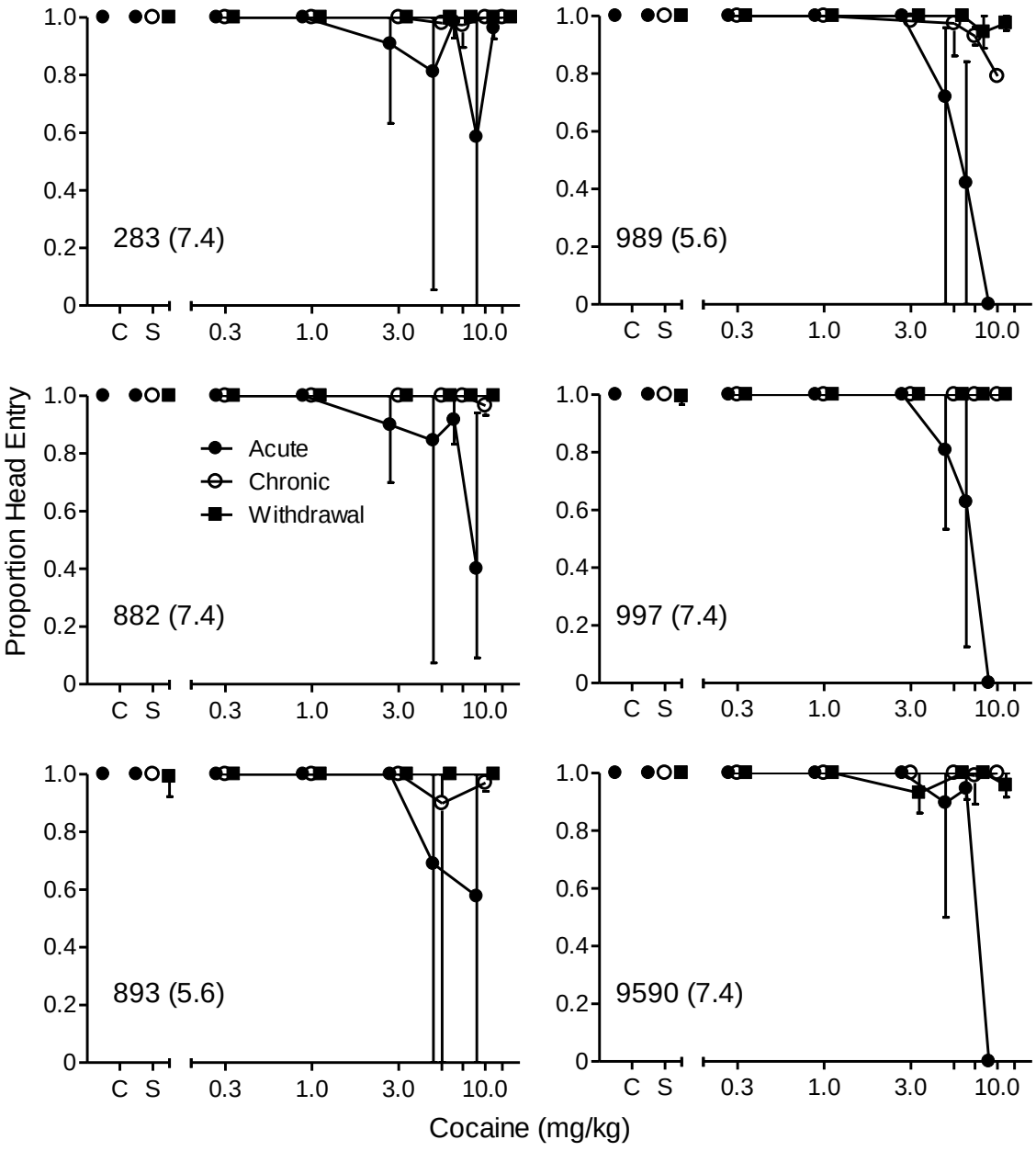

Figure 2-6. Dose-effect curves for proportion head entry. Data are taken from the FI component. All details of are the same as Figure 2-2.

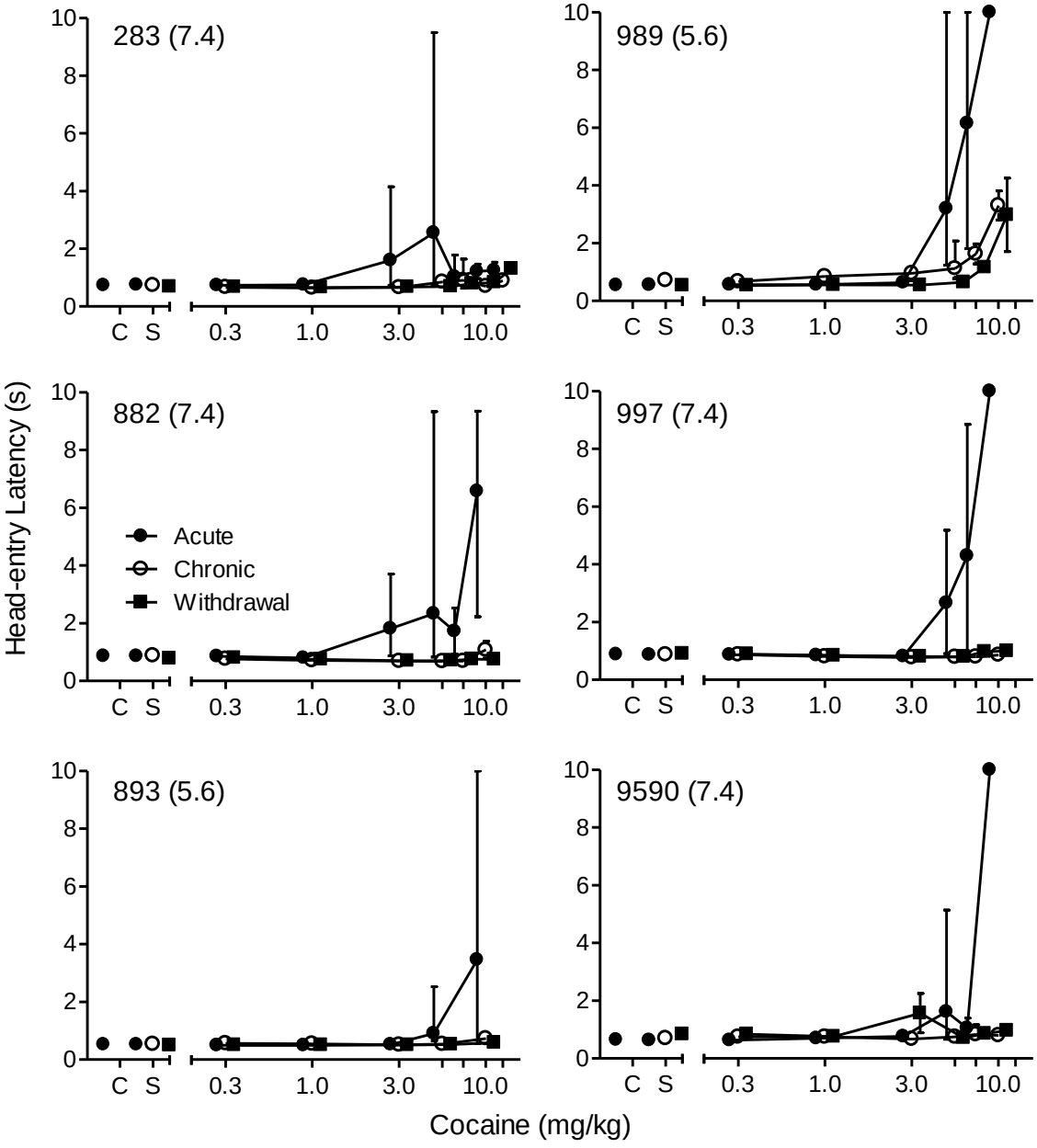

Figure 2-7. Dose-effect curves for head-entry latency. Data are taken from the FI component. All details of are the same as Figure 2-2.

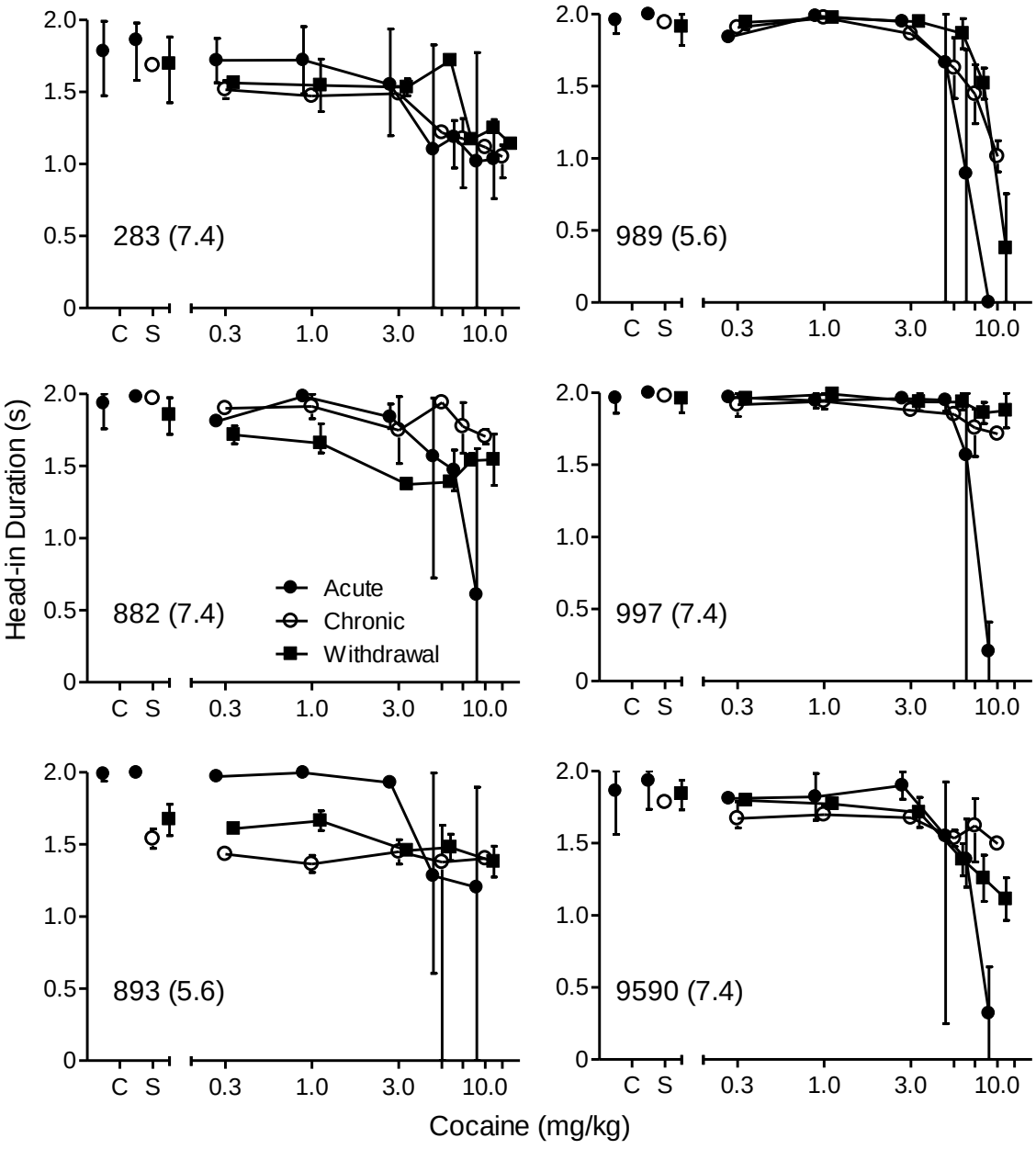

Figure 2-8. Dose-effect curves for head-in duration. Data are taken from the FT component. All details of are the same as Figure 2-2.

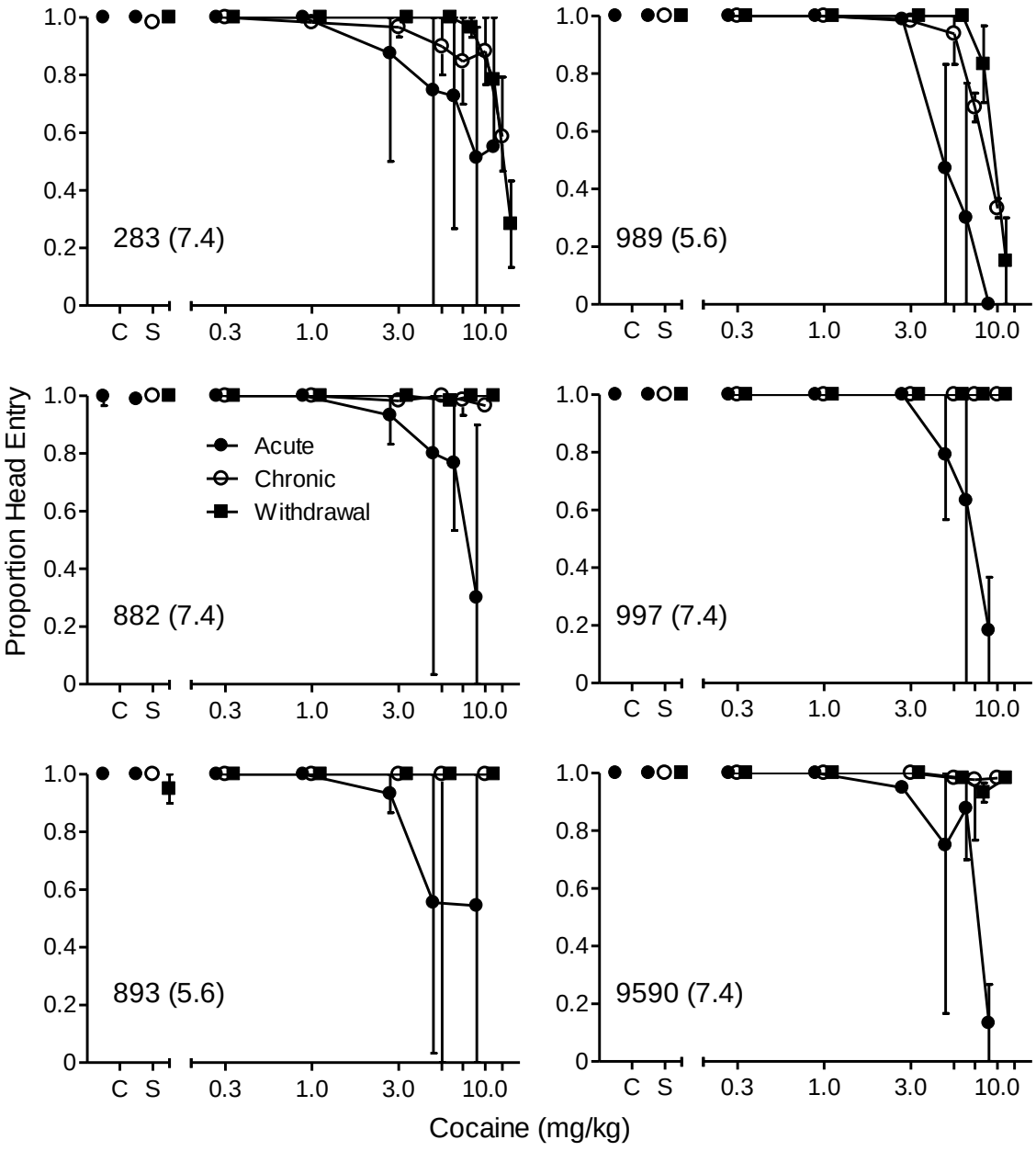

Figure 2-9. Dose-effect curves for proportion head entry. Data are taken from the FT component. All details of are the same as Figure 2-2.

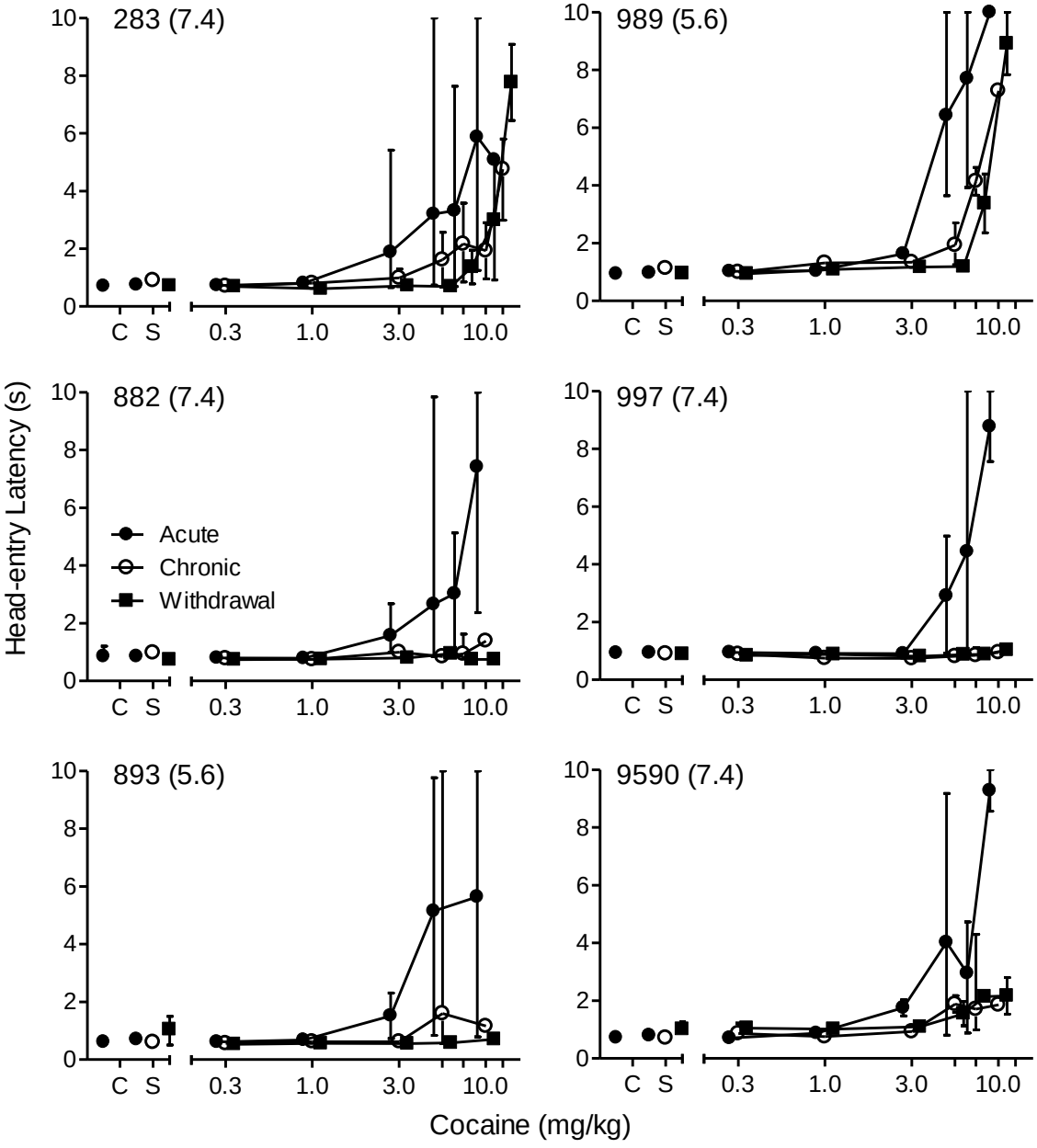

Figure 2-10. Dose-effect curves for head-entry latency. Data are taken from the FT component. All details of are the same as Figure 2-2.

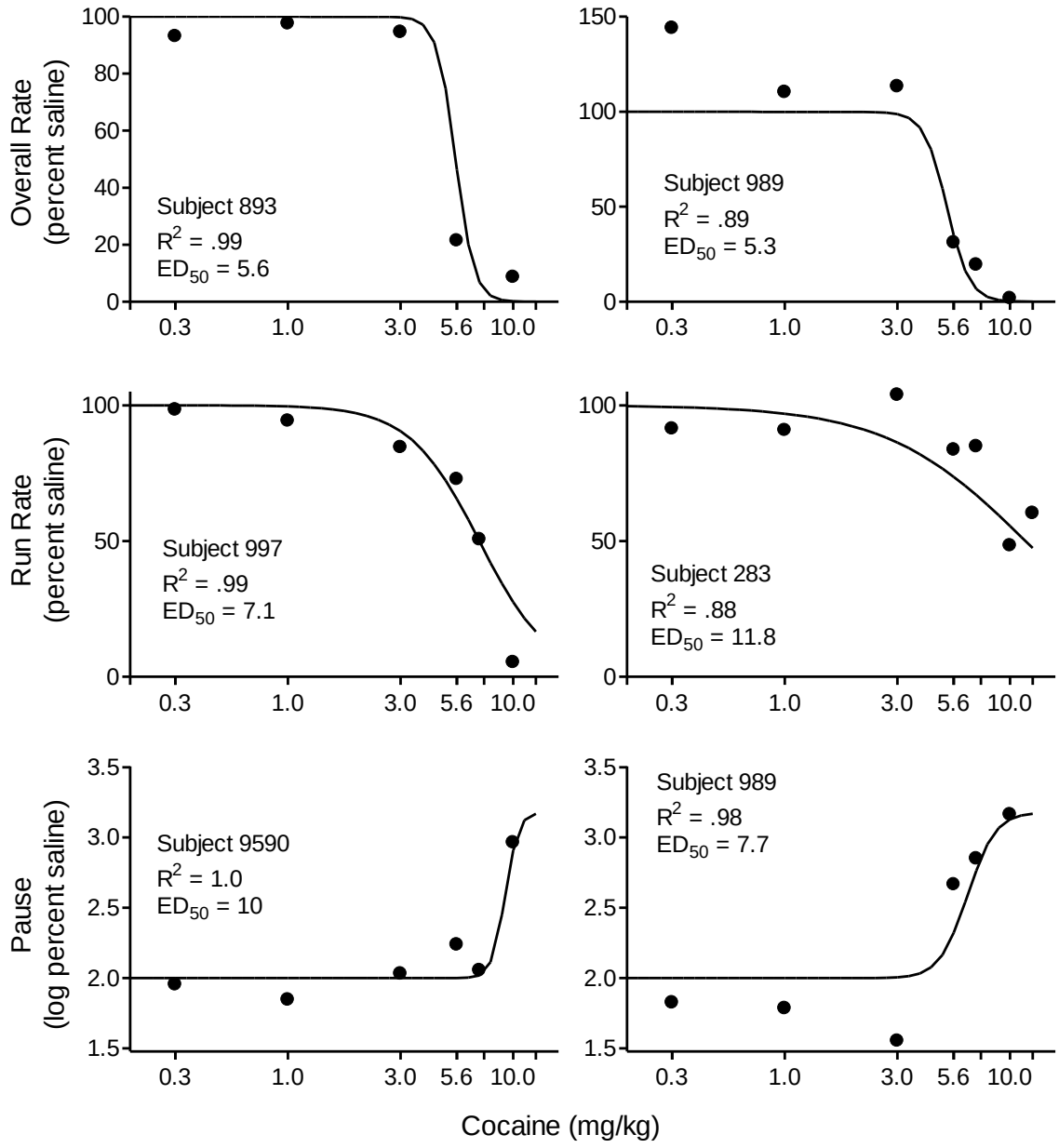

Figure 2-11. Representative fits of Equation 2-1 to key-pecking dose-effect curves. Data points show the mean effect. The line shows the least-squares fit. Panels in the left column show fits with the highest R^2 for each measure (shown across rows) and panels in the right column show the lowest R^2.

