6-2007

Behavioral Tolerance under Variable Ratio Schedules of Reinforcement

Barry Eshkol Adelman
Western Michigan University

BEHAVIORAL TOLERANCE UNDER VARIABLE-RATIO SCHEDULES OF REINFORCEMENT

by

Barry Eshkol Adelman

A Disseration
Submitted to the
Faculty of the Graduate College
in partial fulfillment of the
requirements for the
Degree of Doctor of Philosophy
Department of Psychology

Western Michigan University
Kalamazoo, Michigan
June 2007

BEHAVIORAL TOLERANCE UNDER VARIABLE-RATIO SCHEDULES OF REINFORCEMENT

Barry Eshkol Adelman, Ph.D.

Western Michigan University, 2007

Previous studies (e.g, Hoffman, Branch, & Sizemore, 1987) have demonstrated that greater drug tolerance develops in responding under fixed-ratio (FR) schedules of reinforcement when the schedule parameter is small than when it is large; little research has been done on related schedules such as variable-ratio (VR). In Experiment 1, three pigeons responded under a multiple FR 5 FR 125 VR 5 VR 125. A range of prechronic doses of cocaine produced dose-dependent reductions in response rates under the component schedules. Following chronic dosing with daily administrations of 5.6 mg/kg, similar dose-response curves were derived by substitutions of the usual dose. In Experiment 2, the procedure was similar but the chronic dose was adjusted to ensure reductions of response rate and reinforcers earned within the range of doses tested. Dose-response curves were similarly derived following chronic dosing with daily administrations of a dose that initially produced substantial decreases in responding and reinforcement. The results replicated earlier findings for FR, with less tolerance under the larger response requirement than the smaller. Tolerance under VR schedules was similar to that under FR schedules of the same schedule parameter. These results favor the response strength hypothesis, which posits greater recovery in situations associated with greater reinforcement rate. Directions for future research on tolerance are discussed.

ACKNOWLEDGMENTS

I would like to thank the following individuals for their help and assistance in the writing of this dissertation: Nancy Ann Adelman, for her support and efforts to keep me on track; Dr. Saul Joseph Adelman and Carol Jeanne Adelman, for supporting me throughout my schooling; Dr. Alan Poling, for his help, guidance, amazing patience, and feedback, and for his efforts as part of my graduate committee; Drs. Lisa Baker, Cynthia Pietras, and Steve Ragotzy, for their efforts as part of my graduate committee; Matthew Porritt and Adam Rapp, who helped with running this study and without whose help I would have never been able to do this study; and Elizabeth Ann Whitlock and Nicholas Alexander Whitlock, for being understanding and letting me get some writing done. I would also like to thank previous researchers in the field whose work has provided a basis for this study, especially Sandra H. Hoffman, Marc N. Branch, and Glen M. Sizemore who first used the research paradigm that appears here in modified form. Finally, I would like to thank my subjects for generously giving of their time and efforts, without which this study would have been impossible.

Barry Eshkol Adelman

TABLE OF CONTENTS

Table of Contents—continued

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Behavioral Tolerance

Drugs are substances that, in relatively small amounts, have effects on an organism. Although physiological effects are often of interest, these effects may also be behavioral. For example, administering cocaine not only may produce vasoconstriction, tachycardia, and hypertension, but also increased motor activity and private experiences of euphoria and delusions. Evaluating the behavioral effects of drugs is complicated as they may be influenced by dose and prior exposure to the drug. *Tolerance* is often defined as a reduction in drug effects with repeated exposure to a drug (e.g., Goudie & Demellweek, 1986), sometimes with the additional requirement that the original level of effect can be achieved by an increased dose (e.g., LeBlanc, Poulos, & Cappell, 1978). Thus, in the above example, a given dose of cocaine that initially results in a certain level of increased motor activity may, after several administrations, produce less of an increase in motor activity. Some prefer to define tolerance in terms of a rightward shift in the dose-response curve rather than by a change in response at a particular dose (e.g., Dews, 1978), although there are instances of reductions in responding at particular doses without such a shift (e.g., Branch, 1979). The phenomena in which changes in the magnitude of drug effects are important include drug addiction and dependence, in which

performance may be affected by previous history (Weiner, 1981) and may involve drug tolerance (e.g., Siegel, 1984). Furthermore, although the terminology for abuse and dependence is inconsistent, tolerance has been identified as a component of or equated with drug dependence, an important factor in drug addiction (e.g., Brady et al., 1987). Some authors (e.g., Corfield-Sumner & Stolerman, 1978) have also expressed interest in the phenomenon because of its relation to other topics of interest, such as the development of effects of medications over time (e.g., antidepressants) and for understanding homeostatic or physiological mechanisms. Hence, factors that affect tolerance have become an important research topic.

Tolerance is not necessarily a simple reaction to drug exposure, but may be affected by several variables. For example, in a typical operant paradigm, a laboratory animal (usually a rat or a pigeon) can freely respond on a manipulandum (pressing a lever or pecking a key); responding is maintained by a contingency related to the responding (such as lever-pressing or key-pecking resulting in the animal getting access to food). If the animal is given a dose of a drug that ordinarily has rate-reducing effects, the animal's response rate will initially decrease, but after several administrations, the animal's response rate will move closer to predrug levels (*baseline*). Suppose at the same time another animal, similarly trained, is given the drug but is not given the opportunity to respond thusly; if this animal is given a chance to respond, several sessions later, the animal's response rate will be much lower (it will show less tolerance) than one which had the previous opportunities to respond (cf. Chen, 1968; Harris & Snell, 1980). Although use of the term at times is inconsistent (cf. Krasnegor, 1978), tolerance that

depends on the subject's exposure to the drug during responding is often called *behavioral tolerance*.

Tolerance has been examined in several experimental contexts. Many early studies investigated the effects of drugs on reactions to aversive stimuli, with inferences being made of the subjects' private experiences (e.g., D'Amour & Smith, 1941); such "hot plate tests" have been criticized, however, as the overt behavioral measures being used (e.g., latency to removing foot from a hot plate) may be affected by factors other than the subject's private discomfort, such as reinforcement schedule (Corfield-Sumner & Stolerman, 1978). In many early studies using behavioral measures, tolerance was sometimes found (e.g., Himmelsbach, Gerlach, & Stanton, 1935; Macht, 1939; Macht, 1947) but often not (e.g., Searle & Brown, 1938; Simon & Eddy, 1935). Studies eventually used more systematic, controlled, but nevertheless varied paradigms. Of those using a respondent conditioning context, one of the more important was Siegel et al.'s (1982) study of heroin tolerance. Treatment rats were injected with heroin and dextrose on alternate days, with the dose of the heroin gradually increased from 1 to 8 mg/kg, while a group of control rats was given injections of dextrose only. For the last injection, all rats were given 15 mg/kg of heroin. Some of the treatment rats received this last dose in the same environment they received the previous injections, whereas other treatment rats received it in a different environment. In the former treatment group, only 32% of the rats died, whereas in the latter, 64% of the rats died. This indicated that the environment where the drug was injected acted as a cue influencing drug effect. Some studies have supported the generality of such findings to tolerance in the natural environment. For example, Siegel (1984) also found a similar relationship in people who

survived heroin overdoses, the majority having taken the drug outside of their usual drug-taking environment and thus lacking the usual cues thought to elicit responses that control the activity of the drug.

A considerable amount of research has examined behavioral tolerance in operant contexts. Much of this research has demonstrated that the tolerance demonstrated by a behavioral measure is in part a function of the schedule of reinforcement for the behavior. Dews (1955) first investigated drug effects on behavior using an operant chamber, setting the basis for modern behavioral pharmacology. This study examined the effects of phenobarbital on performance under a fixed-interval (FI; Ferster & Skinner, 1957, pp. 133ff., 727) schedule of 15 min versus under a fixed-ratio (FR; op. cit., pp. 39ff., 727) of 50. The effects of the drug on response rate varied with the schedule; under FR 50 there was no change or an increase in response rate, whereas under FI 15-min, the response rate decreased.

While some studies have been done which only examine performance under a single schedule (e.g., Schuster and Zimmerman's [1961] study of the effects of *dl*-amphetamine on performance under a single differential reinforcement of low rate [DRL; Ferster & Skinner, 1957, pp. 33, 726] schedule), the general trend has followed Dews (1955) in making comparisons across schedules. For example, Heifetz and McMillan (1971) examined the effects of morphine and methadone on performance under a multiple (mult; Ferster & Skinner, 1957, p. 503ff.) FR FI schedule. Not only were differences found in the development of tolerance to different drugs, but also to the same drug under different component schedules; in this case, greater tolerance was observed in the FI component than the FR component. The general rationale for such studies is to

compare responding under different kinds of contingencies of reinforcement, time-based versus number-based. Comparisons have also been made by keeping the schedule identical but varying the consequences. For example, Branch (1979) examined tolerance to *d*-amphetamine in squirrel monkeys under a multiple schedule; each component of the multiple schedule was FI 5-min with a different consequence: access to food (positive reinforcement), electric shock (positive punishment), or escape from electric shock (negative reinforcement). Here tolerance to the effects of *d*-amphetamine developed under the reinforcement components but not the positive-punishment component.

A few studies have also investigated the parameters of a schedule as a possible influence. For example, Schama and Branch (1989) investigated the effects of cocaine on responding under a mult FI 5-s FI 30-s FI 120-s schedule. Responding recovered under chronic administration but there were no systematic differences in response rate across time parameters. Similar results have been found even when a tandem (Ferster & Skinner, 1957, pp. 415ff., 733) FR 5 requirement has been added to the component schedules (Pinkston & Branch, 2004b); this was despite the schedule producing a pattern of responding and pausing resembling that under FR. Branch (1990) also studied the development of tolerance to cocaine under random-interval (RI; Millenson, 1963) schedules, in which the interval durations vary and thus do not produce the same pattern of responding as under FI schedules; nevertheless, little relationship between response rate and tolerance was found. However, similar results have not been found with ratio schedules.

Tolerance under Fixed-Ratio Schedules

When FR schedules of different response requirements are compared, a consistent result has been that responding under smaller requirements develops greater tolerance than under larger requirements. For example, Smith (1990) had rats responding on either an FR 10 or FR 40 schedule exposed 0.1 mg/kg of clonidine for 30 daily sessions. Whereas the FR 10 rats' response rate returned to baseline levels during chronic administration, the recovery of the FR 40 rats' response rate was incomplete. Similarly, Genovese, Elsmore, and Witkin (1988) reported greater tolerance developed during chronic administration of 0.4 mg/kg physostigmine under a mult FR 10 EXT than under a mult FR 50 EXT. In a more elaborate study, Smith (1986b) administered 0.03 mg/kg of *l*-nantradol to pigeons under either an FR 100 or FR 300 schedule; tolerance to the rate-decreasing effects of the drug developed much faster under FR 100 than under FR 300. When the schedule was changed from FR 100 to FR 300, there was a decrease in tolerance over a few sessions; a similar increase occurred in subjects in which the schedule was changed from FR 300 to FR 100.

This phenomenon was first examined in a within-subject comparison by Hoffman et al. (1987), who exposed pigeons to a mult FR 5 FR 25 FR 50 or a mult FR 5 FR 25 FR 125 schedule. Acute administrations of cocaine reduced response rate in all components, but under chronic administration, there was substantial recovery of response rate (tolerance) in the FR 5 component, little recovery in the FR 125 component, and an intermediate amount in the FR 25 component. Several studies have since used a similar

procedure (termed here the *mult-FR paradigm*) to study tolerance as a function of response requirement. For example, Nickel and Poling (1990) did a similar study, using heroin instead of cocaine, and found the same relationship between response requirement and tolerance.

Several studies have investigated aspects of the mult-FR paradigm as possible influences on the differential effects of response requirements on tolerance. van Haaren and Anderson (1994) did a similar study in rats using cocaine over a wider range of doses; this study generally replicated the earlier results. Nickel et al. (1993) investigated the role of context on the development of tolerance by running pigeons under FR 5, FR 25, or FR 125 alternating sessions with mult FR 125 FR 250. Tolerance was found under FR 5 but little was found under FR 125, regardless of whether alone or in the multiple schedule. (This result is in contrast with those of Smith [1986a], in which context was important to determining whether or not tolerance was found under a DRL component.) Hughes et al. (2005) noted that in a typical FR schedule, the "unit price" (amount of responding per reinforcer) was not constant across response requirements; they examined tolerance to morphine in pigeons under a modified mult-FR paradigm in which the time the hopper was up during reinforcement was adjusted to be proportional to the response requirement in effect. Under these conditions, the patterns of tolerance were similar to those reported with unequal unit prices. Yoon and Branch (2004) found similar results in a similar study using cocaine.

Antecedents are also important determinants of tolerance. When distinctive discriminative stimuli for each component or ratios within components are not present, tolerance is generally equal across response requirements. For example, Jarema et al.

(1999) utilized a progressive-ratio (PR; Hodos, 1961) schedule, which resembles an FR schedule but in which the response requirement increments every trial (e.g., a PR 25 might begin with a ratio of 25, then 50, 75, etc.); no stimulus that correlates with the size of the current requirement is present. Jarema and colleagues administered chronic doses of morphine that initially eliminated most responding to pigeons responding under a PR 25 schedule; comparable tolerance nevertheless developed in the FR 25 and FR 100 components. A similar investigation has been done using mixed (mix; Ferster & Skinner, 1957, pp. 580ff., 729) schedules, which incorporate two separate response requirements mixed in the same component. Poling et al. (2000) investigated tolerance to cocaine and morphine under a mult (mix FR 5 FR 95) (mix FR 25 FR 75) (mix FR 50 FR 50) schedule, thus equalizing the rate of reinforcement associated with each discriminative stimulus, and found no systematic relationship between response requirement and tolerance.