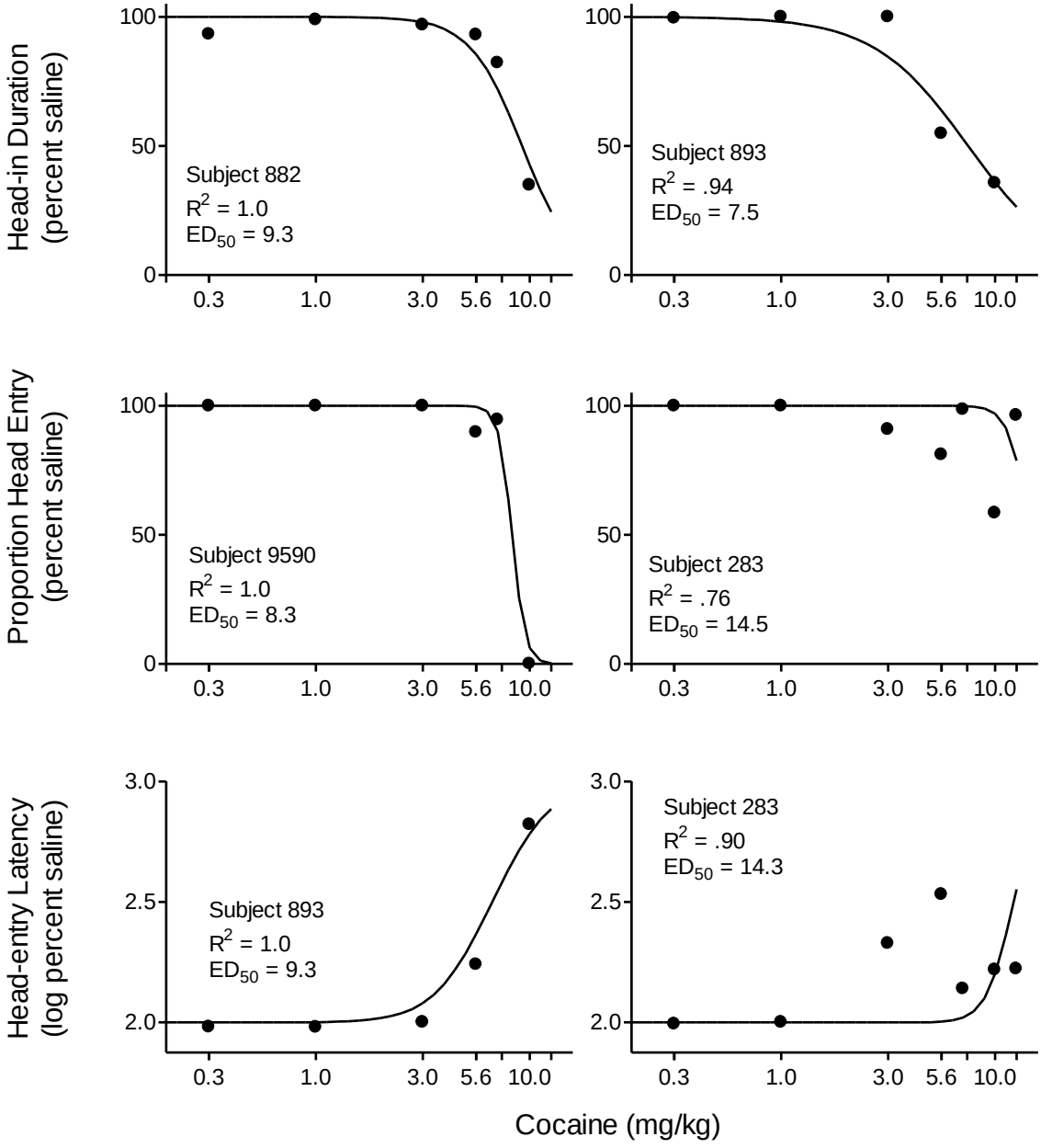

Figure 2-12. Representative fits of Equation 2-1 to feeding dose-effect curves taken from the FI component. Details are the same as in Figure 2-11.

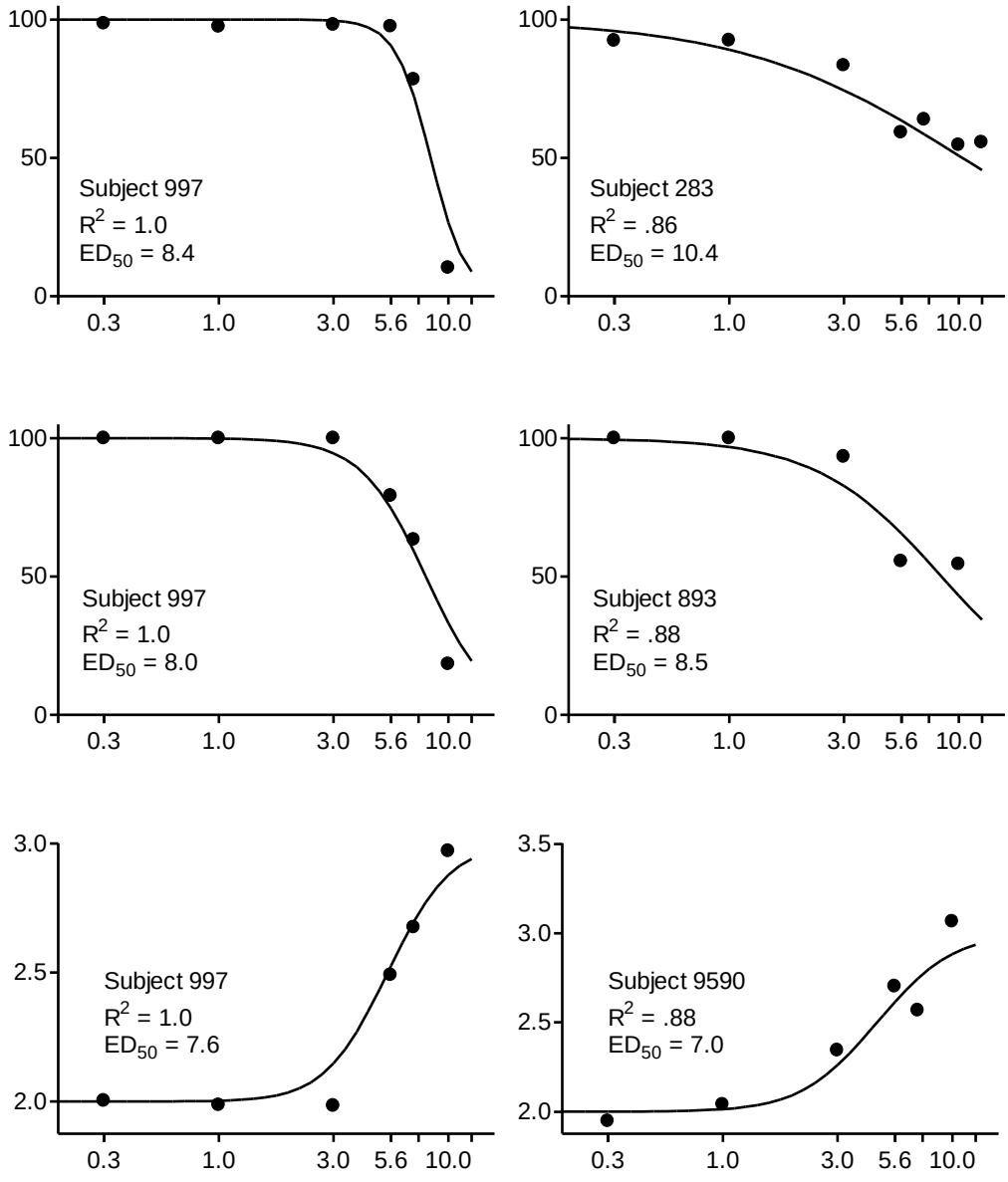

Figure 2-13. Representative fits of Equation 2-1 to feeding dose-effect curves taken from the FT component. Details are the same as in Figure 2-11.

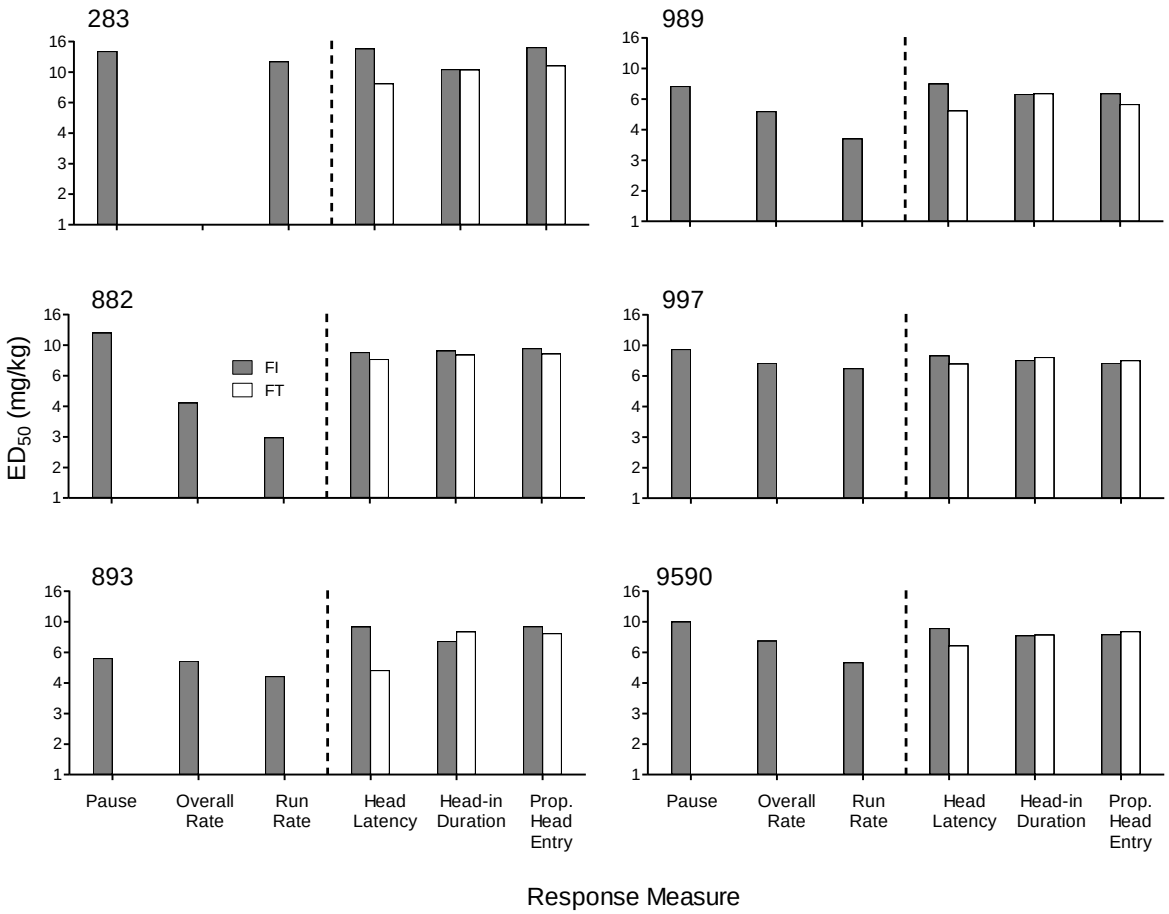

Figure 2-14. Acute ED_{50} values (expressed in mg/kg) plotted for each measure for each subject. Dark and light bars are data from the FI and FT components, respectively. The vertical lines separate key-pecking and feeding measures. Note the logged *y*-axis.

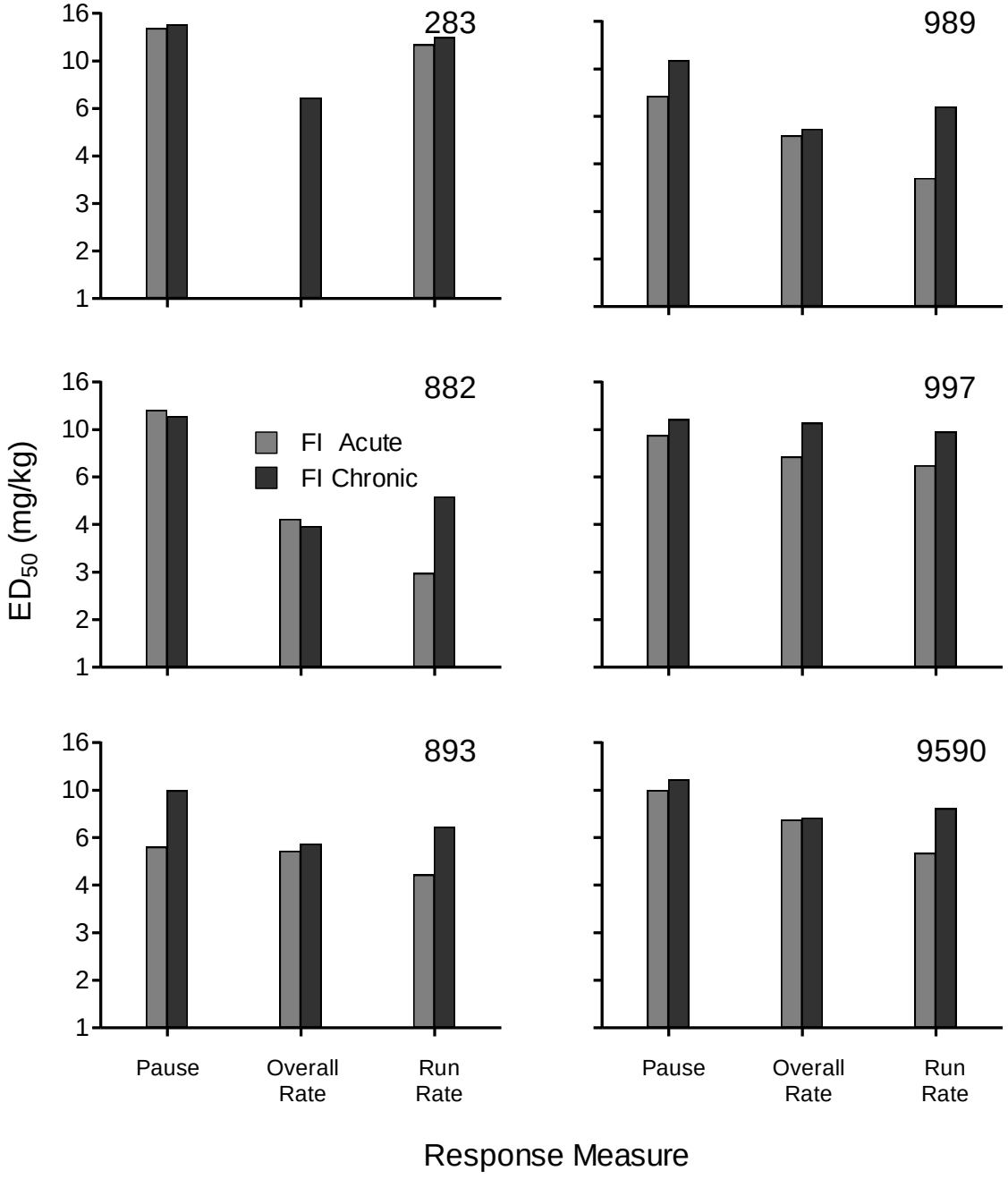

Figure 2-15. A comparison of Acute and Chronic ED_{50} values (expressed in mg/kg) plotted for each key-pecking measure for each subject. Lighter and darker bars are data from the acute and chronic phases, respectively. Note the logged *y*-axis.

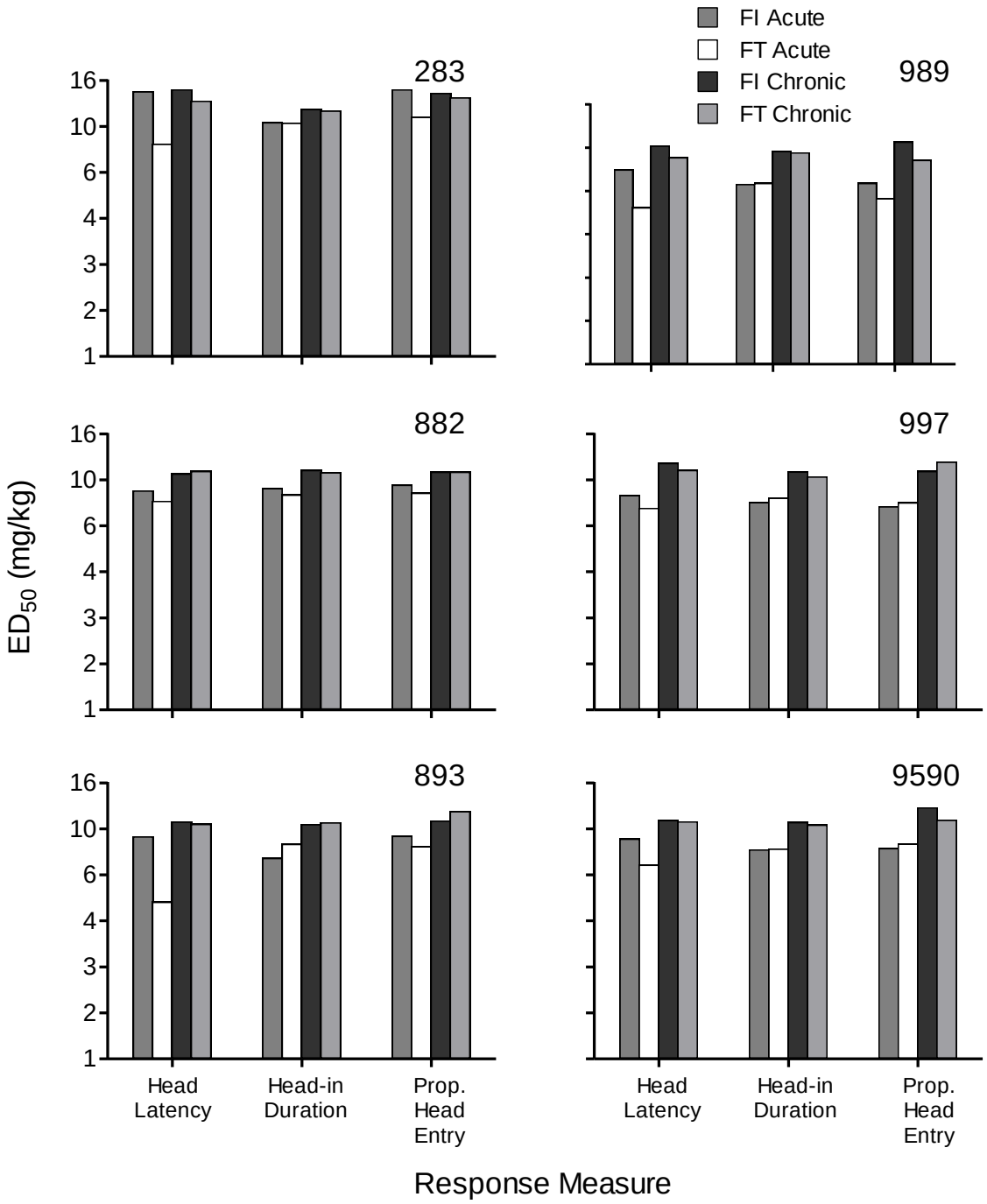

Figure 2-16. A comparison of Acute and Chronic ED_{50} values (expressed in mg/kg) plotted for each feeding measure for each subject. The first and third bars of each cluster are data from the FI component; the second and fourth bars are data from the FT component. The darker bar of each pair is data from the chronic phase. Note the logged *y*-axis.

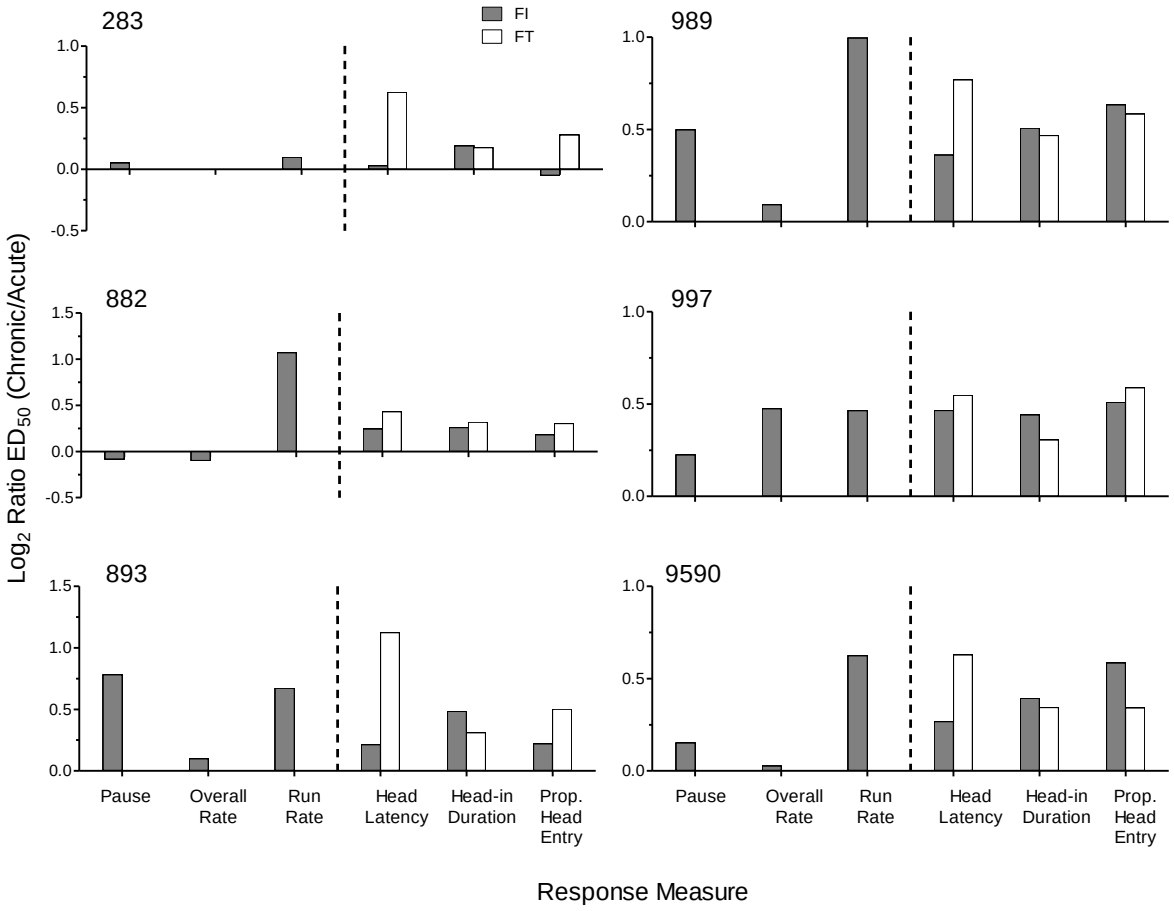

Figure 2-17. The $\log_2$ ratio of chronic to acute ED_{50} values is plotted for each measure for each subject. Dark bars and lighter bars are data from the FI and FT components, respectively. Note the different *y*-axis scales across panels.