The dosing regimen itself has also been investigated as a possible factor. Howell and Morse (1989) administered cocaine to squirrel monkeys continuously rather than in relationship to the sessions; tolerance failed to develop. Krank, Hinson, and Siegel (1984) compared tolerance to morphine when the drug was paired with environmental cues every time versus when it was paired once every four times; less tolerance developed under the latter circumstances. Yoon and Branch (2004) investigated a dosing regimen that varied between administrations instead of being "fixed" as in the usual mult-FR paradigm. Under the variable dosing regimen, tolerance failed to develop in all components regardless of whether or not amount of reinforcement was adjusted for unit price. These results suggest that the drug acts as an antecedent or contextual variable in

the development of tolerance, as any weakening of the relationship between drug dose and the experimental situation results in reduced tolerance. Citing studies where stimuli related to drug administration failed to become conditioned eliciting stimuli (e.g., Demellweek & Goudie, 1983), Wolgin (1989) suggested that tolerance involves drugs developing a discriminative function; the generality of this suggestion may be limited, as there is evidence for such an eliciting function in some paradigms, particularly when postsession administration is involved (e.g., Foltin & Schuster, 1982; Pinkston & Branch, 2004a; Woolverton, Kandel, & Schuster, 1978). For example, Pinkston and Branch (2004a) tested pigeons on a mult FR 5 FR 100 schedule in which responding during sessions was affected by the dose of cocaine administered afterwards; specifically, large doses (10.0 to 23.0 mg/kg) suppressed responding during sessions whereas tolerance developed under smaller doses. These results were interpreted as indicating session-related stimuli were acting as a conditioned stimulus for the drug.

CHAPTER II

UNDERSTANDING BEHAVIORAL TOLERANCE

The studies summarized above clearly show that smaller FR requirements produce more drug tolerance than larger requirements; why this is the case is not clear. To make sense of these data, researchers have attempted to identify *behavioral mechanisms of action*, stimulus functions of drugs and effects of drugs on the functions of other stimuli (Thompson, 1981). By identifying mechanisms by which drugs affect behavior, it is hoped to derive a better understanding of drug-affected behavior. The degree to which actual mechanisms are identified is debatable, and some have found the hypotheses described below weak or insufficient (e.g., Wolgin, 1989).

Reinforcement-Loss Hypothesis

One hypothesis advanced to explain differences in tolerance under different schedules is the *reinforcement-loss hypothesis*, also called the *density hypothesis* by Corfield-Sumner and Stolerman (1978). The hypothesis was originally advanced by Schuster, Dockens, and Woods (1966), who examined tolerance to *d*-amphetamine under a mult FI DRL schedule in rats. One acute effect of *d*-amphetamine was to increase response rate, with the increase being positively related to the dose (though the relationship was more complex in one subject). Across sessions under chronic dosing of 1.0 mg/kg *d*-amphetamine, the response rate under the FI component remained high, and

remained so in a postchronic assessment of the dose-response curve. However, during the DRL components under chronic dosing, the response rate across sessions gradually *decreased*, and in the postchronic dose-response curve the response rate remained low across doses. Thus while little or no tolerance developed to *d*-amphetamine in the FI component, tolerance was evident in the DRL component. These differences were associated with changes in the reinforcement rate; whereas the reinforcement rate in the FI component generally showed little change regardless of whether drug was administered or not, under the DRL component there was a drop in the reinforcement rate under chronic exposure which gradually recovered over sessions. Schuster and colleagues suggested that for tolerance to develop, the drug would have to interfere with the subject performing the requirements for reinforcement; drug exposures that did not so impair the subject's performance would not produce tolerance.

A full review of the reinforcement-loss hypothesis is beyond the scope of this work. Previous reviewers (e.g., Corfield-Sumner & Stolerman, 1978; Wolgin, 1989) have noted that, while some studies support this hypothesis, the evidence overall is mixed. Because the hypothesis posits that decreases in reinforcement associated with the drug are necessary for tolerance, it becomes less tenable when these events do not co-occur. Some notable studies have been done, often using FI schedules, in which there is no increase in reinforcement rate after the response rate reaches a certain level. For example, Schama and Branch (1994) noted the development of tolerance to the rate-increasing effects of cocaine on FI-schedule performance; because there was little change in reinforcement rate, no tolerance would be expected to develop according to the reinforcement-loss hypothesis. Schama and Branch's (1989) parametric study found no

systematic relationship between the duration of the interval in FI schedules and tolerance, again contrary to the hypothesis. Studies have also investigated the development of tolerance when the rate of reinforcement actually increases. Miller, Brodkorb, and Branch (2001) used a correlated FI schedule, in which reinforcer magnitude was systematically related to the amount of responding in the interval; against the prediction of the hypothesis, tolerance developed even when the acute effect of the drug was to increase the response rate and the reinforcement rate accordingly. Although several studies using FI schedules with initial increases in reinforcement frequencies failed to find tolerance (e.g., Cassens et al., 1981; Kuribara, 1980; Liebman & Segal, 1976), these often have involved negative reinforcement or positive reinforcement by electrical brain stimulation rather than positive reinforcement by food.

With regards to the mult-FR paradigm, Hoffman et al. (1987) noted that under the large-ratio component there was a decrease in reinforcement rate during chronic administration, but little tolerance occurred. According to the reinforcement-loss hypothesis, greater tolerance should be found under large-ratio component (which experiences the largest reinforcement loss) than under the small-ratio component (which experiences the least), precisely the opposite of what is actually observed. However, the amount of reinforcement that can be earned is in part determined by the schedule; at a given response rate, the amount earned per unit time under an FR schedule is inversely related to the schedule's response requirement. Nickel et al. (1993) suggested this potential confound could be resolved by equalizing reinforcer availability across different response-requirement values. Yoon and Branch (2004) and Hughes et al. (2005), by making duration of reinforcement proportional to response requirement, did so; as noted

previously, adjusting reinforcement duration this way did not equalize tolerance across response requirements.