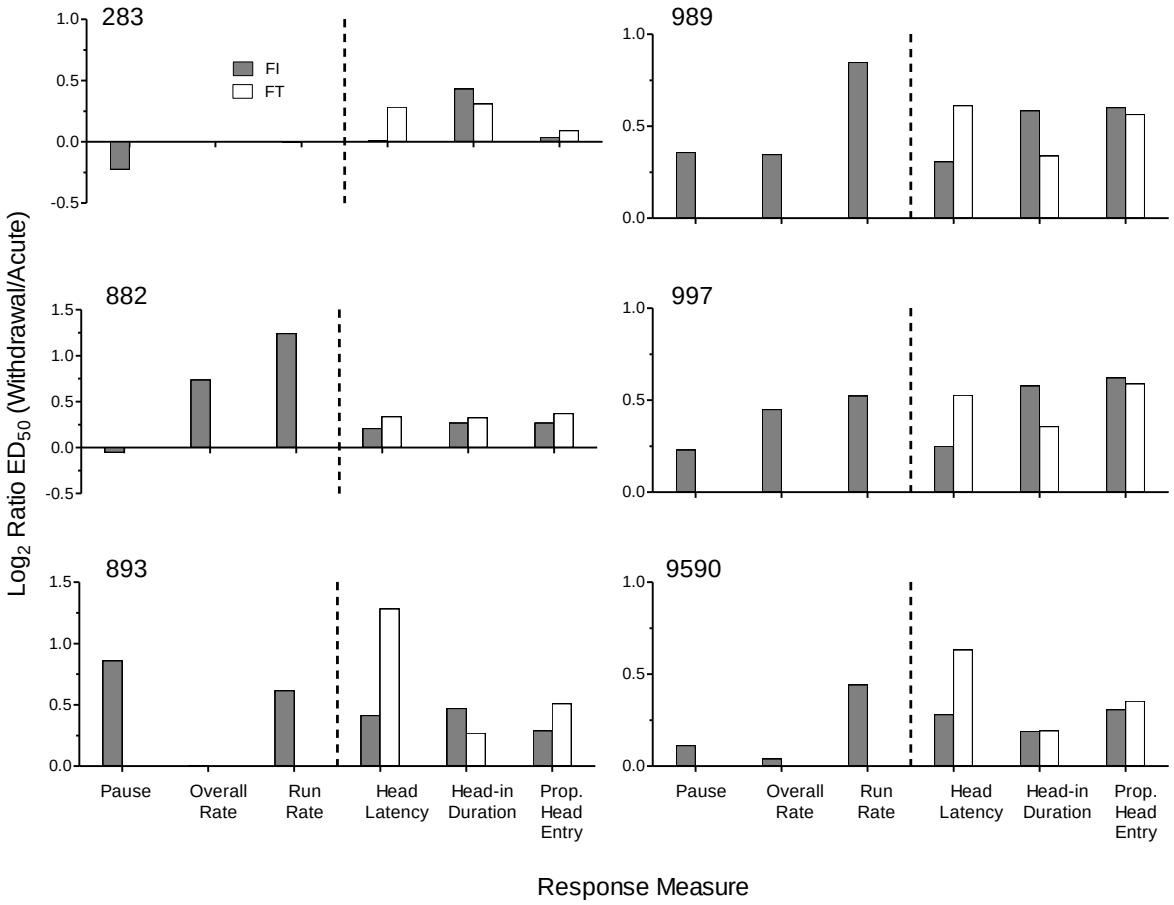

Figure 2-18. The $\log_2$ ratio of withdrawal to acute ED_{50} values is plotted for each measure for each subject. Dark bars and lighter bars are data from the FI and FT components, respectively. Note the different *y*-axis scales across panels.

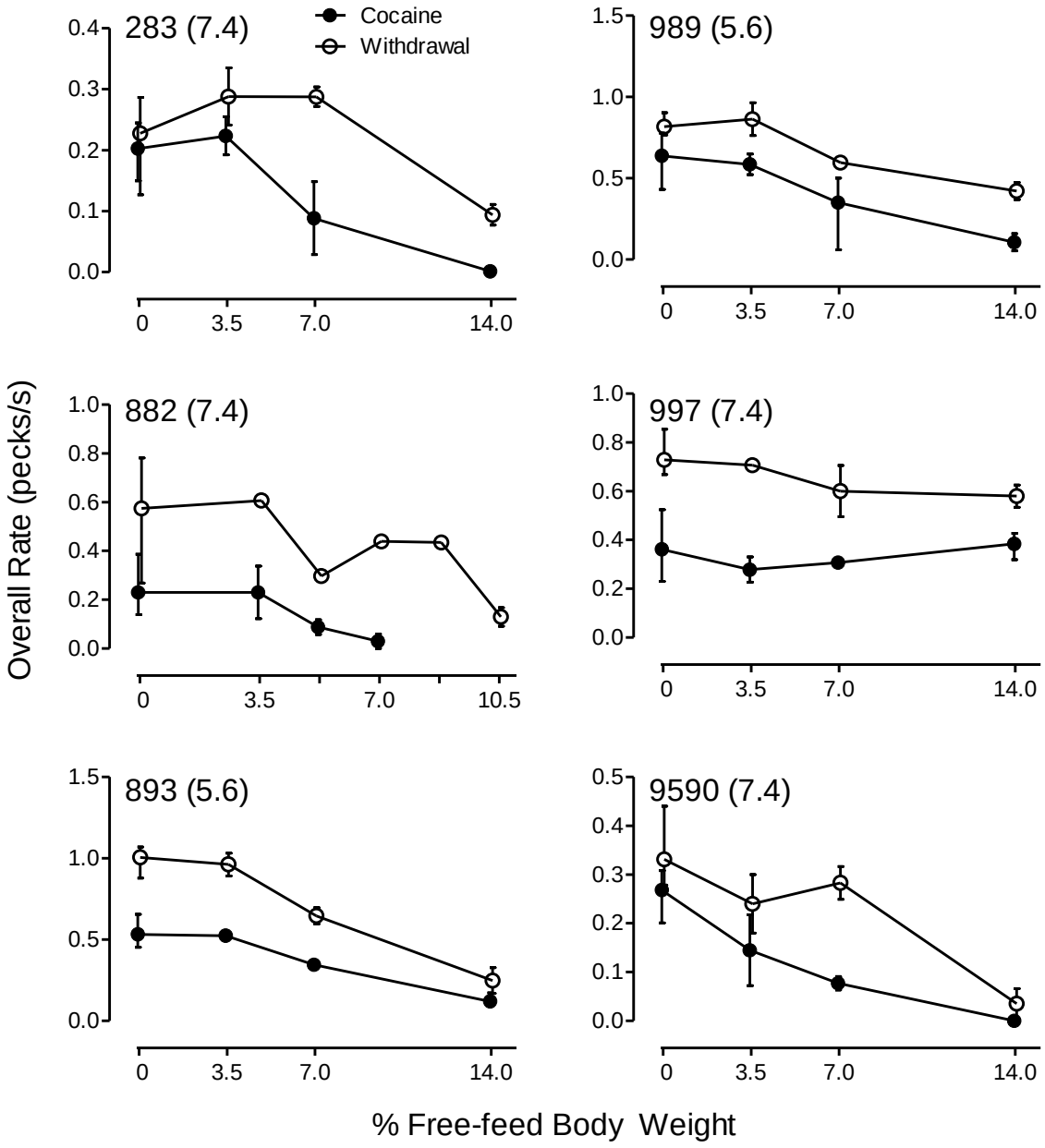

Figure 2-19. Amount-effect curves for overall response rate. Filled and open circles are data from the chronic-drug and withdrawal phases, respectively. Error bars indicate the range.

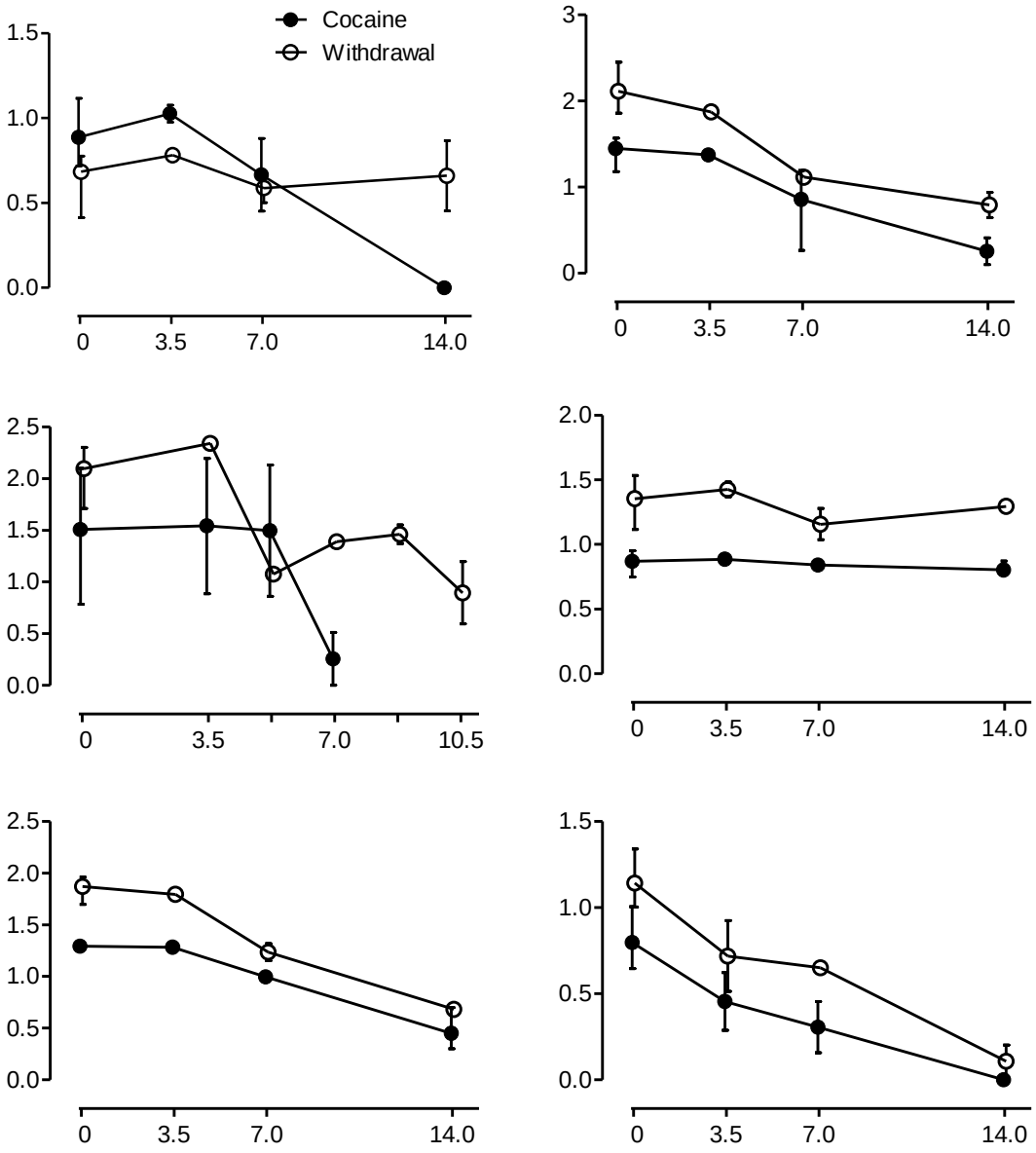

Figure 2-20. Amount-effect curves for run rates. All other details are the same as Figure 2-19.

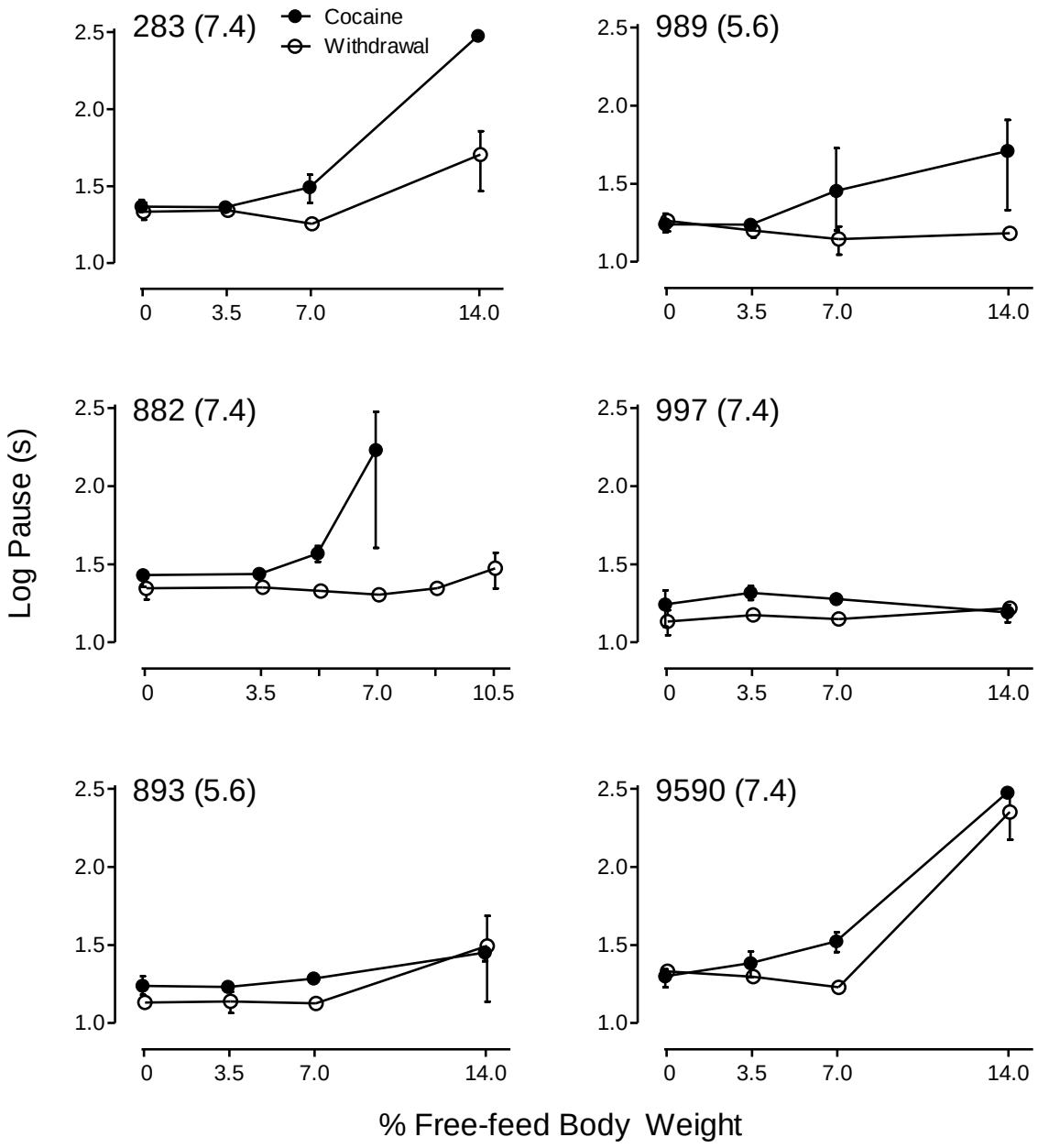

Figure 2-21. Amount-effect curves for pause. Note the log scale on the *y*-axis. All other details are the same as Figure 2-19.

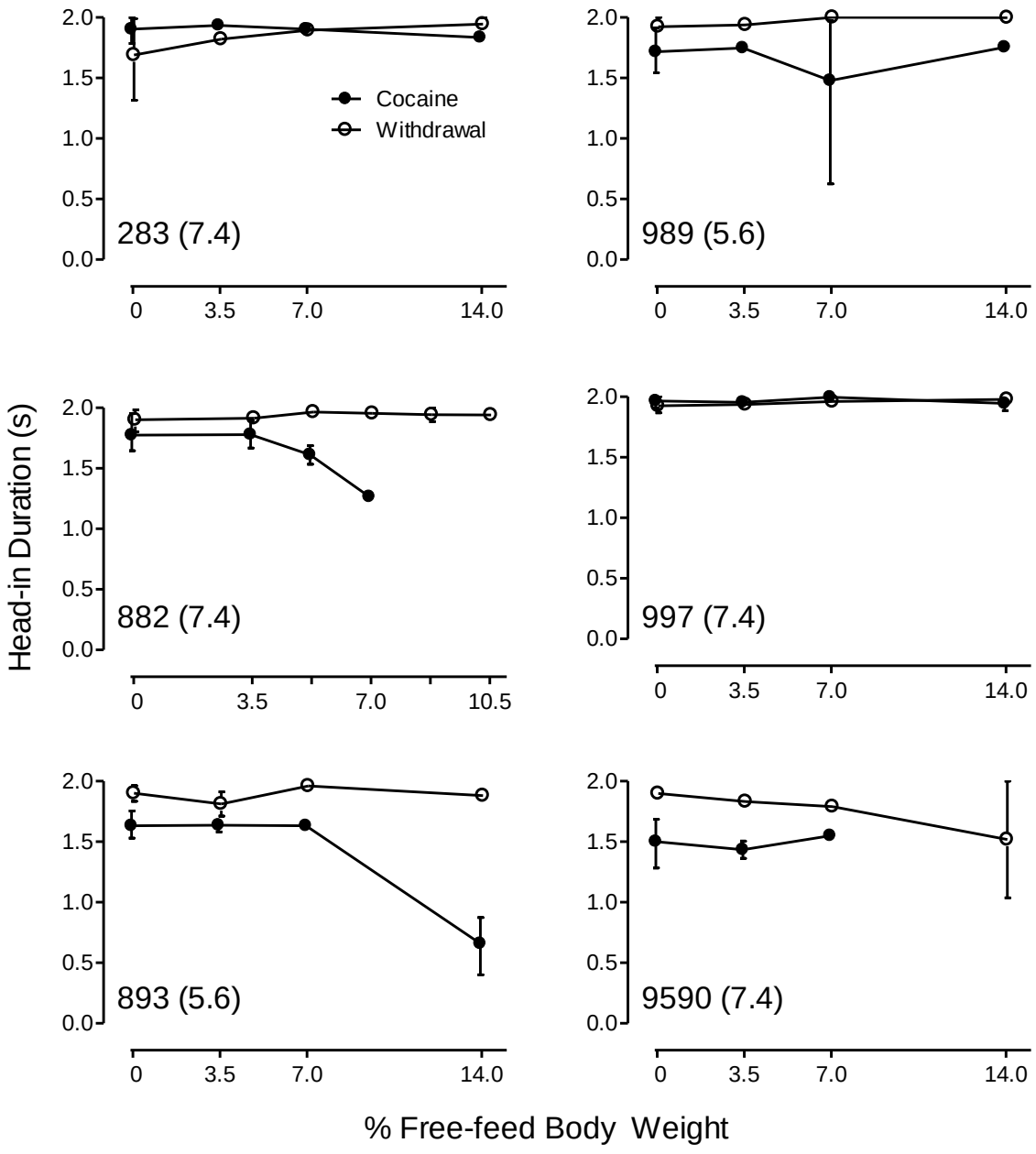

Figure 2-22. Amount-effect curves for head-in duration from the FI component. All other details are the same as Figure 2-19.

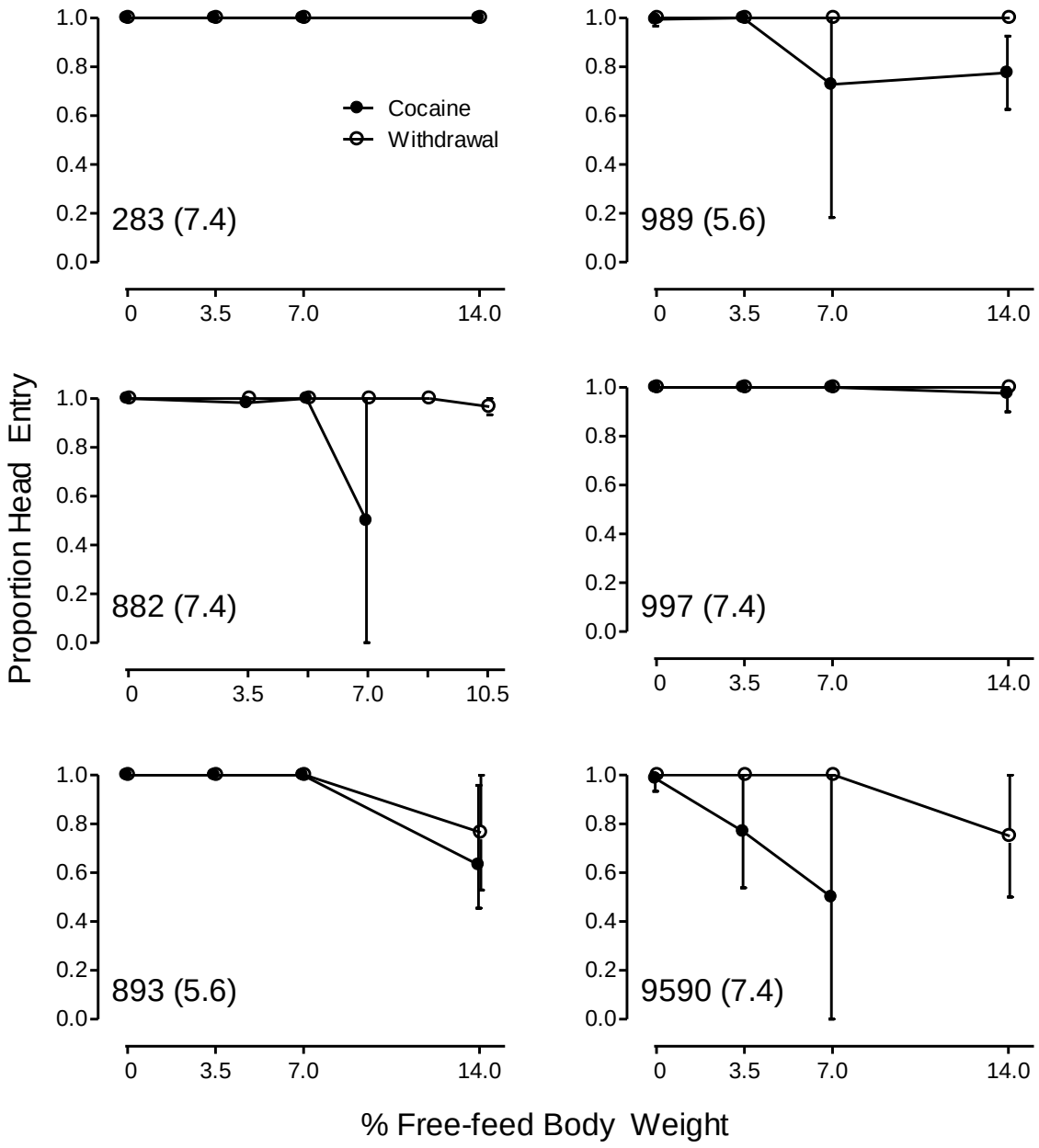

Figure 2-23. Amount-effect curves for proportion head entry from the FI component. All other details are the same as Figure 2-19.

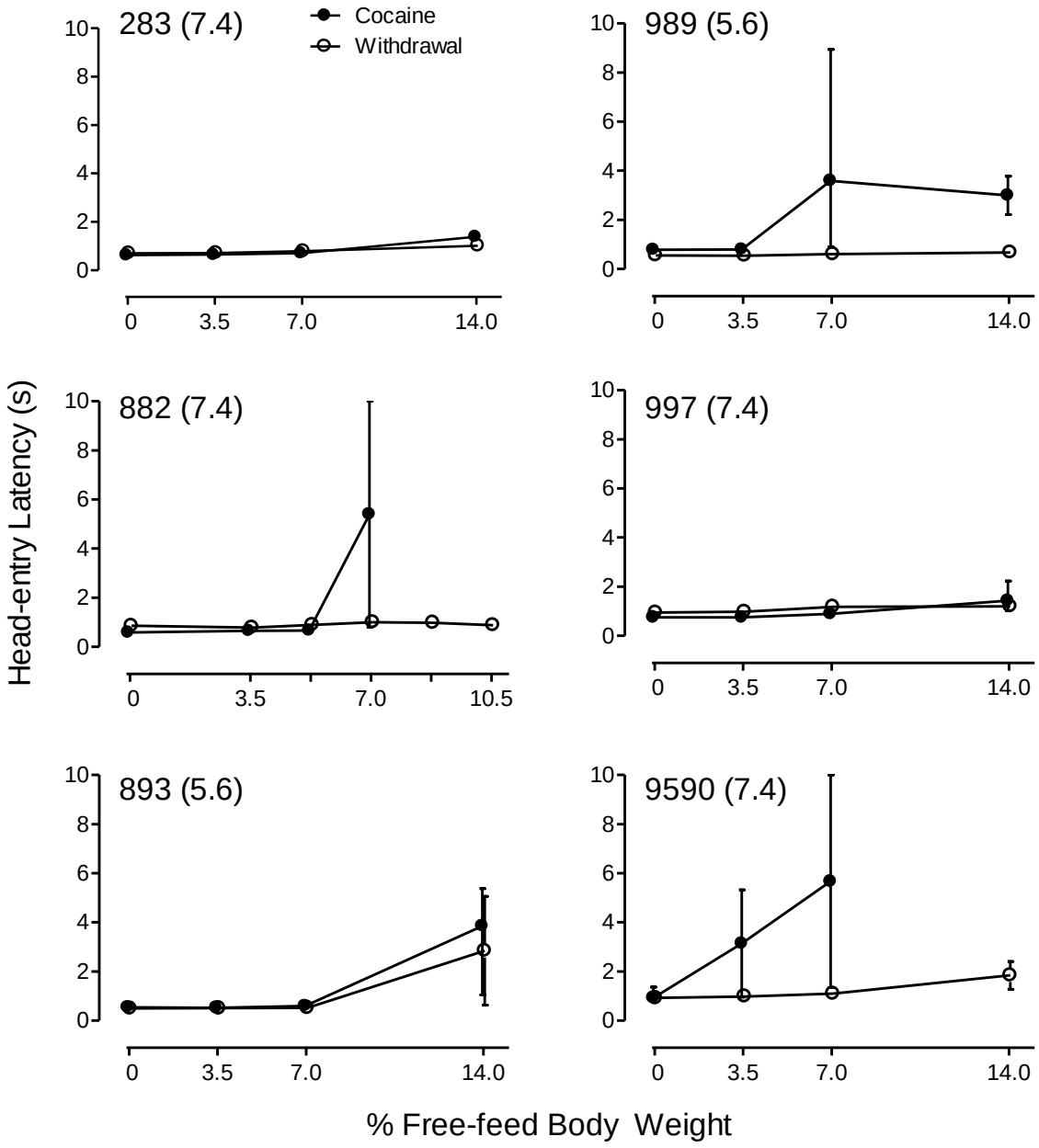

Figure 2-24. Amount-effect curves for head-entry latency from the FI component. All other details are the same as Figure 2-19.

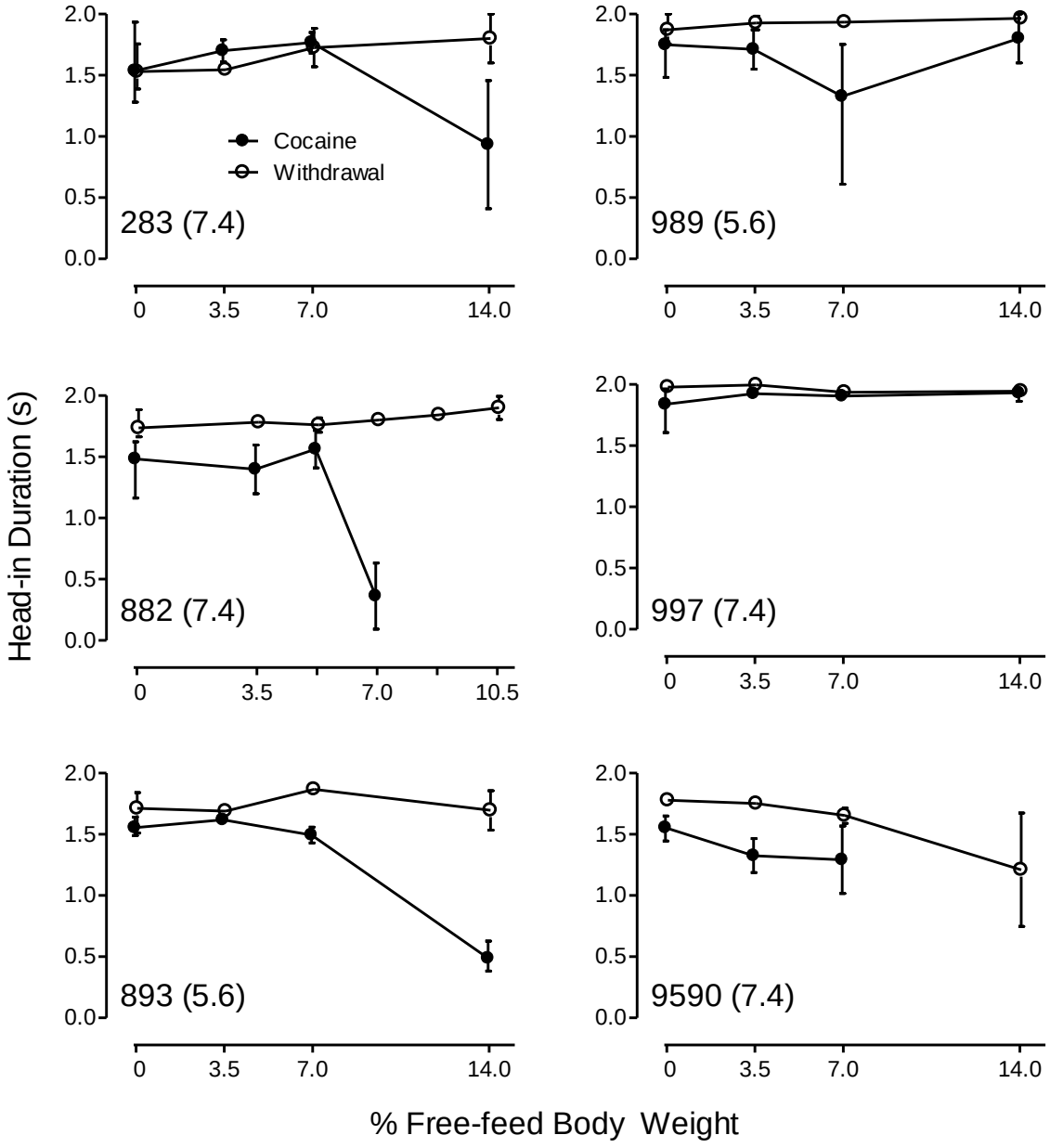

Figure 2-25. Amount-effect curves for head-in duration from the FT component. All other details are the same as Figure 2-19.

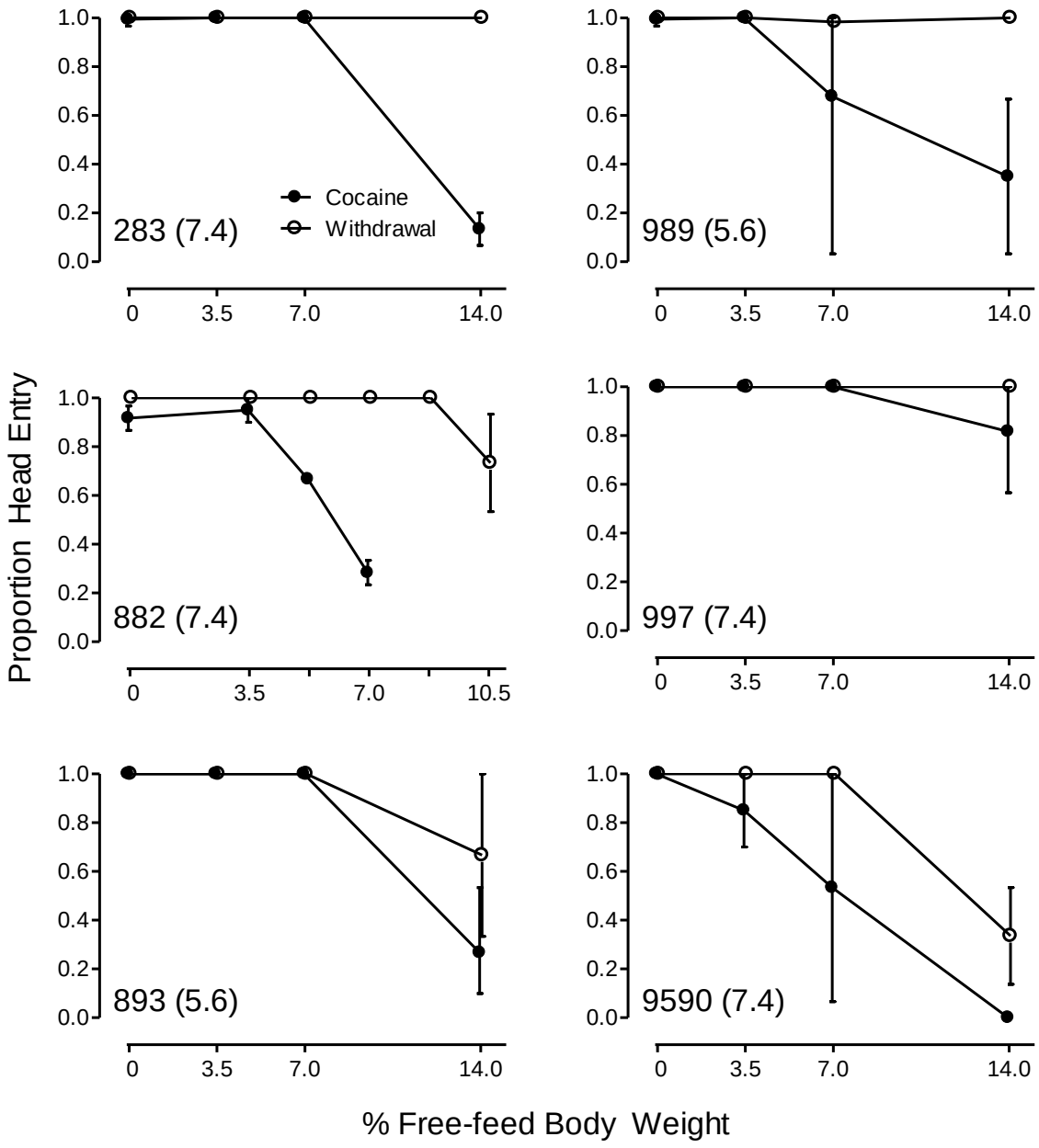

Figure 2-26. Amount-effect curves for proportion head entry from the FT component. All other details are the same as Figure 2-19.

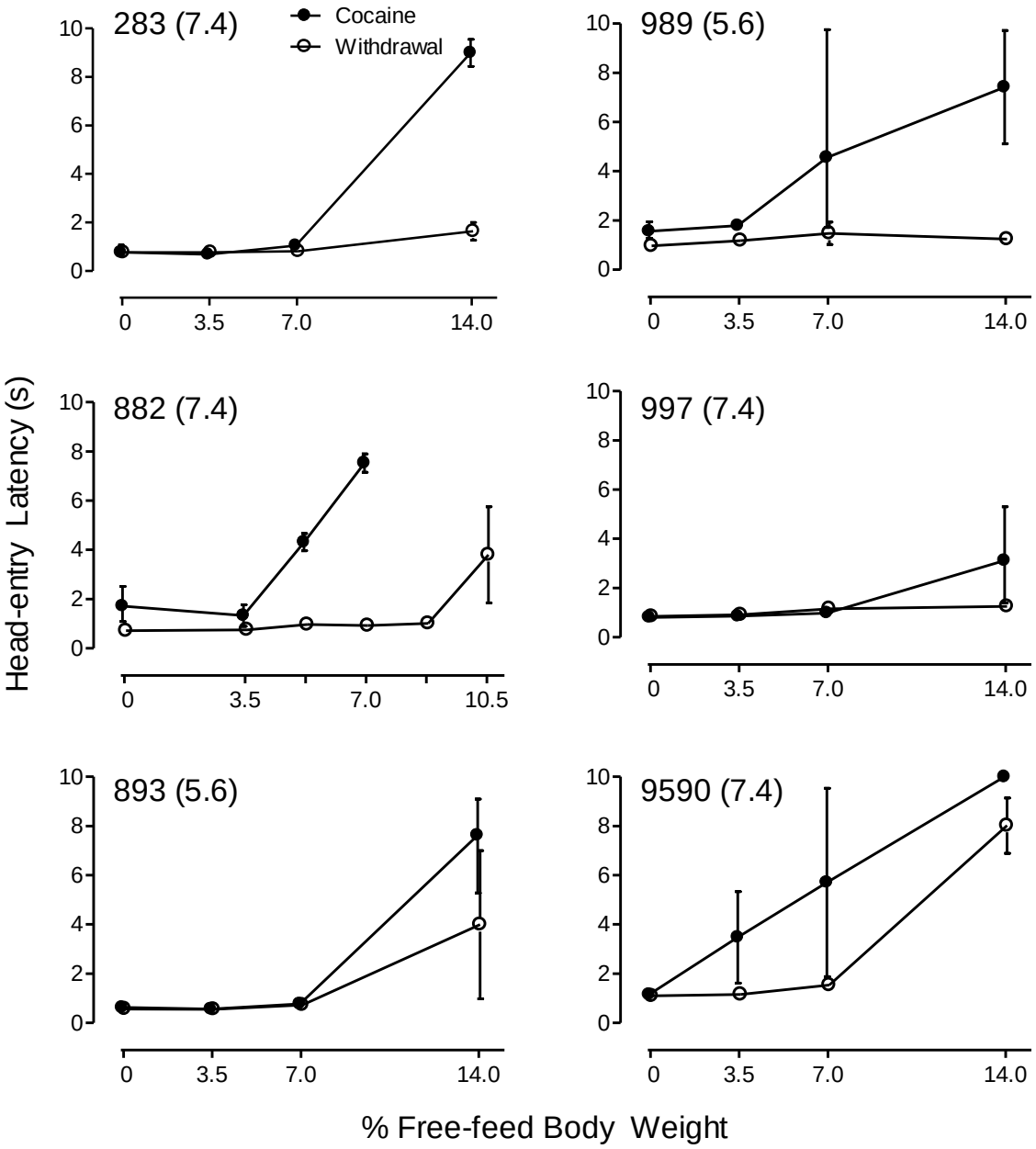

Figure 2-27. Amount-effect curves for proportion head entry from the FT component. All other details are the same as Figure 2-19.

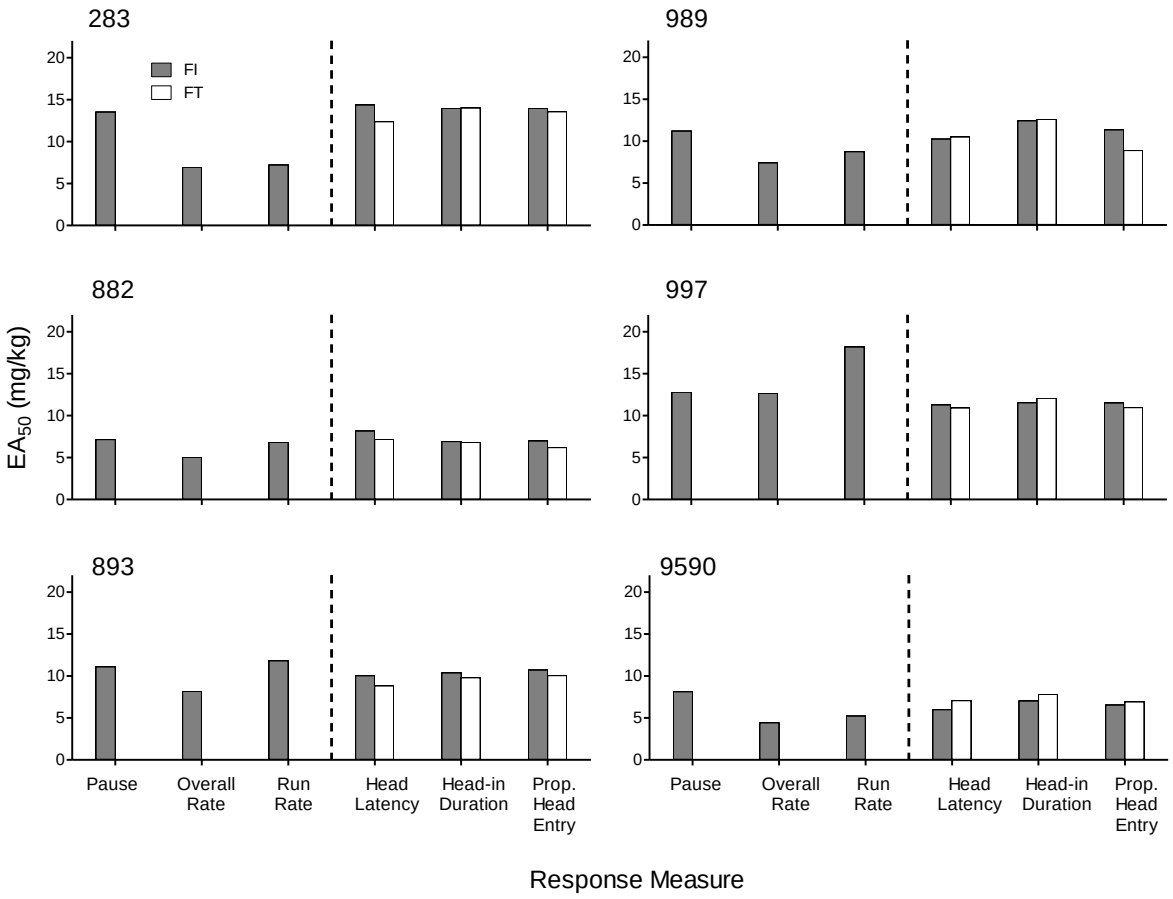

Figure 2-28. EA_{50} values from the chronic-drug phase plotted for all measures. Dark bars and lighter bars are data from the FI and FT components, respectively.

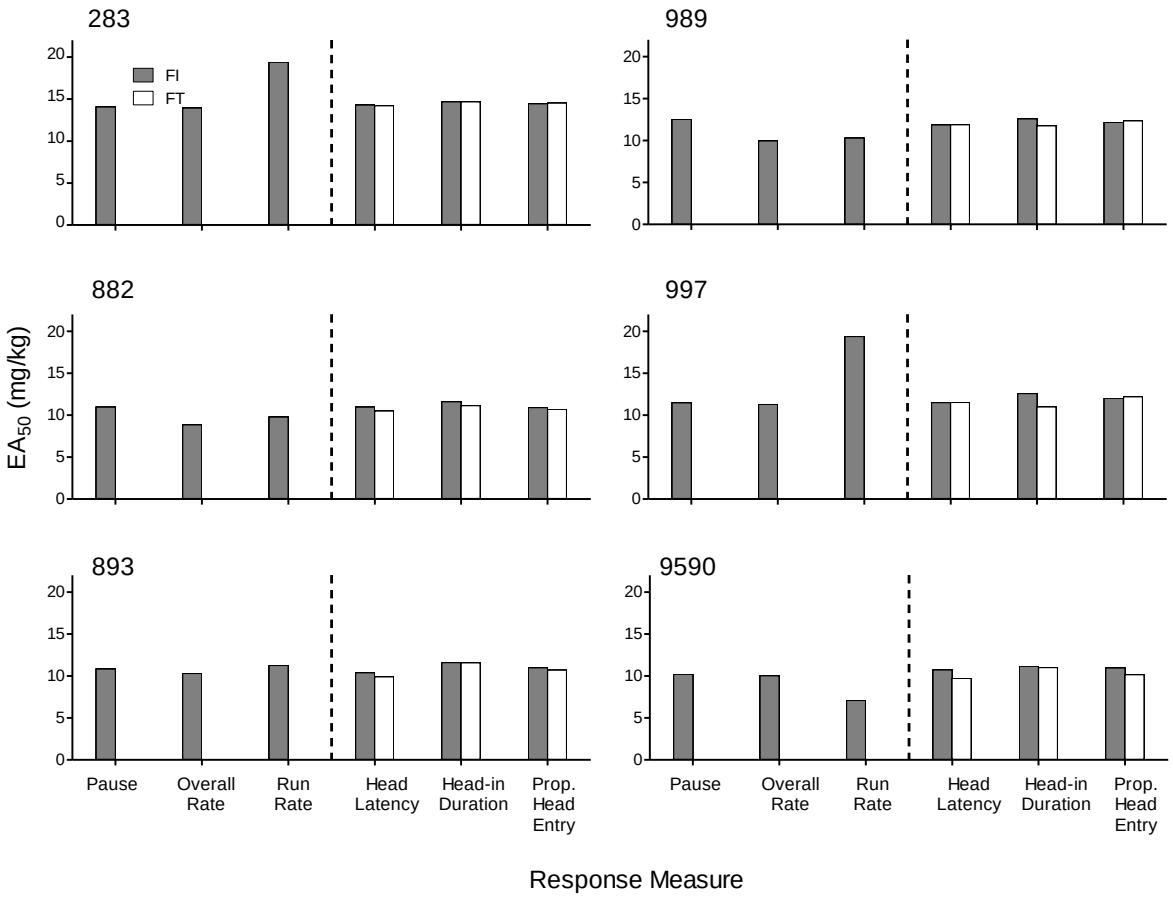

Figure 2-29. EA_{50} values from the withdrawal phase plotted for all measures. Dark bars and lighter bars are data from the FI and FT components, respectively.