Response-Strength or Behavioral-Momentum Hypothesis

An alternative to the reinforcement-loss hypothesis mentioned by Hoffman et al. (1987) is based on Nevin's (1974, 1979) conceptualization of response strength. Whereas Skinner (e.g., 1953, p. 65) conceptualized response strength primarily in terms of rate or probability, Nevin used the term to refer to the persistence of behavior despite changing conditions (cf. Hull, 1943, pp. 260-262), which he related to the reinforcement rate experienced by the subject before the change; this is the same conceptualization Nevin and colleagues later elaborated into the concept of "behavioral momentum" (Nevin, Mandell, & Atak, 1983). Although the difference in how the term is used by Skinner and by Nevin is confusing, the latter's is relevant to explaining tolerance under ratio schedules. For any given response rate, the rate of reinforcement will be inversely related to the schedule parameter; that is, smaller response requirements will produce denser reinforcement rates than larger requirements. Hence, the difference in behavioral tolerance across different components of a mult FR schedule may reflect the reinforcement rates and hence the "response strengths" of the different components, with greater "strength" leading to greater recovery (tolerance) when a disruptive condition (drug) is presented. Sizemore and colleagues were cautious in advancing this explanation, however, noting a study (Cohen, 1986) which examined resistance to change in compound schedules; whereas the behavioral-momentum hypothesis predicted the

least resistance in the initial link of a chain schedule and in the leanest schedule in a multiple schedule, these results were not consistently found when several drugs were tested. Studies where "unit price" for reinforcers is equalized by making reinforcer duration to the response requirement (Hughes et al., 2005; Yoon & Branch, 2004) would also be predicted to equalize tolerance across different response requirements; nevertheless, this manipulation did not have such an effect. However, the hypothesis has been invoked to explain certain results involving antecedent manipulations. Poling et al. (2000) noted it was consistent with their data from a multiple schedule with components consisting of mix FR FR schedules, the FR subcomponents varying between components but overall having identical reinforcement rates; tolerance to cocaine and morphine were similar across components. As the discriminative stimuli for the different components were associated with the same rate of reinforcement, the resistance of behavior to change (and recovery) in each component was also similar.

As with the reinforcement-loss hypothesis, not all data can be accounted-for with the response-strength hypothesis. As noted by Poling et al. (2000), there are findings it does not account for, such as the comparable levels of tolerance that occur under interval schedules of different durations (Branch, 1990; Pinkston & Branch, 2004b; Schama & Branch, 1989).

Purpose

There are many different kinds of possible schedules, but only a few have been investigated to any extent with regards to tolerance. A variant of the FR schedule, the

variable-ratio (VR; Ferster & Skinner, 1957, pp. 391ff., 734) schedule, is similar to FR except the response requirement changes each time a reinforcer is earned. The patterning of responding over time is different in FR and VR schedules; both are characterized by high rates of responding (op. cit., pp. 39, 391), but in responding under FR, there is a characteristic pattern of pauses after runs which end in reinforcement, whereas VR responding is much more steady (op. cit., p. 391). Furthermore, VR responding is much less liable to demonstrate *ratio strain*, large pauses in responding that may develop under FR responding with large response requirements (Catania, 1998, p. 168; cf. Ferster & Skinner, p. 518).

No studies of tolerance under VR schedules have so far have been made, though one study (Branch, 1990) has investigated random-ratio (RR; Millenson, 1963) schedules, in which there is a set probability of reinforcement for each response rather than a number set for each trial (that is, a MR schedule with a very large number of component ratios). Branch compared the development of tolerance to cocaine under a multiple schedule with three RR components, the probabilities set to produce the same ratio of reinforcements to responses as in FR 5, FR 25, and FR 125 components (cf. Hoffman et al., 1987). As with the mult-FR paradigm, the amount of tolerance was inversely related to the richness of the schedule component.

The overall relationship between response rate and reinforcement rate under VR and FR schedules is identical; that is, for any given response requirement, if the response rate on a VR and an FR are the same, the rate of reinforcement over time will also be the same. Relatively molar hypotheses such as the reinforcement-loss and the response-strength hypotheses would both thus predict that VR schedule-controlled behavior would

develop tolerance similar to that of FR schedule-controlled behavior. However, VR schedules produce very different patterns of behavior over time than FR schedules, producing relatively high, steady responding rather than a cycle of runs and pauses. It should be noted that the schedules often used to study tolerance (e.g., FR, FI, DRL) often produce cycles of increases and decreases in responding rather than steady responding. Picker et al. (1982) found that under automaintenance (cf. Brown & Jenkins, 1968; Williams & Williams, 1969) and discrete-trial FR 1 procedures (which produced regular patterns of responding), response rates under chronic dosing with morphine recovered. These same authors also examined the development of morphine tolerance under a negative-automaintenance procedure (Williams & Williams, 1969), which combines the fixed-time presentations of an antecedent stimulus and a reinforcing stimulus with a negative-punishment contingency for the same reinforcing stimulus ("response cost"); this contingency is disruptive to regular responding, and little or no tolerance developed. If the temporal patterning of behavior has any relationship to tolerance, then one might expect a VR schedule to not engender the same levels of tolerance an FR schedule does. Although the overall pattern of tolerance may be similar between FR and VR performances (cf. Hoffman et al., 1987, vs. Branch, 1990), the comparison is being made across different subjects undergoing similar but not necessarily identical procedures; thus it cannot be inferred that with similar parameters these schedules would necessarily produce similar levels of tolerance. The purpose of these experiments is to compare the development of behavioral tolerance under FR and VR schedules within the same individual.

CHAPTER III

EXPERIMENT 1

The most direct approach meeting the criteria above would be to use a multiple schedule containing both FR and VR components. By matching the ratio parameters of pairs of component schedules (e.g., FR 5 vs. VR 5), the specific contribution of the schedule's variability (fixed versus variable) can be isolated. Multiple levels of both the FR and VR are required to examine tolerance across multiple response requirements and make comparisons of each between FR and VR. Given the limitations of the equipment and potential problems discriminating a large number of component schedules, a comparison between two levels of response requirement for FR and VR schedules spanning "small" versus "large" requirements (FR 5 vs. FR 125 vs. VR 5 vs. VR 125) was selected for this experiment.

Method

Subjects

The subjects were three adult female White Carneau pigeons (*Columba livia*): Tova, Yovel, and Bluma Shalom. The subjects were obtained from Palmetto Pigeon Plant in Sumter, South Carolina, and were naïve previous to their participation in the study. The subjects were reduced to 80% free-feeding body mass to motivate food-maintained behavior. When not in sessions, the subjects were housed in individual cages

in a room with maintained temperature and free access to water and grit, the lighting on a 12-h on/12-h off cycle. The procedure experienced by the subjects was submitted to the interdepartmental animal care and use committee and approved.

Apparatus

The subjects were tested in operant chambers obtained from MED Associates, Inc. (St. Albans, VT) with dimensions of 30 cm × 25 cm × 30 cm. On one wall of each chamber were three circular keys 2 cm in diameter, 21 cm from the floor and spaced 6 cm apart; keys could be activated by a force of approximately 0.2 N. The lights behind the keys could be illuminated white, green, or red. By illuminating a key both green and red simultaneously, a fourth color was produced which was a light brownish yellow. Below the keys was a square opening 7 cm × 7 cm in size through which grain could be presented by raising a grain hopper. During sessions illumination was provided by a 7-W houselight. The chambers were placed in sound-attenuating boxes that were ventilated by a small fan that also provided white noise. A NEXlink™ computer running MED-PC IV® under Microsoft® Windows® 98 was used to control experimental events and collect data.

Procedure

The procedure was modeled closely on previous research on behavioral tolerance using the mult-FR paradigm, particularly Hoffman et al. (1987). The subjects were trained to peck a key in an operant chamber using an autoshaping procedure, which in previous studies has reliably produced key-pecking in pigeons (e.g., Brown & Jenkins, 1968). The autoshaping procedure was based on that used by Picker, Blakely, & Poling (1986). In brief, subjects were regularly presented with keys lit in one of the primary key

colors for 6 s, followed by access to food for 4 s, after which the key went dark until the next trial began; no contingencies were placed on responding. The intertrial intervals averaged 60 s and varied between 1.53 s and 239.74 s according to the distribution described by Fleshler and Hoffman (1962). Key color and location varied randomly across trials. Once key-pecking occurred reliably, the schedule was switched to an FR schedule wherein pecking the relevant key for a specific number of times resulted in 3 s access to grain via the raised hopper. Sessions were programmed to end after 50 trials or 60 minutes whichever occurred first. Key color and location varied randomly across trials. The schedule parameter was initially set at FR 1 and gradually increased over sessions to FR 249 (the largest ratio requirement in the VR 125 component); this was to ensure subjects would be able to complete the requirements of all components. Once reliable FR performance was achieved, the subjects were then exposed to a multiple schedule for the experiment proper. Sessions were conducted once daily, six days per week.

The multiple schedule in this experiment had four components, each marked by a different key color (red, white, green, or yellow); the assignment of key colors to component schedules varied across subjects. Two of these components were FR schedules, one small (FR 5), one long (FR 125); the others were VR schedules with the same response requirements (VR 5 and VR 125). The ratio distributions of the VR schedules were arithmetic, each composed of nine equidistant requirements, the smallest always being 1; the selection of ratios for individual trials was always without replacement. The sessions were divided into two "blocks," in each of which the four component schedules occurred in random order; during each component, five trials of the

component schedule were programmed. The component would continue until either all five trials were completed or a predetermined amount of time had expired; this was to prevent components from continuing indefinitely should the drug eliminate responding altogether. Based on the values used in Hoffman et al. (1987), the FR 5 and VR 5 components timed-out after 120 s and the FR 125 and VR 125 components timed out after 1500 s. After each component was a 60-s blackout during which no keys were lit and pecking did not produce access to food. The subjects performed under the multiple schedule for several sessions until performance was determined stable by visual inspection over five sessions; this occurred after 38 sessions for Bluma Shalom, 19 for Yovel, and 15 for Tova. During these and all sessions, the duration, number of responses, and number of reinforcements were recorded for each schedule component; the measure of component duration excludes the time the hopper was up.

The subjects' performance was measured in two distinct phases. In the prechronic drug phase, cocaine was administered according to a BBBCD design, a cycle of five daily sessions. In this cycle, B represents baseline sessions (no injection) on the first three day, C represents vehicle control sessions (injection of 1 ml/kg 0.9% saline solution) on the fourth, and D represents drug sessions on the fifth. During drug sessions, subjects were given cocaine hydrochloride dissolved in the same saline solution, injected into the pectoral muscle 5 min before sessions start. The exact sites of the injection were varied and the side into which the injection was made alternated daily to reduce bruising that typically accompanies repeated injections. The cycle was repeated with doses of 1.0 mg/kg, 3.0 mg/kg, 5.6 mg/kg, and 10.0 mg/kg administered individually in an ascending

series; after the highest dose was reached, the subject was returned to baseline and a second ascending series conducted.

In the chronic drug phase, after 5 consecutive baseline sessions, the subjects were injected with 5.6 mg/kg cocaine 5 min before sessions; this dose was the same as the chronic dose used by Hoffman et al. (1987). Sessions continued until performance was stable as assessed by visual inspection over five sessions; this occurred after 41 sessions for Bluma Shalom, Yovel, and 29 sessions for Tova. Thereafter postchronic dose-effect curves were determined comparably to those in prechronic testing. Doses of 0 (vehicle), 1.0, 3.2, or 10.0 mg/kg were substituted for the 5.6 mg/kg dose every fifth session in ascending order; once the highest dose was reached, the next substitution was vehicle and the cycle repeated a second time. When doses of 1.0 and 3.2 mg/kg were given, a second injection of a dose sufficient to raise the total to 5.6 mg/kg was administered immediately after the session.

Results

Prechronic versus Postchronic Performance

Baseline rates of responding are listed in Table 1. Consistent with the previous literature, the response rates under FR 5 were higher than those under FR 125, though to a variable extent (cf. Felton & Lyon, 1966; Hoffman et al., 1987, Figure 3). In contrast, the response rates under VR 125 were consistently higher than those under VR 5. In general, response rates were greater under VR schedules than under FR schedules with

the same parameter, though the difference was somewhat larger under the greater response requirements.

	Component Schedule			
Subject	FR 5	VR 5	FR 125	VR 125
Bluma Shalom	2.60 (0.11)	2.62 (0.34)	2.53 (0.24)	3.13 (0.22)
Yovel	2.04 (0.43)	2.27 (0.18)	1.90 (0.30)	2.81 (0.31)
Tova	1.75 (0.31)	1.83 (0.20)	1.02 (0.19)	2.33 (0.16)

Table 1. Mean baseline response rates in responses per second. Means (and standard deviations) are derived from the last five sessions before drug testing.

Pre- and postchronic dose-response curves are shown in Figures 1 through 3. These data are shown in Figures 4 through 6 as percentages of vehicle control response rates. Due to a computer malfunction, the data for one session at 10.0 mg/kg during the prechronic phase for Yovel (Figures 2 and 5) were not recorded. Unlike the other two subjects, the values at this dose during the prechronic phase for Y are derived from a single session.

The prechronic responding under FR 5 for Bluma Shalom (Figures 1 and 4) and Yovel (Figures 2 and 5) was relatively stable across doses, with little decline save for under the highest dose, where there was little responding. The performance for Yovel was less stable than that of Bluma Shalom, with a slight increase in rate at 1.0 mg/kg and a modest decrease at 3.2 mg/kg. The corresponding performance for Tova (Figures 3 and 6) had a general downward trend across increasing doses but was highly erratic.