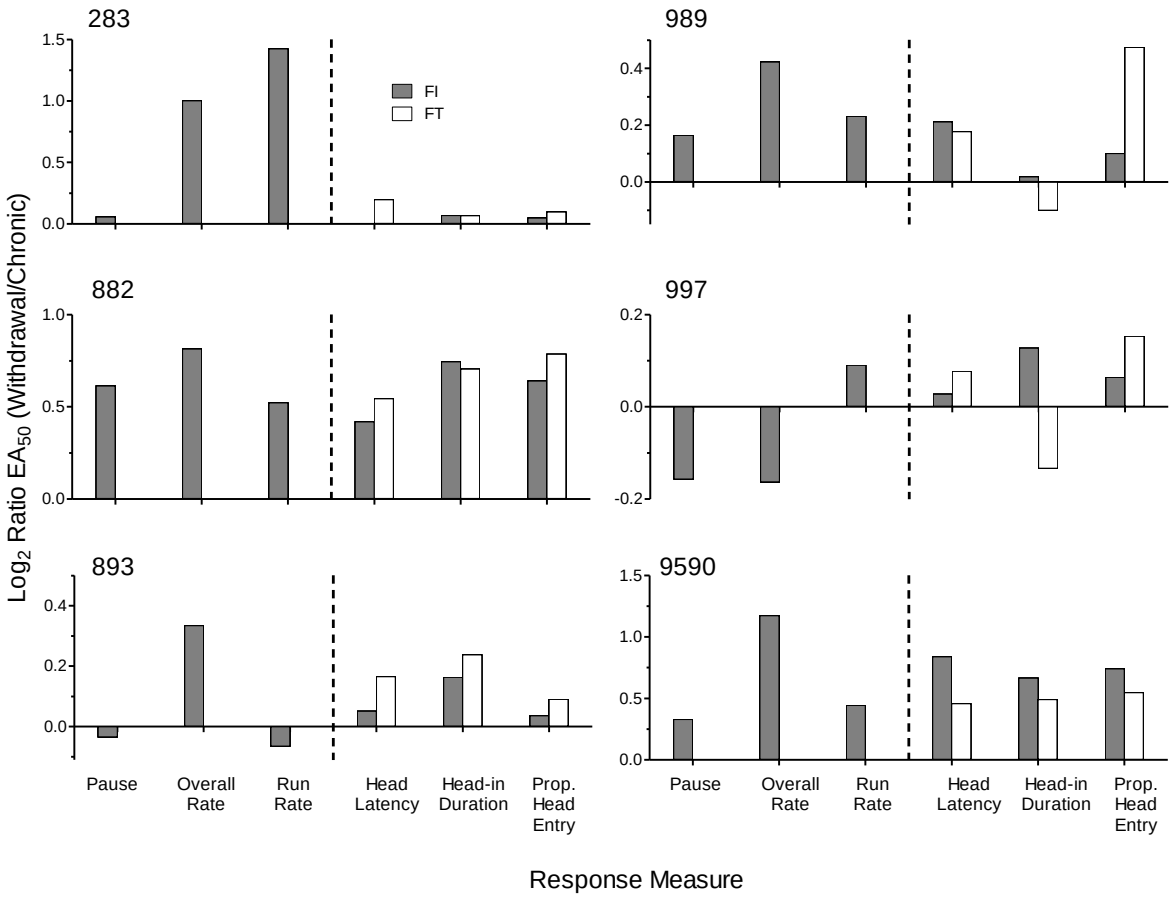

Figure 2-30. The log ratio of withdrawal to chronic-drug EA_{50} values are plotted for each measure for each subject. Dark bars and lighter bars are data from the FI and FT components, respectively.

CHAPTER 3
STUDY 2: EFFECTS OF COCAINE ON KEY-PECKING MAINTAINED BY DIFFERENT SOURCES OF FOOD

Study 2 Introduction

The purpose of Study 2 was to assess whether rate-decreasing effects of stimulant drugs, such as cocaine, on food-maintained operant behavior in pigeons, under a variety of experimental procedures (e.g., Gonzalez & Goldberg, 1977; Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1992; Hughes, Pitts, & Branch, 1996; Jones, LeSage, Sundby, & Poling, 1995; Makhay, Alling, & Poling, 1994; Kleven & Woolverton, 1996; Pinkston, Ginsburg, & Lamb, 2009; Ross & Schaal, 2002; Schama & Branch, 1989; C. Smith, 1964; J. Smith, 1986; Woolverton, Kandel, & Schuster, 1978b) may be the result of a reduction in reinforcer efficacy owing to increased aversiveness of stimuli associated with the presentation of the food hopper. Anecdotal evidence suggests that the effects of cocaine on eating in pigeons may be specific to the experimental chamber and the food-delivery mechanisms used therein. We have frequently observed in the laboratory that a large dose of cocaine, that has substantially suppressed key-pecking and feeding in the experimental chamber, often has no effect on consumption of post-session, supplementary food. That is, subjects will neither peck nor eat in the operant chamber but will readily eat the same food in the home cage immediately after the session. This observation suggests that effects of the drug on feeding (and key-pecking that leads to food presentation) may be specific to features of the method of food delivery in the experimental chamber. Operation of the feeder, for example, may acquire some aversive function as a result of stimulant-drug administration and thus reduce the efficacy of food as a reinforcer.

Sufficient evidence exists to suggest that the food-hopper activation can function as an aversive stimulus in pigeons. In many operant-conditioning arrangements using pigeons, mixed grains are delivered via solenoid-driven hopper that raises and lowers a food magazine to a feeding aperture (cf. Ferster & Skinner, 1957). In order to obtain food the pigeon must place its head inside the food aperture. When the hopper is presented, the hopper light and food are often paired with auditory and seismic stimuli that initially may produce a characteristic fear response (e.g., freezing). During the initial stages of magazine training, experimentally naive pigeons will often freeze in the experimental chamber for prolonged periods of time (for description of a typical magazine training procedure, see Ferster & Skinner, 1957, pg. 31; Steinhauer, Davol, & Lee, 1976). Freezing appears to be a generalized response to the presentation of aversive stimuli in pigeons. For example, Stein, Hoffman, and Stitt (1971), recorded the locomotion of pigeons exposed to a conditioned-suppression procedure (cf. Estes & Skinner, 1941), and reported that during the conditioned-stimulus presentation, a 1000-Hz tone that preceded unavoidable shock, locomotion was dramatically suppressed; that is, pigeons tended to freeze during presentation of the conditioned aversive stimulus. Based on their results and subsequent review of the relevant literature, Stein et al. concluded that in pigeons freezing was a common response to aversive stimuli. It is, therefore, possible that the food hopper, which initially produces freezing, can function as an aversive stimulus. After repeated presentation, and repeated consumption of food (an appetitive stimulus), hopper presentation may become less aversive as a result of habituation, extinction, or counterconditioning, and that it may become more aversive following a history of cocaine exposure.

Research on the effects of cocaine and other stimulant drugs on fear responses (e.g., on the fear-potentiated startle response; cf. Brown et al. 1951; Borowski & Kokkinidis, 1994; Davis, 1990; Gordon & Rosen, 1999) suggests that exposure to cocaine may enhance the startle reflex to a previously established aversive conditioned stimulus. Therefore, to the extent that food-hopper initially functions as an aversive event, it may be the case that the food hopper (re)acquires an aversive function following cocaine administration that then reduces the reinforcing efficacy of food in operant conditioning studies using pigeons. The cocaine-enhanced aversiveness of hopper presentation may reduce reinforcer efficacy through a process akin to reinforcer devaluation (cf. Colwill & Rescorla, 1985). Thus, disruptions in operant behavior maintained by food may owe, at least partially, to this (re)acquired aversive function.

In Study 2, the aversive-food-hopper account was tested by comparing the effects of cocaine on key-pecking maintained by two sources of food. One source was the standard solenoid-driven food hopper that provided brief periods of access to mixed-grains along with the supposed aversive auditory and seismic stimuli. The other source of food was a quieter, presumably less aversive, pellet dispenser that delivered pigeon pellets. By comparing sensitivity of responding maintained by both food sources to a range of doses of cocaine, we attempted to determine whether an interaction between some feature of the delivery mechanism and the drug contributes to the rate-suppressive effects of the drug.

This experiment was comprised of several phases. In the first phase, both food types were available via concurrent schedules, and a range of doses of cocaine was administered to determine whether responding would shift toward the less aversive

alternative. In the latter phases, only one food type was available each session, with type alternating quasi-randomly across sessions. The effects of acute- and chronic-cocaine administration on key-pecking were determined in these phases.

Method

Subjects

Six experimentally naïve male White Carneau pigeons (*Columba livia*) (numbered 77, 79, 803, 804, 916, and 8290) served as subjects; all were approximately 12 to 15 months old at the beginning of the experiment. All pigeons were maintained at 85% of their free-feeding body weight (FFBW) via post-session access to a 50:50 mixture of Purina Pro-11® mixed grain and Purina Pigeon Checkers®, and they were housed individually in a colony room under a 16:8-hr light:dark cycle where water and health grit were continuously available.

Apparatus

An operant-conditioning chamber was used (BRS/LVE, Inc. model SEC-002) that had an internal space of 35.0 cm deep by 30.5 cm wide by 36.0 cm high. One wall of the chamber was constructed of aluminum and contained three 2.5-cm (diameter) response keys arranged in a horizontal line, 26 cm above the chamber floor and 8.5 cm apart (center to center). The keys could be transilluminated red, green, or yellow and required approximately 0.25 N of force to activate their corresponding switches. Only the left and center keys were used in the current experiment, and, when active, they were lit yellow. A 1.1-W houselight was located 6.5 cm directly above the center key. Two 5.0 cm by 6.0 cm rectangular apertures were located 11.0 cm directly below the left and center keys; each could be illuminated by a hopper light. The aperture under the left key contained a food trough (Med Associates® ENV-200R2M) and was connected to

a pellet dispenser (Med Associates® Model ENV-203-20) that delivered a single 20-mg Test Diet Pigeon Tablet per activation. The pellet dispenser was mounted on the outside wall of the operant chamber. The aperture located under the center key provided access to mixed grain delivered via the solenoid-driven hopper that was located immediately behind the wall. The mixed grain consisted of 5 parts milo (average mass of 33 mg per grain), 4 parts buckwheat (average mass 13 mg), and 1 part sterilized hemp (average mass of 25 mg). Entries into both apertures were detected using a MED Associates® Single Channel I/R Source, Detector, and Control that generated an infrared beam across the opening. The chamber was also equipped with a Mallory Sonalert, ® which generated a 30-ms feedback tone (2900 Hz) each time a key was pecked, and an exhaust fan for ventilation White noise was present in the room during the session to mask extraneous sounds. Experimental events were programmed and data recorded by a dedicated computer system (Palya & Walter, 1993). In addition, a Gerbrands® cumulative recorder (Model C-3) provided an online record of responding during each session.

Behavioral procedure

Preliminary training. All subjects were experimentally naïve at the beginning of the experiment; therefore, all subjects underwent preliminary training that included an adaptation period, magazine training, key-peck shaping, and a determination of functionally equivalent food amounts. Preliminary training began after weights reached 85% FFBW. Each subject was placed in the operant chamber for one 20-min adaptation session during which only the houselight was illuminated, and there were no programmed contingencies or data collection.

Following adaptation, magazine training was conducted to ensure that each subject would approach and eat from both feeders when food was available. Each subject was placed in the operant chamber, and access to either pellets or mixed grain was provided response-independently until the subject reliably approached and ate from either of the feeders. The houselight was illuminated between feeder cycles. During food presentation, the houselight was turned off, a feeder-aperture light was turned on, and either three pellets or approximately 3-s access to mixed grain were available. Pellets were delivered successively one every 0.5 s. Access to both food types was controlled by a hand switch, operated by an experimenter. The first operation of the switch initiated food presentation (turned on the feeder light and either began the pellet-delivery sequence or raised the food hopper); the subsequent operation turned off the feeder light (and removed access to the food hopper if it was elevated). The duration of the feeder-light illumination (and hopper presentation) was, therefore, determined by the experimenter on a presentation-by-presentation basis. In both cases the goal was to provide approximately 3-s feeder light (and hopper presentation) every food presentation. Three subjects (77, 79, and 803) were trained first to eat from the pellet dispenser and then from the grain hopper; the other three were trained in the opposite order. Sessions lasted for 50 food presentations. Only one food type was presented during each of these sessions.

After each subject reliably ate from both feeders, key-pecking was shaped via differential reinforcement of successive approximations. The houselight was illuminated, one of the keys was illuminated yellow, and approximations of a key peck on the lit key resulted in brief access to the food available from the hopper located

directly below that key. That is, left-key pecks were shaped using pellets as a consequence and center-key pecks were shaped using access to mixed grain as a consequence. During food presentation, the key light and houselight were extinguished, and the hopper light was turned on. Three subjects were trained to peck the left key first and the remaining three subjects were trained to peck the center key first. Food delivery consisted of either a 3-s period of access to mixed grain (for center-key pecks) or 3 food pellets (left-key pecks). During shaping, the period of access was timed from the elevation of the food hopper; during subsequent phases, the period of access was timed from the initial head entry (see below). Each peck of sufficient force on the lit key produced immediate access to the associated food type. Pecks during this phase and all phases thereafter resulted in a 30-ms beep from the Sonalert. Each session lasted 50 food presentations. Once pecking on one key was established, one session of fixed-ratio (FR) 1 reinforcement on that key was conducted for 50 food presentations during the subsequent session. After successful shaping of pecking on one key was complete, key-peck shaping on the alternate key began the following session. Responding on the second key typically required much less time to establish than on the first; for some subjects, the alternate key was pecked immediately upon the beginning of the session (i.e., as soon as the alternate key was illuminated). For those subjects, responding was considered established if the session was completed (i.e., the subject obtained all 50 food presentations) in a reasonable amount of time (typically less than 5 min), and they continued on to the next training phase during the next session.

Food-amount determination. After key-pecking was established on both keys, a concurrent schedule was arranged in order to determine functionally equivalent food amounts. Both response keys were available simultaneously, and the amount of food available from each alternative was adjusted across phases until each alternative received comparable numbers of responses each session for several consecutive sessions. The houselight and both response keys were illuminated at the beginning of the session. Responding on either key produced access the food type associated with that key according to a variable-interval (VI) schedule. At the beginning of the session and following each food presentation, inter-food intervals were selected randomly without replacement from a 12-term Fleshler-Hoffman (1962) series. Both VI schedules were comprised of the identical distributions of intervals across all experimental phases; however, the two schedules were implemented independently. That is, responses and food presentation on one alternative had no effect on the scheduling of food presentation on the other alternative except that during food presentation of either food type both VI timers were paused (and scheduling resumed at the end of food presentation). Initially, a VI 2-s schedule was arranged on each key. The VI parameters were increased across the subsequent nine sessions of the first condition (P1 in Table 3-1) to a VI 60-s schedule. Thereafter (and for the remainder of the experiment) each key when lit arranged food presentations according to a VI 60-s schedule.

During the first condition for all subjects, pecks on the left key produced 2 food pellets, and pecks on the center key produced 2-s periods of access to mixed grain. All food presentations were delivered immediately following the peck that produced them.

During presentation of either food type, the houselight and key lights were extinguished, and the associated feeder light was illuminated. If the center key had been pecked, the grain hopper was raised. If the left key had been pecked, the arranged number of pellets were delivered sequentially, one every 0.5 s. The feeder light was extinguished (and hopper removed) after a pre-determined period of time following the initial head entry; otherwise, in the event that a head entry did not occur, the feeder light was extinguished (and hopper lowered) after 10 s. Feeder-light durations were equated across alternatives for the entire experiment. That is, if 2-s access to grain was arranged on the center key for a particular subject, the pellet feeder light for that subject would also be illuminated for 2 s following a head entry. Pellets that had been delivered remained available until either they were consumed or removed by the experimenter at the end of the session.

Across successive conditions, the amount of food available from each alternative was adjusted until the total number of responses on each alternative for each session was approximately equal. For example, if after 10 sessions, responding heavily favored the center-key (mixed-grain) alternative, either the duration of access to mixed grain was reduced, or the number of food pellets was increased. The progression in food amounts is summarized for each subject in Table 3-1; the amounts from the final preliminary-training phase for each subject (e.g., P4 for subject 77) served as the final food amounts for the remainder of the experiment (i.e., for all experimental phases) for each subject. A change-over delay (COD) was also introduced across successive phases during preliminary training. The COD is a contingency arranged to prevent immediate reinforcement of switches between alternatives. Initially for all subjects, a

two-response COD was in effect that required at least two responses be made on the same key, consecutively, before a response could produce food. Thereafter, the COD was based on the time since a switch. Ultimately, a 2-s COD was in effect for all subjects that prevented responses from producing food for at least 2 s following a switch.

Experimental phases. The effects of cocaine on key-pecking were assessed under two behavioral procedures, concurrently or alternately available foods, and across two pharmacological phases (acute- and chronic-cocaine administration). Acute effects were assessed under both procedures; however, effects of chronic-cocaine administration were only assessed under the alternately-available-foods procedure. Sessions were conducted once daily, seven days per week, at approximately the same time each day and lasted either 45 min or 60 food presentations, whichever occurred first. Sessions began with a 5-min blackout period during which the subject was placed in the chamber with all lights turned off, and there were no programmed contingencies during this time, nor were data collected.

During the first experimental phase, food presentations were scheduled via the concurrent schedule described above. Acute-drug administration (see below) began after daily response counts across alternatives under the concurrent schedule were stable according to visual inspection of the data. Stability was defined as limited session-to-session variability in response counts and the lacks of trends. The second experimental phase began after acute dose-effect determinations under the concurrent-schedule procedure. Under the second procedure, only one response key (and its associated food type) was functional during each session. The alternate response key

remained dark and that food type was unavailable. Pecks on the alternate response key had no programmed consequences, and they were not recorded. The available food type alternated quasi-randomly from session to session with the constraint that there were no more than three consecutive sessions of one food type; all other procedural details remained the same. The reinforcement schedule arranged during the subsequent phases therefore constituted a multiple schedule wherein each component was available for an entire session and was signaled by distinctive stimuli (i.e., either the left or center key was illuminated). Each food type continued to be available according to the same VI 60-s schedule. Both acute and chronic effects of the drug were determined under the multiple schedule. Table 3-1 shows a summary of the number of sessions conducted prior to and during the determination of dose-effect curves during each phase. The numbers in parentheses indicate the numbers of sessions from the beginning of dose-effect curve determinations in that particular phase to the beginning of the subsequent phase.

Pharmacological procedure

Prior to selected sessions, either a dose of cocaine hydrochloride, dissolved in 0.9% sodium chloride (saline) solution, or saline was administered via intramuscular (pectoral muscle) injection immediately before the subject was placed in the operant-conditioning chamber. The doses tested (expressed as total salt) were 1.0, 3.0, 5.6, 7.4, and 10.0 mg/kg (13.0 mg/kg was administered to subjects 79, 804 and 916); injection volumes were 1 ml/kg.

Doses were tested in descending order with the constraint that each dose was given once before a second determination of any dose was made and that at least four no-administration sessions (during acute administration) or chronic-dose-administration

sessions (see below) intervened between successive administrations of test doses. All doses for all subjects were administered at least twice during each phase; in some cases (e.g., when the results from the first two determinations of a dose were discrepant), additional determinations were made in order to reassess the reliability of the effect of that particular dose. The effects of all doses administered were included in data analysis. During the multiple-schedule phase, each dose was administered at least twice prior to both session types; therefore, there were at least four probe-dose determinations total during both acute- and chronic-administration phases. Saline was administered as the zero-dose, administration control as part of the sequence regular dosing sequence. Additional control data under all phases were taken from the sessions immediately preceding probe-dose determinations; these data served as no-administration controls for acute administration and chronic-dose controls under chronic administration to provide a measure of baseline responding.

After acute-dose-effect curves were determined during the multiple-schedule phase, a single dose that produced a substantial reduction in response rates was selected and administered daily prior to the experimental session for at least 30 consecutive sessions (range: 30 to 41) prior to a reassessment of the dose-effect curve. All subjects received 7.4 mg/kg as the chronic dose. Tables 3-2, 3-3, and 3-4 show the number of determinations made of each dose during each of the three dosing phases, respectively.

Data analysis

All experimental events were time-stamped for data analysis. Unless otherwise noted, all data presented are based on session means. Overall responses rates on each key were calculated by dividing total responses on each key by total session time

exclusive of hopper-cycle time. Local response rates under the concurrent schedule were calculated by dividing total responses on each key by total time spent responding on that key. Time on a key was accumulated from the first peck of a visit to a key until the next peck on the other key, or until the end of the session, whichever occurred first. Overall rates provide a measure of output on a particular alternative over the course of the session and allows for comparison of rates across phases (i.e., it provides a comparable measure of output under the concurrent and multiple schedules) whereas local rates provide an estimate of responses rate on a particular alternative once the subject has switched to that alternative.

In addition, a measure of preference (during the concurrent-schedule phase) was derived that provides a relative measure of response allocation across alternatives. The log-response ratio was calculated by taking the log of the ratio of the number of responses on the left key to the number of responses on the center key. This measure provides an index of the direction and magnitude of biases in response allocation.

Dose-effect curves for each measure from each phase were plotted to facilitate comparison of behavioral sensitivity to cocaine across food types. Normalized dose-effect curves were constructed by dividing the means from all determinations of each dose within a phase (and for each food type) by the mean saline value for that phase and multiplying by 100.

Results

Procedure 1: Concurrent schedule

Figure 3-1 shows cumulative-response records for each subject from a representative saline-administration session under the concurrent schedule. Both schedules produced moderate, steady rates of responding in all subjects. Closer

inspection reveals that responding on each alternative consisted of a repetitive sequence of breaks and runs (Baum, Schwendiman, & Bell, 1999; Silberberg & Fantino, 1970); that is, responding occurred in bouts consisting of several rapidly emitted responses on one alternative followed by a switch to the other alternative. Preference for one alternative is indicated by the degree of similarity in the two curves. Generally, overall rates tended to be similar across alternatives; although, there were clear differences across alternatives in most subjects. Some subjects showed a slight left-key bias (77, 803, and 916) whereas other showed a center-key bias (804 and 8290).

Table 3-2 shows a summary of the mean effect for each measure for control and saline and across all doses of the drug that were administered. Comparison of overall and local rates during control sessions indicates that, for some subjects, the overall distribution of responses across alternatives (as indicated by differences in overall rates) did not match relative local rates. For example, subject 79 tended to distribute total pecks evenly across alternatives; that is, overall rates are similar across alternatives (mean rates were 0.53 and 0.56 pecks/s on the left and center keys, respectively). Local rates for this subject, however, were quite different (mean local rates were 1.29 and 1.67 pecks/s on the left and center keys, respectively) suggesting that, even though overall response allocation appeared to be similar, time allocation was not. Indeed, the mean total time spent responding on the left key was 933 s per session whereas the mean total time spent responding on the center key was 751 s. Similar discrepancies in response- and time-allocation biases emerged for subjects 804, 916; however, the differences in bias were in the degree of bias rather than the direction. For 804, the ratio of responses on the left key to the center key was

approximately 0.64 (favoring the center key) and the ratio of time spent responding on the left key to the center key was approximately 0.5 (also favoring the center key). Response allocation for subject 916 was biased toward the left key (response ratio of 1.2) as was time allocation (time ratio of 2.06). For the remaining subjects, response and time allocation were biased in the same direction within subject but varied across subjects. Subjects 77 showed a general center-key bias, whereas 803 and 8290 showed a general left-key bias.

Figure 3-2 shows normalized dose-effect curves for overall response rates. Panels show the mean effect on rate as a function of dose of cocaine and saline for individual subjects. The observed values on which the normalized data are based are summarized in Table 3-2. Across subjects, cocaine produced dose-dependent, monotonic decreases in response rate on both alternatives. Larger doses occasionally suppressed rates completely. For subject 916, rates were moderately suppressed across the entire range of doses tested (including 1.0 mg/kg, the smallest dose tested); however, rates were never completely suppressed. For three subjects (77, 79, and 8290), there was little difference in sensitivity across alternatives; that is, cocaine decreased rates to similar degrees on each key across the range of doses administered. In subject 803, smaller doses (1.0 and 3.0 mg/kg) produced larger relative decreases on left-key rates although larger doses had similar effects. For subject 804, larger doses produced more substantial decreases in rates on the left key. For subject 916, center-key rates were more consistently decreased across the entire range of doses.

Figure 3-3 shows dose-effect curves for log-overall-rate ratios (left-key rate divided by center-key rate). For some dose determinations, cocaine produced substantial decreases in response rates such that no responses occurred on one or both keys in which case, the ratio of responses was either indeterminate (if there were no left-key responses) or 0 (if there were no center-key responses). In both cases, the log ratio is indeterminate, so these points are not shown on log-ratio graphs. Values near zero on the y-axis indicate little difference in rates across the two alternatives; positive values indicate that rates were proportionally higher on the left key; negative values indicates that rates were proportionally higher on the center key. Non-zero log-ratios during control sessions (located over the C on the *x*-axis) indicate the direction of the response-rate bias during control sessions. Generally, saline and smaller doses had little effect on preference relative to control. Rates in subject 804 were slightly biased toward the center key under control sessions that persisted under the smaller doses tested (indicated by a negative log ratio). Rates in subject 916 were biased toward the left key (indicated by a positive log ratio). For all subjects (except 803), cocaine dose-dependently shifted response ratios toward one alternative; however, the direction of the shift was not consistent across subjects. For subjects 77, 916, and 8290 cocaine shifted ratios in a positive direction (enhancing the bias toward left-key responding), and for subjects 79 and 804 the shifts were in the negative direction (enhancing the bias toward center-key responding). For Subject 803, the log-ratio remained near zero across the entire range of doses tested.

Figure 3-4 shows normalized dose-effect curves for local response rates. Generally for most subjects, cocaine produced dose-dependent decreases in

responding on both alternatives. For most subjects (except 804 and 916), the curves tended to be separated to some degree. The direction of the difference, however, was not consistent across subjects. For subjects 803, 804, and 8290, local rates on the center key tended to be decreased more substantially at smaller doses than those on the left key; larger doses had similar effects across alternatives. The curves for 77 showed the opposite effect; that is, left-key rates tended to be decreased to a greater degree. There was, however, a significant degree of overlap in the error bars indicating that there was substantial variability in the effects of these doses across determinations. For subject 916, all doses tested consistently produced a 50% decrease in left-key rates and dose-related decreases in center-key rates. Relative to control, the decreases at larger doses are more substantial in left-key rates.

Procedure 2: Multiple schedule

Figure 3-5 shows cumulative-response records for each subject from representative saline-administration sessions during the acute-administration, multiple-schedule phase. The figure shows cumulative records from both session types plotted in a single panel to facilitate comparison of responding across components. Both schedules produced moderate to high, steady rates of responding. In some subjects (804, 916, 8290, and 803 in the grain component) rates on a particular key were increased substantially compared to those observed under the concurrent schedule (compare with Figure 2-1); however, this might be expected given that only one alternative was available each session. For a majority of subjects, the number of responses emitted each session under the multiple schedule approximated the total number of responses emitted (left- and right-key responses) during the concurrent-

schedule phase; therefore, the overall response rate remained relatively unchanged across phases.

For four subjects, response biases that developed under the concurrent schedule carried over to responding under the multiple schedule (see Tables 3-3 and 3-4). For example, responding in subjects 77 and 79 slightly favored the center key under the concurrent schedule with response ratios (left to center) of 0.85 and 0.95, respectively. Under the multiple schedule, the ratio of responses during pellet sessions (when only the left key was functional) and grain sessions (when only the center key was functional) were 0.72 and 0.91, respectively. Responding in 804 was heavily biased in favor of the center key under the concurrent schedule with a response ratio of 0.64; the bias became slightly less extreme with a response ratio of 0.75 (recall, ratios of 1.0 indicate no bias). Response biases in 803 and 916 shifted to the other alternative. Response ratios for these two subjects under the concurrent schedule were 1.32 and 1.2, respectively (in favor of the left key); under the multiple schedule, ratios shifted to 0.98 and 0.84, respectively.

Acute dose-effects. Table 3-3 shows a summary of the mean effect for each measure for control and saline and across all doses of the drug that were administered during the acute-administration, multiple-schedule phase. During control sessions, the mean rates across components ranged from nearly equal (subjects 79, 803, and 8290) to slightly higher on the center key (subjects 77, 804, and 916).

Figure 3-6 shows normalized dose-effect curves for response rates across component type for each subject during the acute-determination phase. The values on which the normalized data are based are summarized in Table 3-3. For all subjects, the

drug produced little to no effect at the smaller doses (in some cases rates were increased slightly) and dose-dependently decreased rates in both components. Some determinations of the larger doses produced complete suppression of rates. Selective effects were present across subjects at some doses, particularly at smaller doses. For subjects 804, 916, and 8290, small to moderate doses (1.0 to 5.6 mg/kg) tended to produce more substantial decreases in one component. The largest differences in rate decreases across components occurred under 5.6 mg/kg in subjects 804 and 8290; rates during the pellets sessions were close to saline range whereas rates during the grain sessions were reduced more than 75%. Overall, however, there was no consistent difference in sensitivity to the drug across components or across subjects.

Chronic-administration dose-effects. Figure 3-7 shows cumulative-response records for each subject from representative saline-administration sessions during the chronic-dose administration. For all subjects except 77, saline rates during the chronic-administration phase were decreased relative to rates prior to chronic administration (compare with Figure 3-5). Rates were increased slightly in subject 77.

Table 3-4 shows a summary of the mean effect for each measure for control and saline and across all doses of the drug that were administered during the chronic-administration, multiple-schedule phase. During this phase, a single dose was selected (7.4 mk/kg for all subjects) and was administered prior to every session.

Figure 3-8 shows normalized dose-effect curves for response rates across component type for each subject during the chronic-administration phase (dashed lines) superimposed on the acute-administration curves (solid lines; shown in Figure 3-6). For five of six subjects (except 79), the effects of the larger doses were greatly diminished

compared to their effects under acute administration. Initially, larger doses (5.6 to 10.0 mg/kg) produced substantial decreases in rates and, for some determinations, complete suppression of key-pecking. After chronic-drug administration, the effects of these doses were diminished. The dose-effect curves at the largest doses tested were flattened out with most means across the range of doses tested falling within or above the range of effect under saline. For Subject 79, rates following saline administration were much lower than those observed during the acute-administration phase and cocaine dose-dependently increased rates relative to the observed saline rates under the highest doses tested (7.4, 10.0 and 13.0 mg/kg). For four subjects (except 79 and 916), the magnitude of the rightward shift in the curves does was not related to component type; that is, the chronic-administration dose-effect curves from both components tended to closely overlap. For subject 79, the dose-effect curve for responses rates during grain sessions was shifted upward to greater extent than the dose-effect curve for response rates during pellet sessions. For subject 916, the only differential effect of the drug occurred following administration of 13.0 mg/kg during pellet sessions; rates during these sessions were substantially decreases, whereas rates during grain sessions were less affected.

Study 2 Discussion

The purpose of the current experiment was to assess whether cocaine would differentially affect responding maintained by different sources of food. One source of food was available from a solenoid-driven food hopper and the other from pellet dispenser. We hypothesized that cocaine might enhance fear (i.e., startle) responses elicited by the auditory and seismic stimuli produced by the presentation of the solenoid-driven hopper, enhancing the aversiveness of hopper presentation, and, thus, reduce

response rates on the associated (center) key. Cocaine has been shown to enhance fear responses to conditioned aversive stimuli (e.g., Borowski & Kokkinidis, 1994; Davis, 1990; Gordon & Rosen, 1999). After determining the amount of food provided by each alternative that would sustain similar amounts of responding, we compared the effects of a range of doses of cocaine on key-pecking maintained by each alternative. The acute effects of the drug were compared using two different procedures that differed with respect to the context in which each food was available, and the effects of chronic-cocaine administration was assessed only under the multiple-schedule procedure. According to our aversive-food-hopper hypothesis, cocaine should alter the function of the solenoid-driven food hopper (making it an aversive stimulus) and, thus, produce more substantial rate-decreasing effects on responding maintained by the food delivered from the hopper (mixed-grains). Under the concurrent schedule, this effect would be revealed in a shift in response allocation away from the center key (on which responding produced the supposed aversive stimulus) and toward the left key (on which responding produced the supposedly less aversive stimuli). Under the multiple schedule this effect would be revealed by differential effects of the drug on rates during each component type; rates during grain sessions would be suppressed to a greater degree than those during the pellets sessions.

Generally, the results of the current experiment do not support the aversive-food-hopper hypothesis of cocaine's behavioral mechanism of action. The drug failed to produce consistent differential effects across alternatives. Under the concurrent schedule, cocaine dose-dependently decreased overall rates on both alternatives, replicating a frequently reported effect of the drug (e.g., Gonzalez & Goldberg, 1977;

Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1992; Hughes, Pitts, & Branch, 1996; Jones, LeSage, Sundby, & Poling, 1995; Makhay, Alling, & Poling, 1994; Kleven & Woolverton, 1996; Pinkston, Ginsburg, & Lamb, 2009; Ross & Schaal, 2002; Schama & Branch, 1989; C. Smith, 1964; J. Smith, 1986; Woolverton, Kandel, & Schuster, 1978b). These effects, however, generally were not differential with respect to the particular source of food, and, when there were differential effects, they were not consistent across or even within subject. In overall rate, of the 32 possible comparisons (the sum of the total number of doses tested across subjects), rates on the center key were selectively decreased (i.e., the drug produced larger decreases relative to control) in 16 instances; of those only 5 occurred without substantial overlap in the range of effect. More pronounced differential effects occurred in local rates; however, of the 32 possible comparisons, rates on the center key were selectively decreased in 21 instances. Of those only 8 occurred without substantial overlap in the range of effect. Under the multiple-schedule, acute administration of cocaine produced dose-dependent decreases in overall rates as it had in the previous phase. Differential effects of the drug across components were not observed. In overall rate, of the 33 possible comparisons, rates on the center key were selectively decreased in only 12; of those only 4 occurred without substantial overlap in the range of effect.

Cocaine tended to produce dose-dependent shifts in response allocation, as indicated shifts in the ratio of left-key pecks to center-key pecks, especially at the larger doses (5.6 mg/kg and above). The direction of the shift in log-response ratios, however, was not consistent across subjects. For three subjects (77, 916, and 8290), response ratios were shifted in favor of the left key, indicating an enhancement of preference for

pellets whereas for two subjects (79 and 804), response ratios were shifted in the in favor of the center key, indicating an enhancement of preference for grain. There is, however, a noteworthy correlation. For four subjects (except 77 and 803) the drug tended to enhance the bias that developed during baseline (see Figure 3-3). The slight center-key bias in subjects 79 and 804 and the slight left-key biases in subjects 916 and 8290 were all enhanced by the drug. In contrast, for the remaining two subjects (77 and 803), the drug effect was to counteract the baseline bias. Response allocation in 77 (initially biased toward the center key) was shifted toward the left key, and vice versa for subject 803. Note, however, that these shifts in response allocation occurred concomitantly with significant disruption in overall response rate for all subjects, and the effects were quite variable across individual dose determinations; therefore, interpretations of these effects are complicated by effects of the drug beyond a simple shift in preference. Shifts may have resulted from drug-induced persistence wherein once the subject began responding on the favored key, responding persisted on that key longer than under control conditions resulting in enhanced allocation on that particular key. The failure to observe a difference in the acute effects of cocaine across behavior maintained by identical schedules of food reinforcement is not surprising given the large number of studies that have shown a drug's effects on operant behavior (especially stimulant drugs such as cocaine) to depend on the schedule of reinforcement maintaining behavior rather than the type of consequence (e.g., Kelleher & Morse, 1968; see the review by McMillan & Katz, 2002).

Despite efforts to produce undifferentiated responding across alternatives in terms of the number of responses emitted on each alternative, there was evidence that

differential responding across alternatives had developed prior to acute-drug administration. Initially, response counts were very similar; however, for each subject different patterns of responding began to emerge. For example, for subject 79, the average number of responses during control sessions on the left and center keys were relatively close (1204 and 1255, respectively); however, total time spent responding on the left key was greater than time spent responding on the center key, which resulted in different local rates of responding (1.3 and 1.7 pecks/s on the left and center keys, respectively; see Table 3-2). Although total responses initially matched across alternatives, average time spent responding on each alternative generally did not match. Furthermore, control data indicate that, by the time acute dosing began, some subjects (77 and 804) consistently emitted more responses on the center key whereas other subjects (803, 916, and 8290) consistently emitted more responses on the left key. Similar differences occurred in time allocation and local rate suggesting that all three measures did not correlate perfectly and that different patterns of responding may have developed across keys.

The apparent low correlation between number of responses emitted on an alternative and amount of time spent responding on an alternative contradicts assumptions, about the nature of responding under concurrent-choice schedules, that response and time allocation correlate and both tend to match relative reinforcement value across alternatives (e.g., see Baum & Rachlin, 1969; Davison & McCarthy, 1988). Nevertheless, biases in responding did not preclude determination of differential drug effects across alternatives. A drug-induced shift in preference would still be revealed by an enhancement or reduction in the bias that developed under baseline conditions.

That is, a shift in responding could still be revealed despite an initial bias. In fact, if response ratios had shifted consistently across sessions, given the presence of bias in both directions, a drug effect that shifted responding from preference for one alternative to preference for the other potentially would be a powerful demonstration of the effect.

After repeated administration of a dose that produced substantial decreases in rates during acute administration, the effects of cocaine were reassessed. The initial effects of the drug, particularly at larger doses, generally were diminished; that is, tolerance developed to the initial effects of the drug. Indeed, doses that produced near-complete suppression when administered acutely (e.g., 5.6 to 10.0 mg/kg in subject 77; see Figure 3-8) produced almost no rate decreases after chronic exposure. This pattern of effects emerged in all birds. Tolerance to the effects of cocaine on explicitly reinforced operant behavior following chronic exposure is commonly reported (e.g., Branch, 1990; Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1991; Nickel, Alling, Kleiner, & Poling 1993; Pinkston & Branch, 2004; van Haaren & Anderson, 1994; Yoon & Branch, 2004). The degree of tolerance (i.e., how much responding recovered after chronic-cocaine administration) did not appear to be related to food type (see Figure 3-8). For three subjects (77, 803, and 804), normalized dose-effect curves obtained after chronic-cocaine administration were generally flat across the entire range of doses tested, suggesting that the drug's effects on rates was diminished, and curves overlapped almost completely. For one subject (916) tolerance appeared to develop differentially as rates were selectively decreased in the pellet component after the 10.0 mg/kg dose. For the remaining subjects (79 and 8290), interpretation of the effect of chronic-cocaine administration is complicated by the substantial decrease in rates

following saline administration relative to the effects at other doses of the drug. Compared to the effect of 1.0 mg/kg, the smallest dose of drug tested, saline administration produced a substantial decrease in rate in both (subject 79) or one component (8290; in the pellet component). As a result of the decrease in response rates observed following saline administration, the normalized dose-effect curves (normalized relative to saline values) were shifted upwards. For subject 79, the shift was more substantial in the dose-effect curve for responding in the grain component suggesting that there was a larger degree of drug-induced enhancement of response rates in that component. For subject 8290, the absolute dose-effect curves (not shown) overlap significantly, indicating that the drug had similar effects across components at the larger doses. The rate decreases produced by the larger doses (5.6, 7.4, and 10.0 mg/kg) were diminished after chronic-cocaine administration). Taken together, across subjects, it appears that effects of chronic-cocaine administration on response rate, also, were not related to the food source.

An obvious limitation in the current experiment is the confounding of food type and source. The hopper provided brief periods of access to mixed grains that included milo, hemp, and buckwheat whereas the pellet dispenser provided access to pigeon pellets. Differential effects on responding could have been attributed to an effect on response rates mediated through the food type rather than the food source. One remedy would have been to arrange delivery of the same type of food from both dispensers. For example, the food hopper could have been filled with food pellets thus providing access to the same food type as the pellet dispenser leaving only the actual delivery mechanism to differ across alternatives. Due to a lack of resources (i.e., food pellets)

we opted to forgo putting pellets in the hopper and instead try to determine functionally equivalent food amounts. This approach is justifiable based on the literature with stimulants that show that equivalent performances, even with different consequences, are generally affected similarly (e.g., Barrett, 1976; Kelleher & Morse, 1964). Identification of functionally equivalent food types was accomplished by providing intermittent and simultaneous access to both foods and adjusting the food amounts available from alternative according to the distribution of responses across alternatives. Preference for one food type resulted in either a reduction in the amount of food available from that alternative or an increase in the amount of food available from the other alternative. For all subjects, this process allowed a determination of functionally equivalent food amounts based on the distribution of responses across alternatives. For all subjects, a very short period of access to mixed grain (0.5 s for most subjects; 0.25 s for 8290) was determined to be functionally equivalent to 4 or 5 food pellets.

On any given food presentation, assuming that a pigeon can obtain one or two grains in 0.5 s (pigeons generally peck for mixed-grain in the food hopper at a rate of about 2.5 pecks/s; see Bertsch & Becker, 1973), the pigeons would obtain 24 to 48 mg of mixed grain (the sum of the average weights of each grain type multiplied by its estimated probability of being selected) per food presentation compared to 80 or 100 mg of pigeon pellets (each pellet weighed approximately 20 mg). We assumed that the equivalence established during preliminary training (e.g., that 0.5-s access to grain was equivalent to 4 food pellets) remain invariant across all experimental phases.

In sum, the purpose of the current study was to assess whether cocaine would differentially disrupt responding maintained by different sources of food-a shaky, noisy

food source, or a quieter, gentler food source. A range of doses of the drug were tested across two different behavioral procedures and before and after chronic administration of a dose that produced substantial response-rate decrements. In all phases, prior to chronic administration, cocaine produced dose-dependent decreases in response rate; generally, across subjects, these decreases were not selective to responding maintained by the louder mixed-grain food hopper. Tolerance developed to the rate-decreasing effects of the drug after repeated exposure; the degree of development of tolerance also was not related to food source.

Table 3-1. Summary of Reinforcement Parameters and Procedural Details

Subject	Condition	Number of Pellets	Duration Access to Grain (s)	Sessions	Other Details
77	P1	2	2	10	VI 2-s to VI 60-s
	P2	2	0.5	40	2-Response COD
	P3	3	0.5	40	1" COD
	P4	4	0.5	27	2" COD
	E1	4	0.5	27 (101)	Concurrent schedule / Acute administration
	E2	4	0.5	30 (138)	Multiple schedule / Acute administration
	E3	4	0.5	30 (148)	Multiple schedule / Chronic administration
79	P1	2	2	10	VI 2-s to VI 60-s
	P2	2	0.5	42	2" COD
	P3	3	0.5	32	2" COD
	E1	3	0.5	32 (96)	Concurrent schedule / Acute administration
	E2	3	0.5	36 (174)	Multiple schedule / Acute administration
	E3	3	0.5	60 (135)	Multiple schedule / Chronic administration
803	P1	2	2	10	VI 2-s to VI 60-s
	P2	2	0.5	40	2-Response COD
	P3	3	0.5	18	1" COD
	P4	4	0.5	56	2" COD
	E1	4	0.5	15 (89)	Concurrent schedule / Acute administration
	E2	4	0.5	30 (142)	Multiple schedule / Acute administration
	E3	4	0.5	63 (115)	Multiple schedule / Chronic administration

Table 3-1. Continued.