The prechronic effects of the drug were less consistent across subjects on FR 125 performance. For Bluma Shalom, response rate declined regularly as the dose increased,

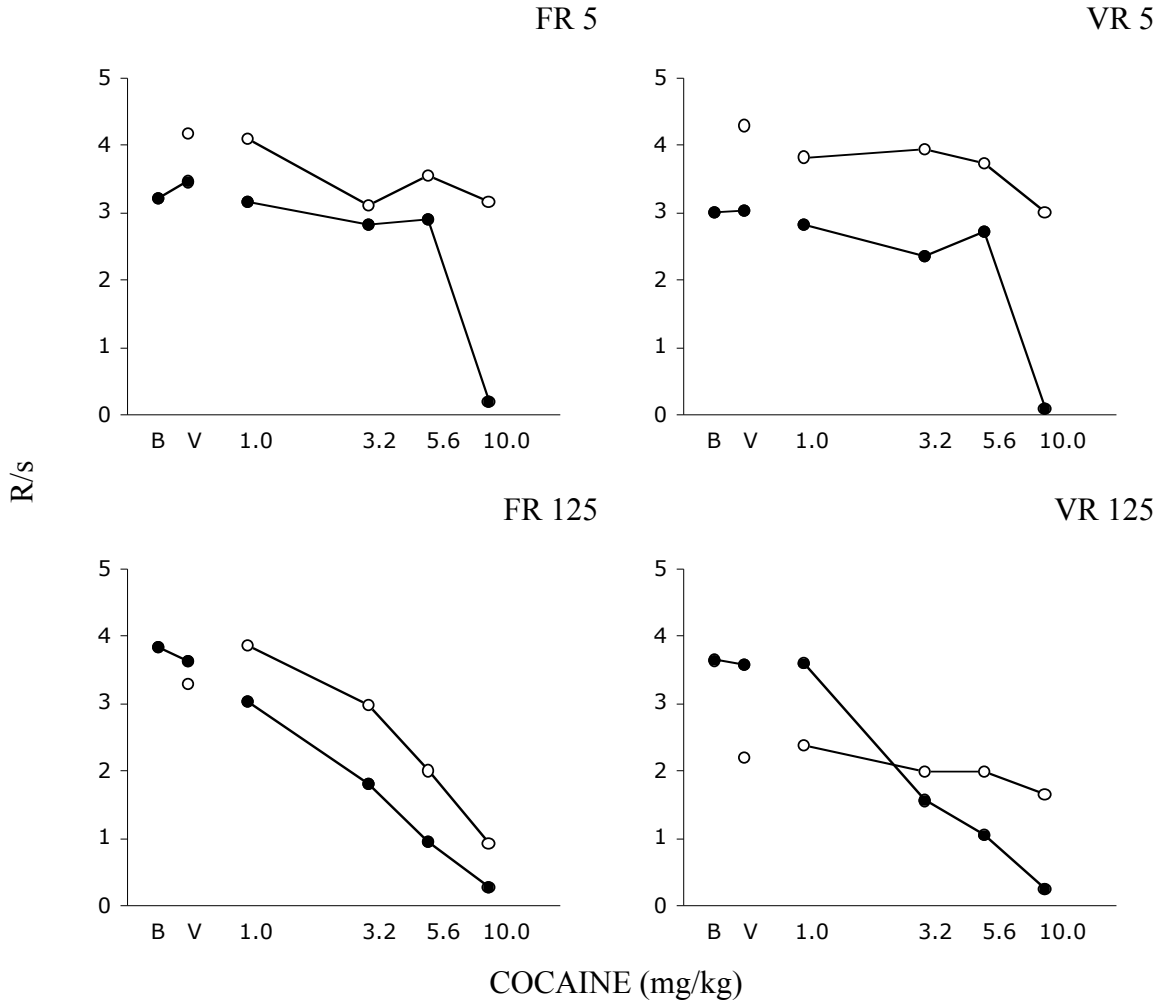

Figure 1. Pre- and postchronic dose-response curves for Bluma Shalom. Mean prechronic response rates are represented by filled circles and postchronic by open circles. B = baseline, V = vehicle. Points for baseline and vehicle in prechronic and 5.6 mg/kg in postchronic are means across all such sessions in those phases; points for drug doses in prechronic and vehicle and substitution doses in postchronic are means of their occurrences in the two ascending series. Values for ranges are listed in Appendix A.

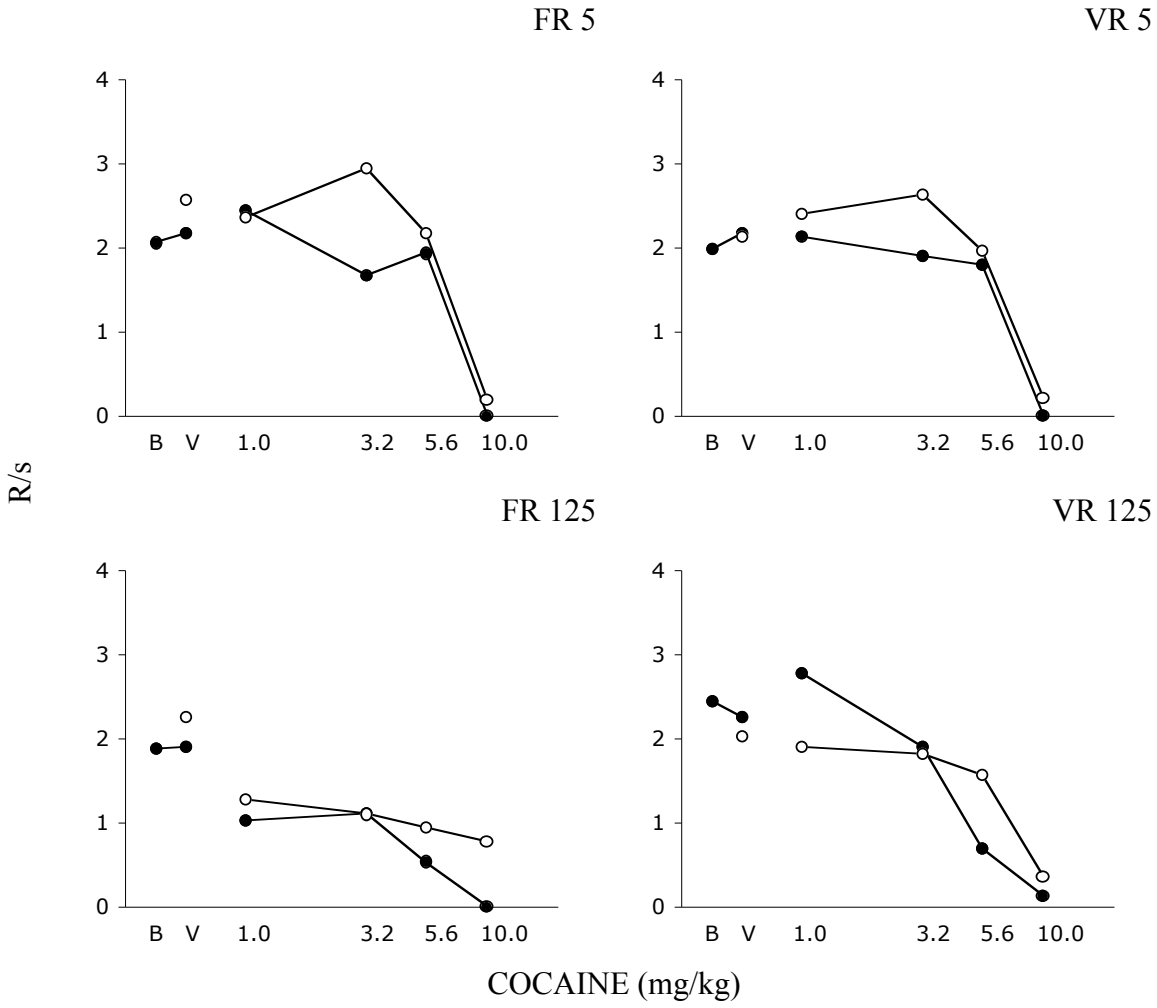

Figure 2. Pre- and postchronic dose-response curves for Yovel. Details are the same as in Figure 1 except that the points for 10.0 mg/kg in the prechronic phase is based on data from only one session.

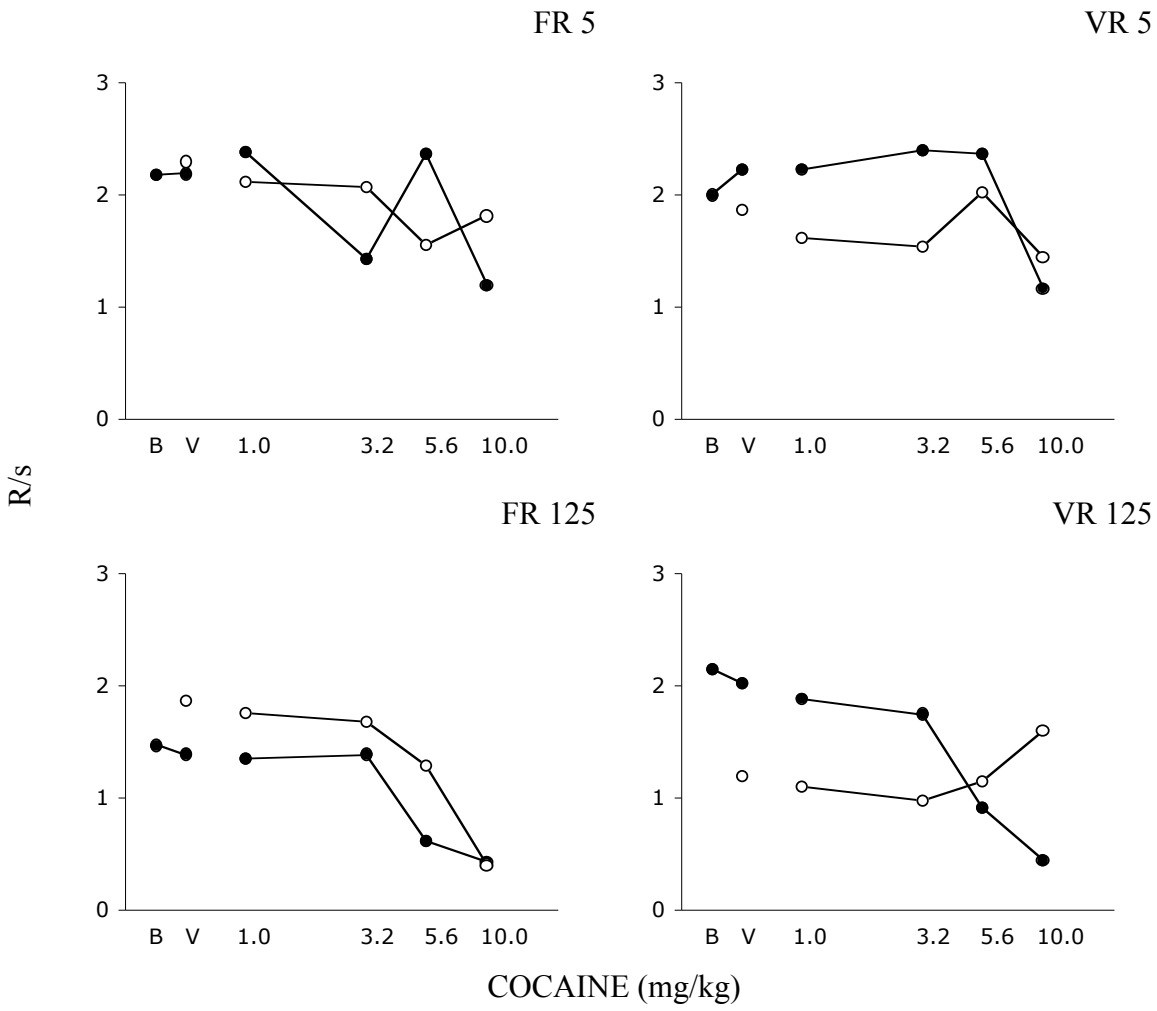

Figure 3. Pre- and postchronic dose-response curves for Tova. Details are the same as in Figure 1.