Subject	Condition	Number of Pellets	Duration Access to Grain (s)	Sessions	Other Details
804	P1	2	2	10	VI 2-s to VI 60-s
	P2	2	0.5	40	2-Response COD
	P3	3	0.5	58	2" COD
	P4	4	0.5	15	2" COD
	E1	4	0.5	15 (103)	Concurrent schedule / Acute administration
	E2	4	0.5	30 (186)	Multiple schedule / Acute administration
	E3	4	0.5	34 (125)	Multiple schedule / Chronic administration
916	P1	2	2	10	VI 2-s to VI 60-s
	P2	2	0.5	40	2-Response COD
	P3	2	0.5	32	2" COD
	P4	2	1	14	2" COD
	P5	2	0.5	13	2" COD
	P6	3	0.5	15	2" COD
	P7	4	0.5	13	2" COD
	E1	4	0.5	13 (117)	Concurrent schedule / Acute administration
	E2	4	0.5	41 (231)	Multiple schedule / Acute administration
	E3	4	0.5	35 (162)	Multiple schedule / Chronic administration
8290	P1	2	2	10	VI 2-s to VI 60-s
	P2	2	0.5	40	2-Response COD
	P3	3	0.5	18	2-Response COD
	P4	4	0.5	49	1" COD
	P5	4	0.25	16	2" COD
	P6	5	0.25	21	2" COD
	E1	5	0.25	21 (94)	Concurrent schedule / Acute administration
	E2	5	0.25	30 (159)	Multiple schedule / Acute administration
	E3	5	0.25	75 (111)	Multiple schedule / Chronic administration

The last condition for each subject indicates the reinforcement parameters used for each alternative for the remainder of the experiment. See text for full descriptions of procedural details.

Table 3-2. Summary of Dependent Measures from the Concurrent-schedule Phase

		Pellets				Grain			
Subject	Dose (mg/kg)	Pecks	Time (s)	Overall Rate (pecks/s)	Local Rate (pecks/s)	Pecks	Time (s)	Overall Rate (pecks/s)	Local Rate (pecks/s)
77	Control (17)	1066	776	0.46	1.37	1253	892	0.54	1.40
	Saline (2)	1381	927	0.56	1.49	1439	959	0.58	1.50
	1.0 (2)	821	722	0.43	1.14	1052	743	0.55	1.42
	3.0 (2)	594	943	0.22	0.63	692	866	0.26	0.80
	5.6 (4)	637	1136	0.24	0.56	451	396	0.17	1.14
	7.4 (5)	426	1047	0.16	0.41	82	272	0.03	0.30
	10.0 (2)	0	0	0.00	0.00	0	0	0.00	0.00
79	Control (14)	1204	933	0.53	1.29	1255	751	0.56	1.67
	Saline (2)	1098	854	0.53	1.28	1132	606	0.55	1.87
	1.0 (2)	1431	1191	0.57	1.20	1224	830	0.49	1.47
	3.0 (2)	991	834	0.47	1.19	819	851	0.38	0.96
	5.6 (2)	900	882	0.33	1.02	1059	1159	0.39	0.91
	7.4 (4)	549	807	0.23	0.68	756	959	0.31	0.79
	10.0 (2)	13	303	0.00	0.04	108	150	0.04	0.72
803	Control (13)	1952	984	0.91	1.99	1468	759	0.68	1.94
	Saline (2)	1793	887	0.85	2.02	1501	853	0.71	1.76
	1.0 (2)	1523	810	0.65	1.88	1652	1103	0.71	1.50
	3.0 (2)	937	586	0.41	1.60	1302	1325	0.57	0.98
	5.6 (2)	927	881	0.35	1.05	775	1138	0.29	0.68
	7.4 (2)	981	775	0.36	1.26	890	1366	0.33	0.65
	10.0 (3)	542	543	0.23	1.00	657	726	0.27	0.91

Table 3-2. Continued.

Subject	Dose (mg/kg)	Pellets				Grain			
		Pecks	Time (s)	Overall Rate (pecks/s)	Local Rate (pecks/s)	Pecks	Time (s)	Overall Rate (pecks/s)	Local Rate (pecks/s)
804	Control (17)	1057	578	0.49	1.83	1641	1138	0.75	1.44
	Saline (2)	1252	694	0.54	1.81	1810	1123	0.77	1.61
	1.0 (2)	994	549	0.44	1.81	1561	1208	0.70	1.29
	3.0 (2)	1125	770	0.44	1.46	1345	1172	0.53	1.15
	5.6 (2)	575	1014	0.22	0.57	723	984	0.28	0.73
	7.4 (3)	215	206	0.08	1.04	725	1293	0.27	0.56
	10.0 (4)	143	211	0.05	0.68	751	1387	0.28	0.54
	13.0 (2)	28	25	0.01	1.12	594	4257	0.22	0.14
916	Control (19)	1808	1187	0.77	1.52	1507	575	0.64	2.62
	Saline (2)	2063	1349	0.76	1.53	1633	619	0.66	2.64
	1.0 (2)	1479	1260	0.64	1.17	1129	381	0.24	2.96
	3.0 (4)	1682	1061	0.54	1.59	1453	545	0.34	2.67
	5.6 (2)	1350	1725	0.64	0.78	615	225	0.12	2.73
	7.4 (3)	1260	1595	0.46	0.79	713	352	0.18	2.03
	10.0 (4)	1829	1175	0.39	1.56	1666	687	0.23	2.42
	13.0 (2)	1752	1089	0.47	1.61	1504	654	0.29	2.30
8290	Control (20)	1547	987	0.67	1.57	1270	808	0.55	1.57
	Saline (2)	1091	721	0.49	1.51	1436	942	0.65	1.52
	1.0 (2)	1681	960	0.68	1.75	1393	927	0.57	1.50
	3.0 (3)	1126	835	0.49	1.35	629	787	0.31	0.80
	5.6 (4)	888	1061	0.34	0.84	466	646	0.19	0.72
	7.4 (6)	451	889	0.17	0.51	220	326	0.08	0.67
	10.0 (3)	61	162	0.02	0.38	6	116	0.00	0.05

Values indicate means from all sessions conducted under each condition. The number of determinations of each dose, and number of control sessions, included in each mean are indicated in parentheses next to the dose.

Table 3-3. Summary of Dependent Measures from the Acute-administration, Multiple-schedule Phase

		Pellets			Grain		
Subject	Dose (mg/kg)	Pecks	Time (s)	Overall Rate (pecks/s)	Pecks	Time (s)	Overall Rate (pecks/s)
77	Control (25)	1104	2482	0.44	1522	2641	0.58
	Saline (4)	1325	2501	0.53	1682	2638	0.64
	1.0 (4)	1284	2511	0.51	1911	2627	0.73
	3.0 (5)	862	2509	0.34	1452	2644	0.55
	5.6 (4)	30	2681	0.01	129	2673	0.05
	7.4 (4)	204	2656	0.08	81	2683	0.03
	10.0 (4)	191	2613	0.07	0	2700	0.00
79	Control (30)	1412	2445	0.58	1545	2630	0.59
	Saline (4)	1633	2505	0.65	1655	2639	0.63
	1.0 (4)	1433	2429	0.59	1628	2654	0.61
	3.0 (4)	1660	2481	0.67	1894	2643	0.72
	5.6 (5)	1324	2419	0.55	1615	2640	0.61
	7.4 (4)	1159	2434	0.48	1183	2637	0.45
	10.0 (5)	1103	2481	0.44	856	2646	0.32
	13.0 (4)	306	2530	0.12	452	2644	0.17
803	Control (25)	2356	2439	0.97	2403	2634	0.91
	Saline (4)	2243	2513	0.89	2079	2623	0.79
	1.0 (4)	1386	2381	0.58	1572	2642	0.59
	3.0 (4)	1017	2522	0.40	1136	2640	0.43
	5.6 (4)	393	2475	0.16	1104	2634	0.42
	7.4 (5)	640	2508	0.26	207	2633	0.08
	10.0 (4)	23	2672	0	783	2634	0

Table 3-3. Continued.

		Pellets			Grain		
Subject	Dose (mg/kg)	Pecks	Time (s)	Overall Rate (pecks/s)	Pecks	Time (s)	Overall Rate (pecks/s)
804	Control (28)	2408	2422	0.99	3239	2629	1.23
	Saline (4)	2308	2448	0.94	3160	2622	1.20
	1.0 (4)	2403	2405	1.00	2749	2636	1.04
	3.0 (4)	2138	2430	0.88	2144	2618	0.82
	5.6 (4)	1818	2435	0.75	821	2613	0.31
	7.4 (4)	480	2454	0.20	242	2596	0.09
	10.0 (4)	78	2615	0.03	803	2603	0.31
	13.0 (4)	288	2475	0.12	233	2573	0.09
916	Control (37)	2307	2424	0.95	2726	2631	1.04
	Saline (4)	2758	2464	1.12	2570	2626	0.98
	1.0 (4)	2516	2471	1.02	3234	2625	1.23
	3.0 (4)	2247	2523	0.89	2858	2638	1.08
	5.6 (4)	2360	2381	0.99	2467	2626	0.94
	7.4 (9)	2181	2522	0.86	1069	2663	0.40
	10.0 (8)	1365	2502	0.55	1750	2656	0.66
	13.0 (4)	1674	2488	0.67	2216	2641	0.84
8290	Control (24)	3100	2384	1.30	3026	2653	1.14
	Saline (4)	2444	2368	1.03	3133	2653	1.18
	1.0 (4)	3092	2429	1.27	2682	2660	1.01
	3.0 (4)	2933	2387	1.23	2986	2650	1.13
	5.6 (4)	1619	2474	0.65	342	2659	0.13
	7.4 (4)	166	2597	0.06	7	2680	0.00
	10.0 (4)	5	2680	0.00	0	2700	0.00

Time during each condition is the total session duration exclusive of hopper-cycle duration. All other details are the same as in Table 3-2.

Table 3-4. Summary of Dependent Measures from the Chronic-administration, Multiple-schedule Phase

		Pellets			Grain		
Subject	Dose (mg/kg)	Pecks	Time (s)	Overall Rate (pecks/s)	Pecks	Time (s)	Overall Rate (pecks/s)
77	Saline (6)	806	2447	0.33	1020	2616	0.39
	1.0 (4)	828	2492	0.33	1220	2629	0.46
	3.0 (4)	917	2450	0.37	1228	2629	0.47
	5.6 (5)	878	2458	0.36	1165	2615	0.45
	7.4 (23)	992	2456	0.40	904	2614	0.35
	10.0 (4)	912	2483	0.37	952	2610	0.36
79	Saline (4)	503	2523	0.20	461	2644	0.17
	1.0 (4)	1054	2516	0.42	1342	2525	0.53
	3.0 (4)	1278	2504	0.51	1301	2642	0.49
	5.6 (4)	1159	2488	0.47	1878	2661	0.71
	7.4 (25)	1400	2467	0.57	2034	2648	0.77
	10.0 (4)	1286	2450	0.52	2086	2637	0.79
	13.0 (5)	1171	2448	0.48	1991	2633	0.76
803	Saline (7)	1563	2486	0.63	1795	2628	0.68
	1.0 (5)	1572	2496	0.63	2026	2645	0.77
	3.0 (4)	1220	2513	0.49	1743	2633	0.66
	5.6 (4)	1516	2465	0.62	1654	2637	0.63
	7.4 (25)	1212	2459	0.49	1570	2636	0.60
	10.0 (4)	1194	2426	0.49	1227	2642	0.46

Table 3-4. Continued.

		Pellets			Grain		
Subject	Dose (mg/kg)	Pecks	Time (s)	Overall Rate (pecks/s)	Pecks	Time (s)	Overall Rate (pecks/s)
804	Saline (4)	1489	2477	0.60	2137	2641	0.81
	1.0 (4)	1457	2456	0.59	1719	2631	0.65
	3.0 (4)	1225	2487	0.49	1665	2630	0.63
	5.6 (4)	809	2483	0.33	1634	2633	0.62
	7.4 (26)	1156	2478	0.47	1858	2642	0.70
	10.0 (5)	1184	2432	0.49	1948	2650	0.74
	13.0 (5)	1300	2370	0.55	1486	2641	0.56
916	Saline (5)	1907	2480	0.77	2083	2633	0.79
	1.0 (5)	2066	2482	0.83	2318	2636	0.88
	3.0 (4)	2260	2518	0.90	2304	2622	0.88
	5.6 (5)	2286	2506	0.91	2443	2628	0.93
	7.4 (28)	2303	2498	0.92	2815	2628	1.07
	10.0 (5)	1118	2549	0.44	2851	2623	1.09
	13.0 (4)	234	2667	0.09	2628	2625	1.00
8290	Saline (4)	654	2487	0.26	1985	2636	0.75
	1.0 (4)	1979	2465	0.80	2295	2647	0.87
	3.0 (4)	1882	2512	0.75	2610	2633	0.99
	5.6 (5)	1118	2490	0.45	1970	2601	0.76
	7.4 (21)	1390	2501	0.56	1768	2583	0.68
	10.0 (4)	1128	2449	0.46	1674	2587	0.65

All details are the same as in Table 3-3.

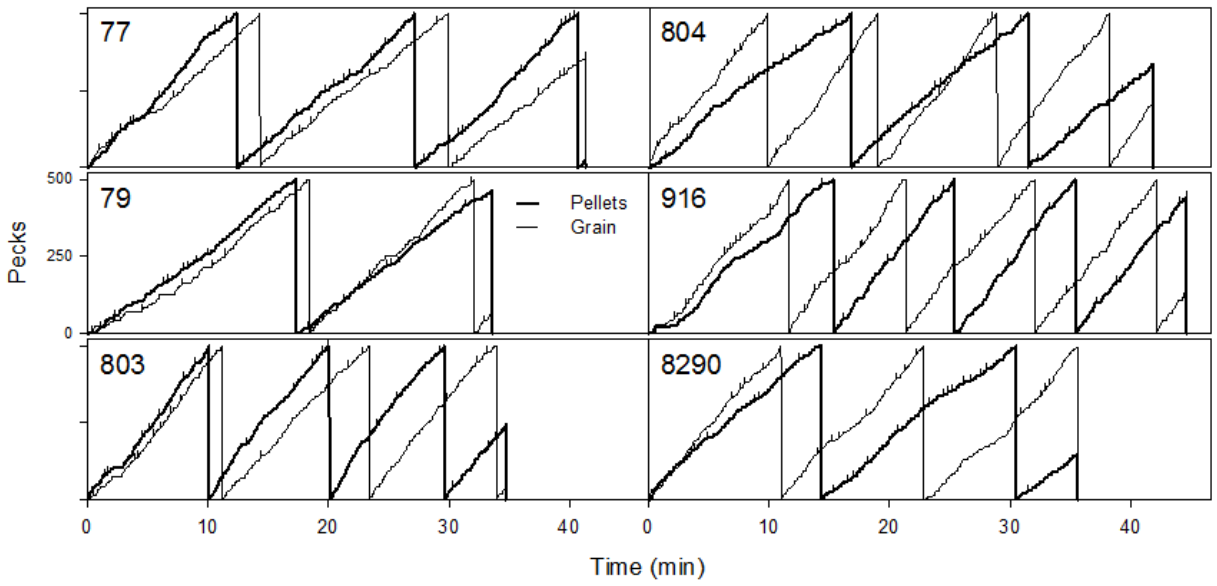

Figure 3-1. Cumulative-response records of key-pecking for each subject during representative saline-administration sessions under the concurrent schedule. Thick and thin lines represent cumulative response counts on the left and center keys, respectively. Pips indicate food presentation; the pen resets every 500 responses.

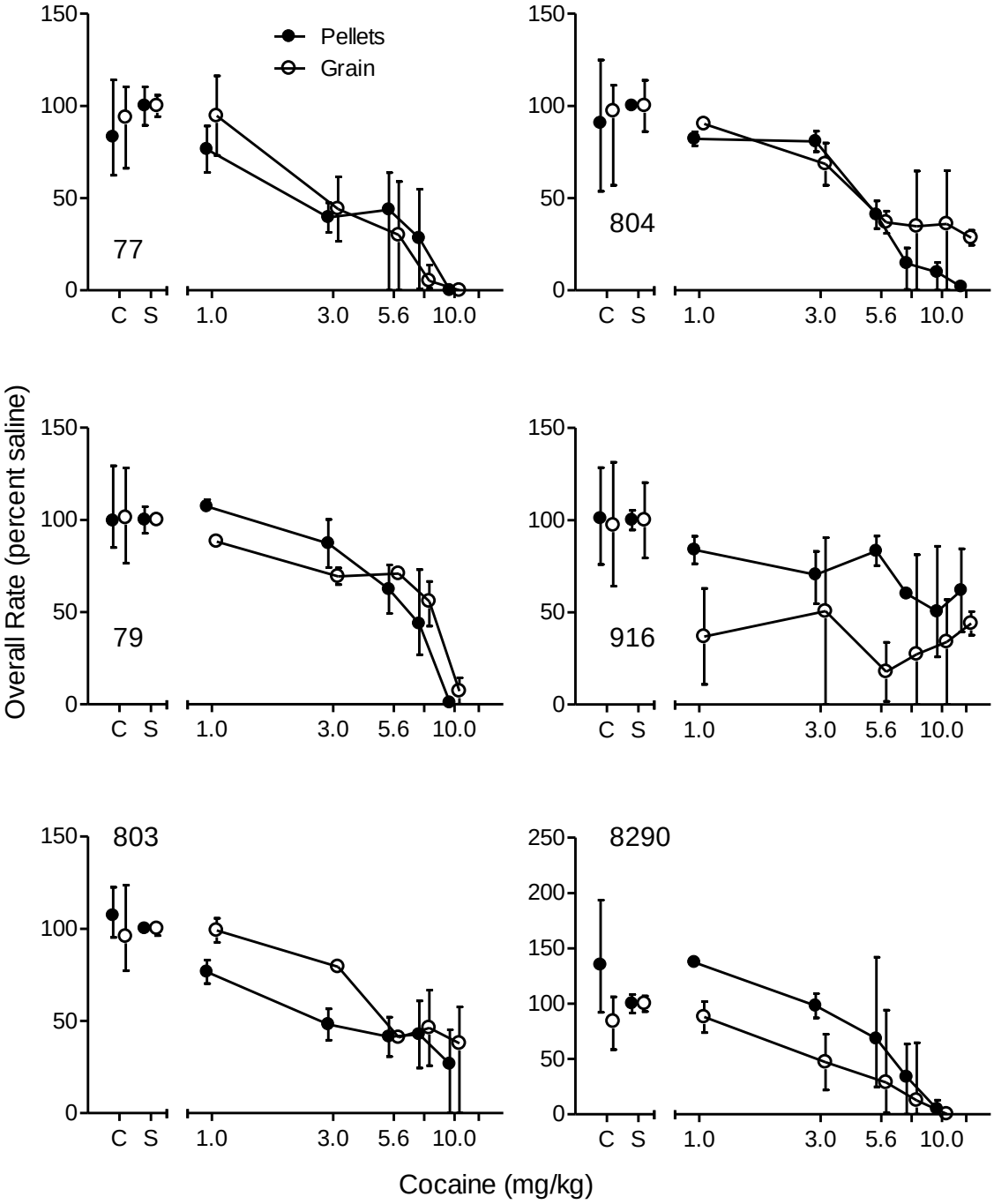

Figure 3-2. Normalized dose-effect curves for overall rate. The mean effect of the drug is plotted as a function of dose. Filled and open circles represent data from the left-key (pellet) and center-key (grain) responding, respectively. Error bars indicate the range.

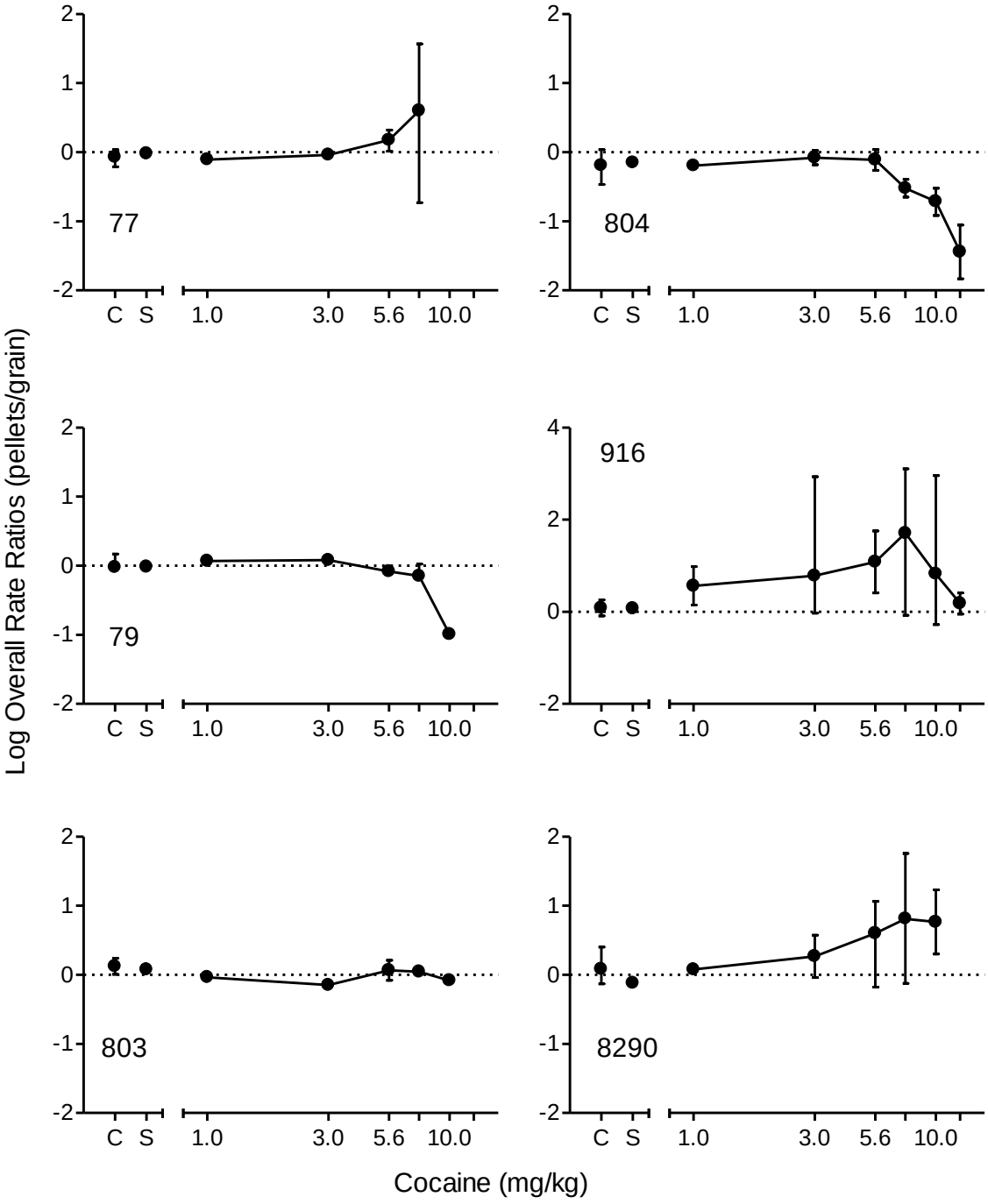

Figure 3-3. Dose-effect curves for log-overall-rate ratios. Each data point represents the mean ratio as a function of dose. Error bars indicate the range.

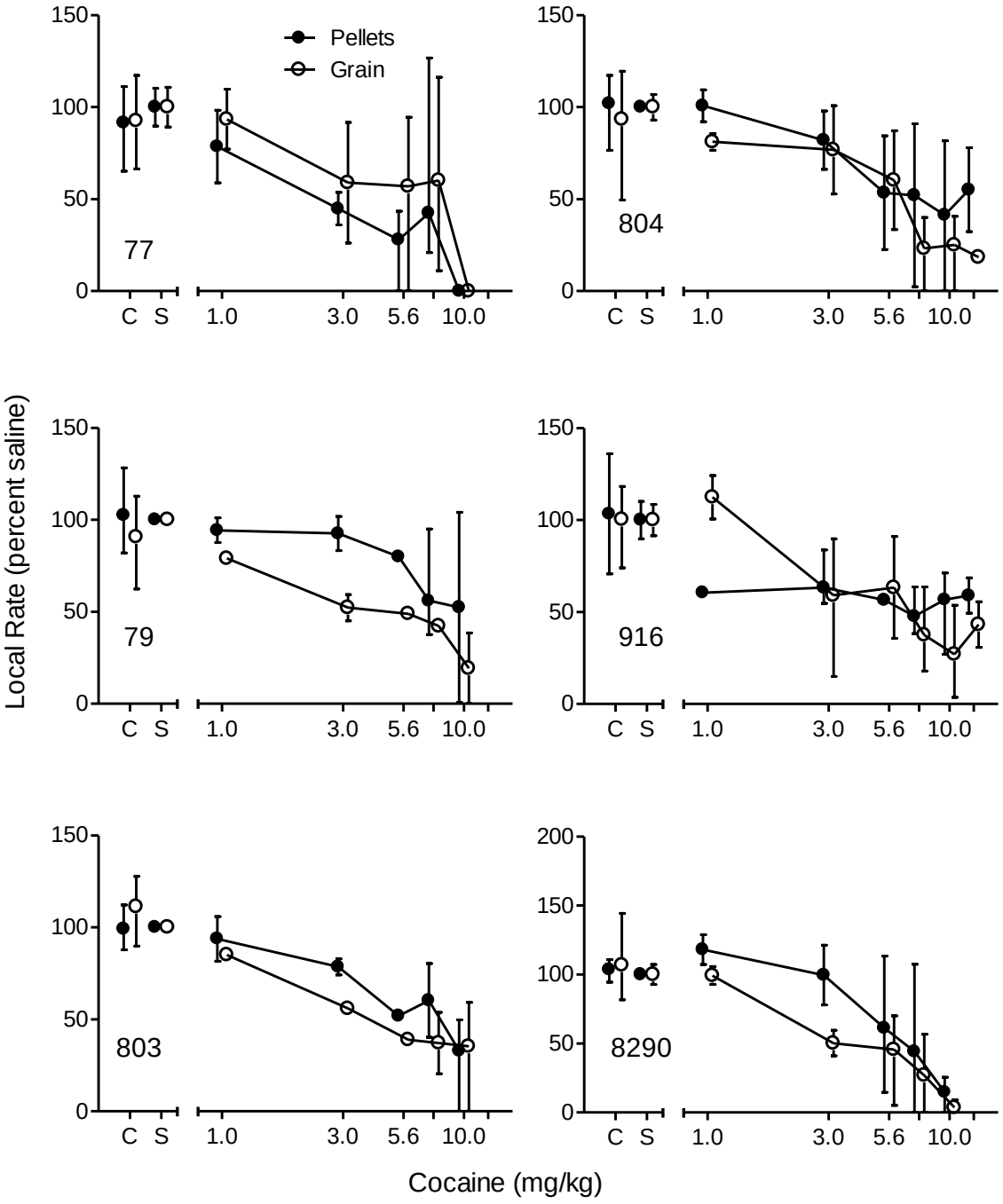

Figure 3-4. Normalized dose-effect curves for local response rates. All details are the same as in Figure 3-2.

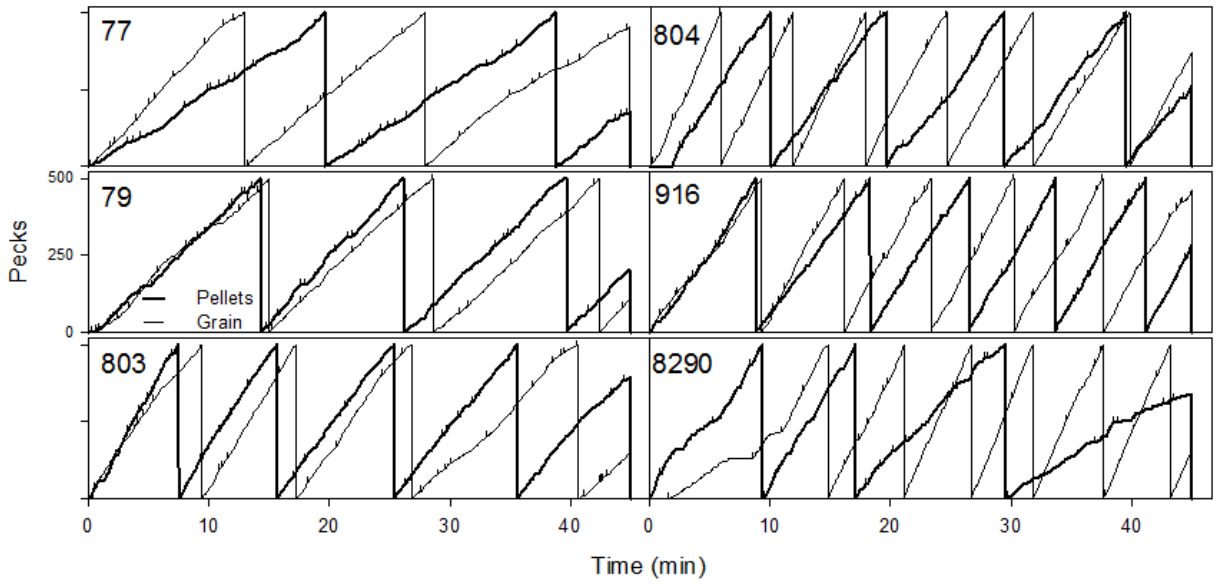

Figure 3-5. Cumulative-response records of key-pecking for each subject during representative saline-administration sessions under the multiple schedule. Thick and thin lines represent cumulative response counts on the left and center keys, respectively. Pips indicate food presentation; the pen resets every 500 responses.

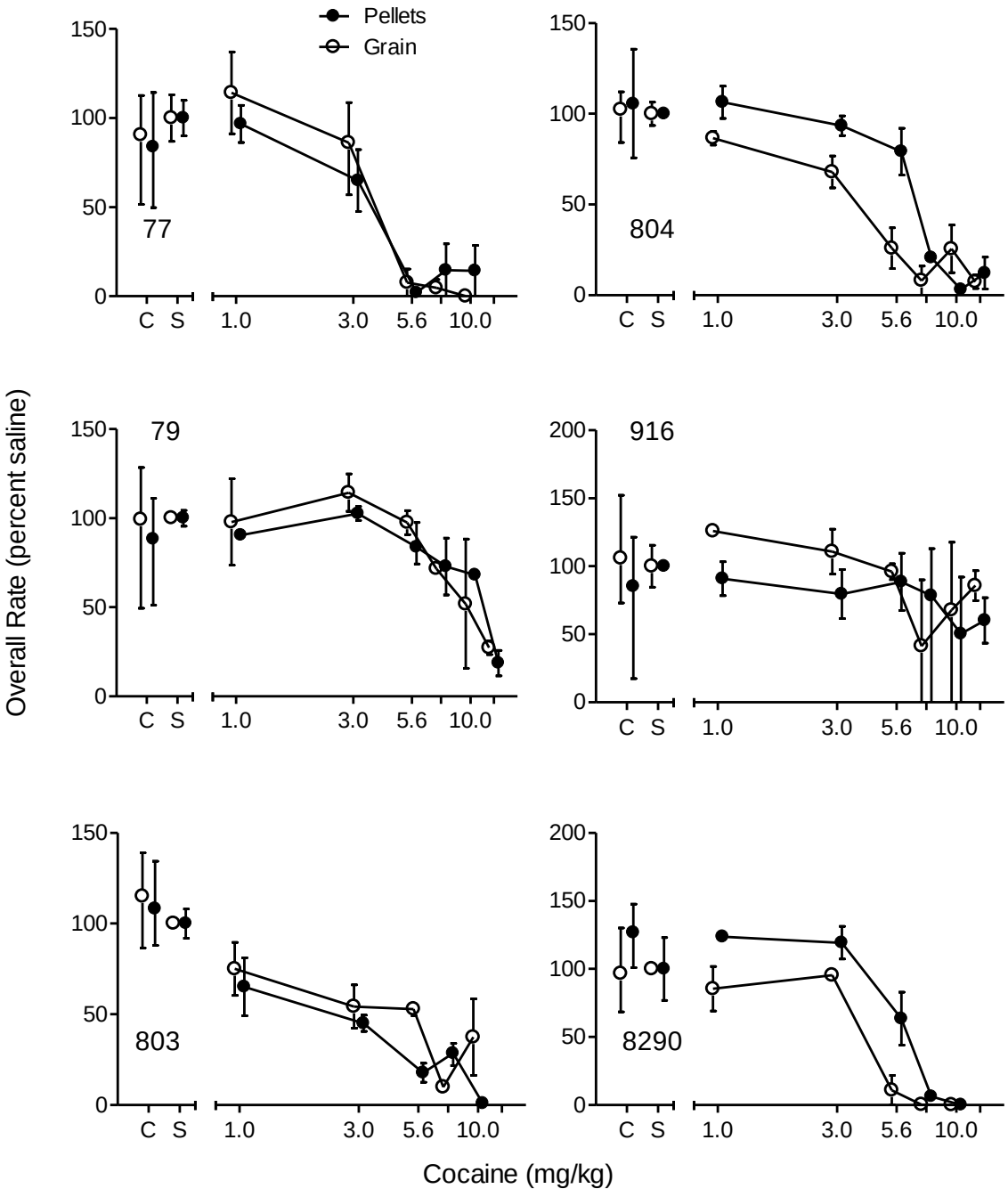

Figure 3-6. Normalized dose-effect curves for overall rates during the acute-administration, multiple-schedule phase. All details are the same as in Figure 3-2.

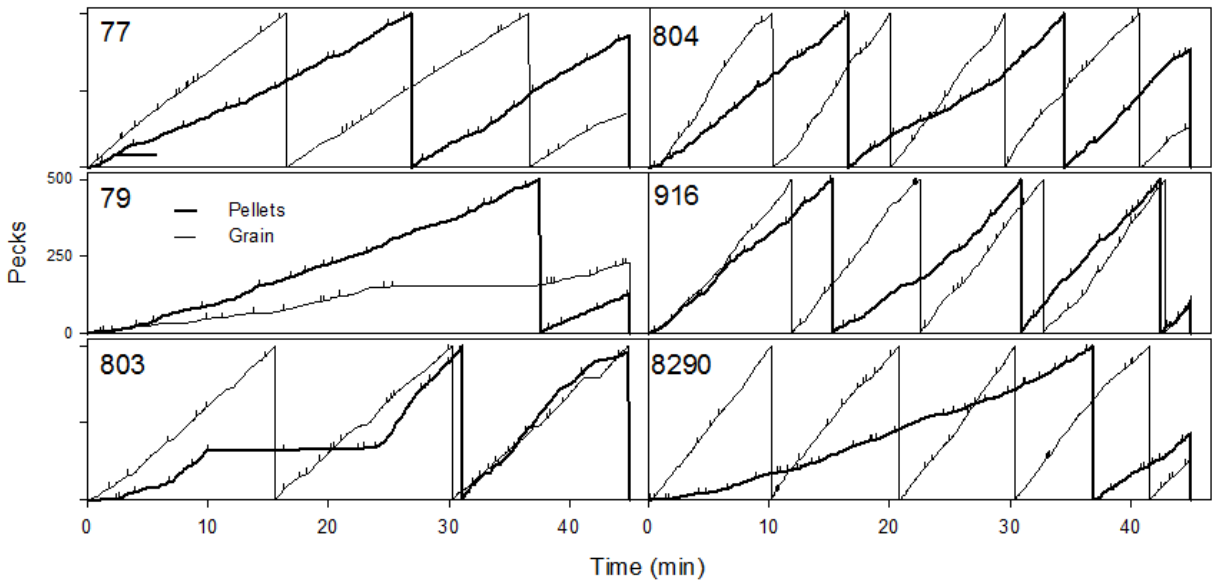

Figure 3-7. Cumulative-response records of key-pecking during representative saline-administration sessions of both session types under the chronic-administration multiple-schedule phase. Thick and thin lines represent cumulative response counts on the left and center keys, respectively. Pips indicate food presentation; the pen resets every 500 responses.

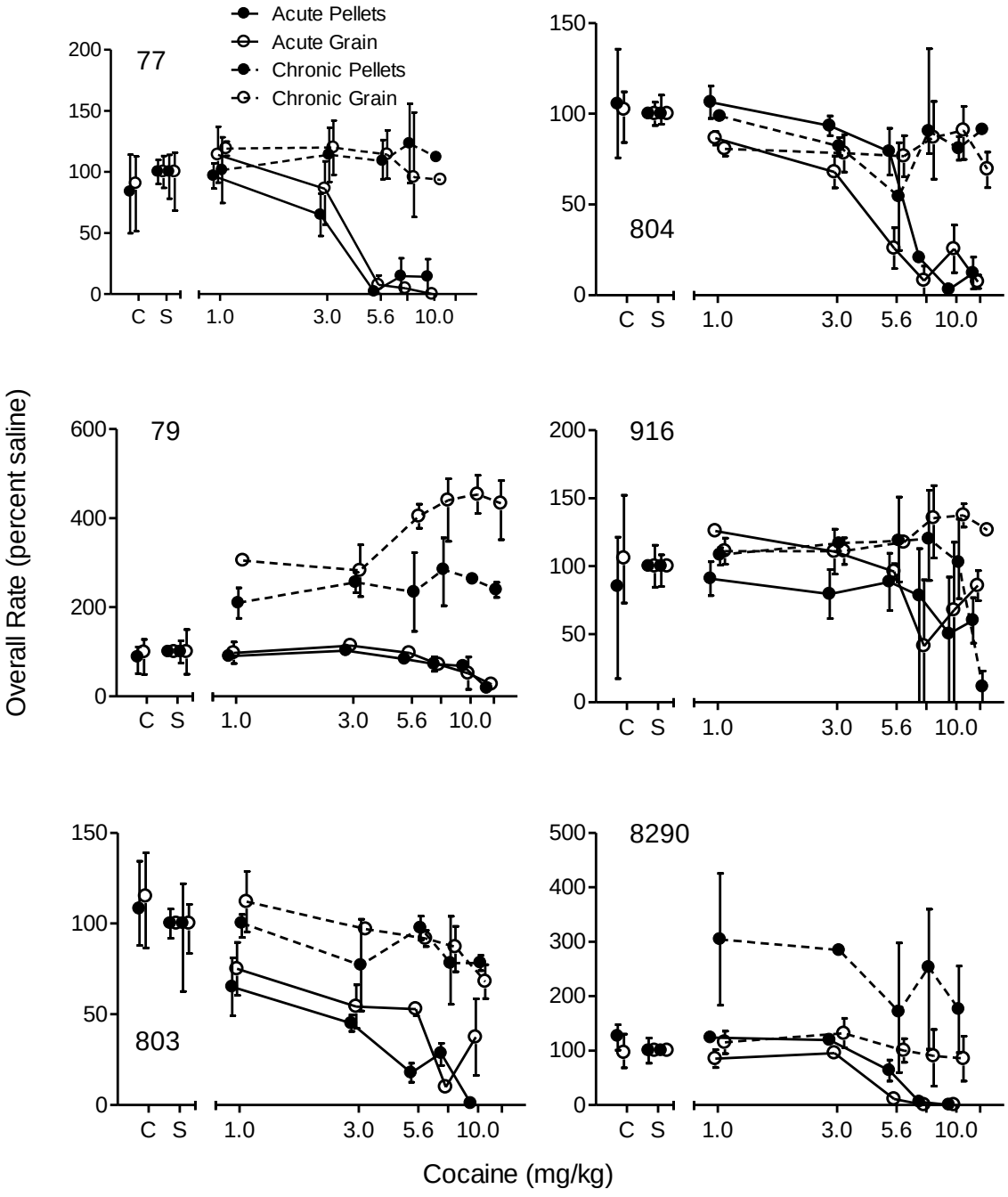

Figure 3-8. Normalized dose-effect curves for overall rates from the acute- and chronic-administration, multiple-schedule phases. Filled and open circles represent data from the pellet and grain sessions, respectively. Solid and dashed lines represent data from the acute- and chronic-administration phases, respectively. Error bars indicate the range.

CHAPTER 4
GENERAL DISCUSSION

The two main purposes of the present research were to examine (1) the putative role of drug-induced changes in reinforcer efficacy in modulating the effects of cocaine on operant responding and (2) the role that these changes might play in the development of tolerance. Whereas research on operant behavior comprises a significant proportion of the research conducted in behavioral pharmacology, and whereas research on operant behavior involves arranging for behavior to be maintained by its consequences, a more in-depth understanding of the role that reinforcement efficacy has in determining the behavioral effects of cocaine will contribute to the rapidly expanding knowledge base in this domain.

Study 1 provided a within-subject comparison of sensitivity of an operant response (key-pecking) to effects of cocaine with sensitivity of feeding. In addition, effects of cocaine on key pecking were compared to effects of another behavioral disruptor, pre-session feeding. Generally cocaine produced dose-dependent disruptions in all measures of responding. After at least 30 sessions of chronic-cocaine administration, effects of the drug were largely diminished in most measures for most subjects, indicating that tolerance to the initial effects of the cocaine on key-pecking and feeding had developed. Comparison of sensitivity across broad response categories (key-pecking versus feeding) to effects of the drug revealed that key-pecking was slightly more sensitive than feeding in some subjects for some measures. Despite the lack of a robust effect, there was a tendency for feeding measures to require larger doses of the drug to produce comparable degrees of disruption.

Pre-session feeding also produced systematic disruptions in responding as well, and the pattern of effects was similar to that produced by cocaine. Response rates were decreased and post-reinforcement pauses were increased. Head-in duration and proportion of head entries were decreased while head-entry latencies were increased. As with cocaine, key-pecking was slightly more sensitive to the effects of pre-session feeding than feeding. Similarities in the pattern of effects across behavioral disruptors taken with the results of previous research (e.g., Schaal & Branch, 1992), suggest that effects of cocaine on rates of operant behavior may be mediated through a modulation of the reinforcing efficacy of food. Moreover, initial observations of differences in sensitivity of key-pecking and feeding to effects of cocaine (see Study 1 Introduction), across subjects and experiments may owe to differences other than a fundamental difference in sensitivity across measures to the effects of cocaine.

If cocaine alters the reinforcer efficacy of food, it stands to reason that food-related behavior in other contexts would also be disrupted. Unpublished observations, however, suggest this is not always the case. For example, one would predict if food consumption was suppressed in the operant chamber due to an effect on the efficacy of food, it would also be suppressed in another feeding context such as the home cage. The generalized suppression of feeding, however, does not often occur in our laboratory when subjects are fed immediately post session. Study 2 was conducted to test a hypothesis about cocaine's apparent context-related effects on feeding.

If cocaine reduces reinforcer efficacy and the effect is observed most robustly in the experimental chamber, then the reduction in efficacy may be mediated through some feature of the experimental chamber. Study 2 was designed to examine the

extent to which the food-hopper mechanism might contribute to the rate-decreasing effects of cocaine. Key-pecking in pigeons was reinforced by either access to mixed-grains available from a solenoid-driven food hopper, or food pellets delivered from a pellet feeder. If cocaine enhanced the aversiveness of food-hopper presentation, it was expected that responding maintained by that food source would be more substantially disrupted than responding maintained by food from the quieter, supposedly less aversive pellet dispenser. Cocaine produced dose-dependent decreases in response rates when administered acutely under two different procedures that differed with respect to which of the two foods were available. After chronic-cocaine administration, the rate decreases were largely diminished demonstrating the development of tolerance. Neither the acute or chronic effects of cocaine appeared to be related to the source of food maintaining behavior, suggesting that the food-delivery mechanism did not play a substantial role in mediating effects of cocaine on key-pecking.

The results of the two studies taken together lead to some general conclusions. Effects of cocaine on feeding are very similar to effects on key-pecking under the circumstances arranged in the current studies. Effects of cocaine on responding in general are very similar to effects of pre-session feeding on responding. Tolerance to the acute effects of the drug can develop after repeated exposure and occurs across a wide range of responses and conditions. Effects of cocaine generally were not mediated by differences in food source or food type.

This research extended upon previous research in a number of ways by (1) providing additional data about effects of cocaine on feeding in pigeons, an area of research largely neglected in behavioral pharmacology, (2) examining effects of cocaine

on key-pecking and feeding within subject, thus providing a more rigorous comparison of sensitivity of different behavioral measures to the effects of cocaine, (3) demonstrating the potential benefit of measuring effects of independent variables on multiple responses in the experimental context, (4) providing an analytical model for comparing sensitivity of responding to the effects of independent variables across multiple response measures, (5) examining effects of cocaine on responding maintained by different food types and sources in pigeons, also an area of research that has not received substantial attention, and (6) comparing drug effects across experimental procedures.

Moreover, this research represents progress toward one of the primary goals of behavioral pharmacology, identifying the behavioral mechanisms of drug action (Branch, 1991; Thompson & Schuster, 1968). The present research contributes to an important field of inquiry, behavioral pharmacology, that will continue to contribute to the understanding of the behavioral effects of psychoactive substances and will also contribute to the discovery of treatments for substance abuse. Cocaine is but one psychoactive substance that is highly addictive and frequently abused. The results of drug use can have devastating effects at both the individual and societal levels. A more in-depth understanding of the behavioral effects of drugs can contribute to the assessment and treatment of substance-abuse disorders which are increasingly viewed as behavioral phenomena (e.g., see Branch, 2011; Heyman, 2009).

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BIOGRAPHICAL SKETCH

David Richard Maguire was born in 1981 in Sanford, North Carolina. After graduating from Lee County Senior High School in 1999, he went on to earn his BA in psychology in December 2003 and his MA in psychology in May 2007 from the University of North Carolina Wilmington (UNCW). While an undergraduate student at UNCW, he began working in a behavioral pharmacology lab with his undergraduate and graduate mentors, Drs. Raymond C. Pitts and Christine E. Hughes, and took a serious interest in behavior analysis and behavioral pharmacology. Because of these experiences, he decided to continue his graduate career at the University of Florida with Dr. Marc N. Branch. His ultimate career goal is to obtain a faculty position at a research or academic institution and continue conducting research in behavior analysis and behavioral pharmacology. A more proximate goal, following completion of his PhD, will be to continue training at the post-doctoral level.