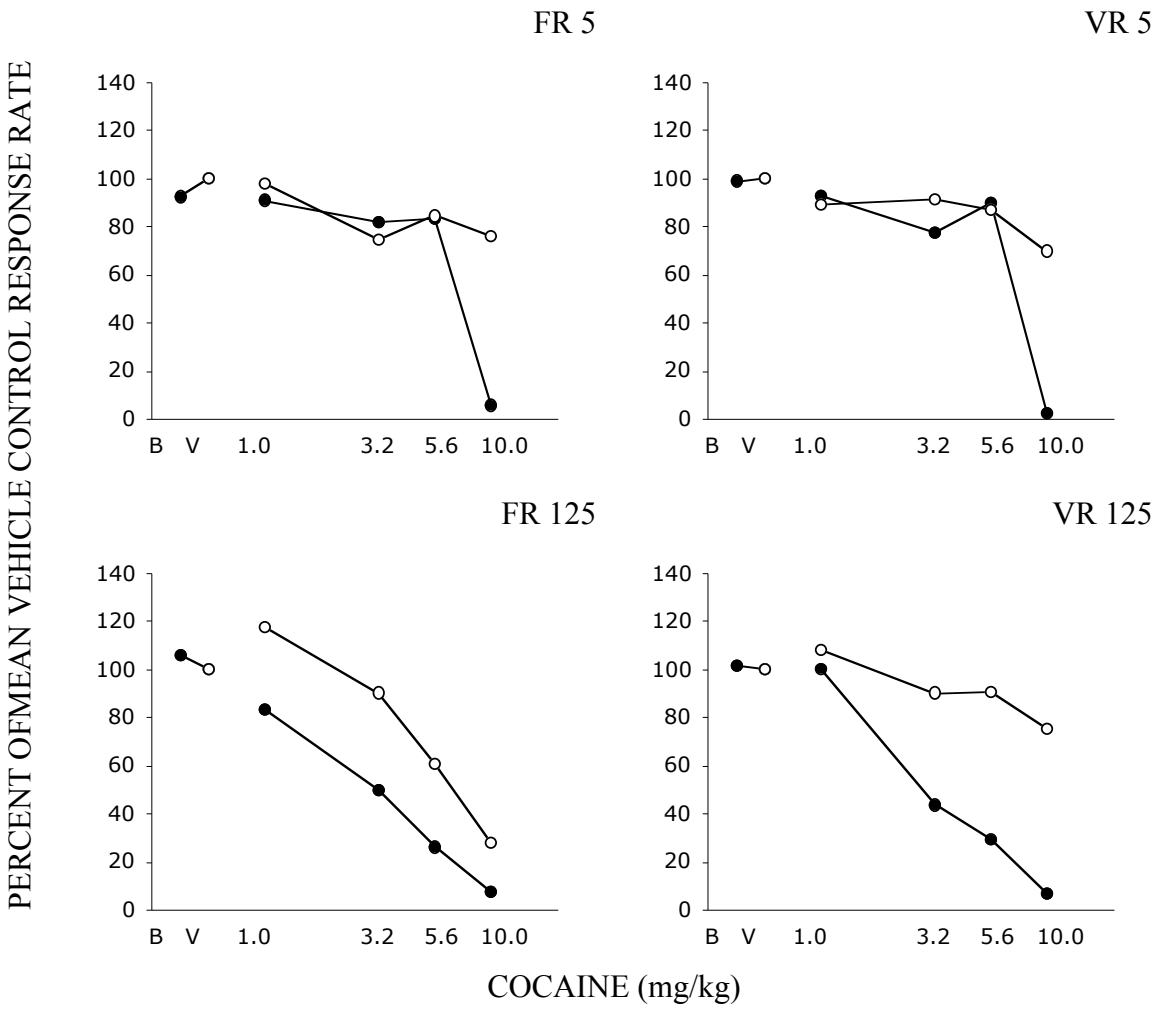

Figure 4. Pre- and postchronic dose-response curves for Bluma Shalom expressed as percentage of vehicle control. Details are the same as in Figure 1.

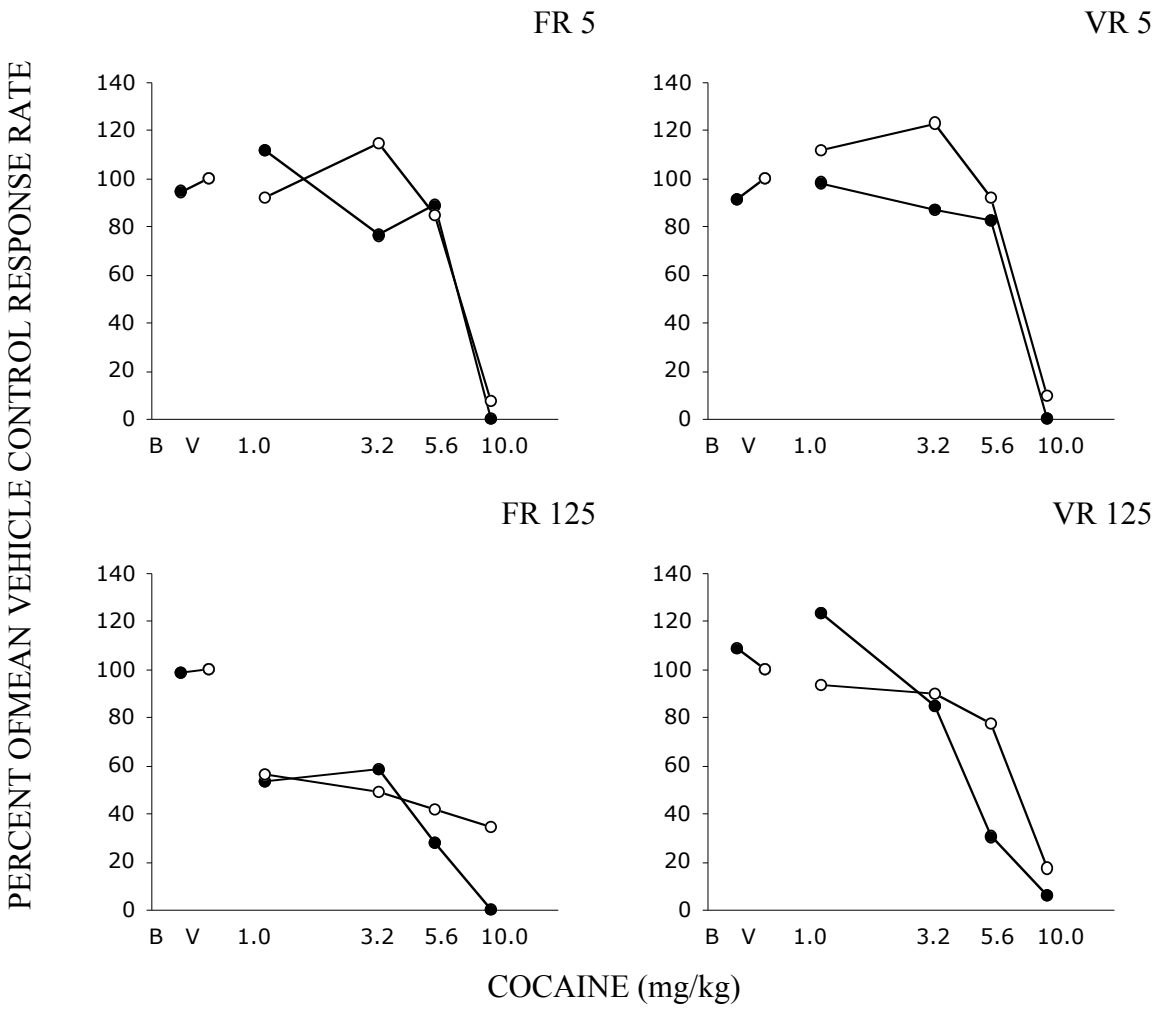

Figure 5. Pre- and postchronic dose-response curves for Yovel expressed as percentage of vehicle control. Details are the same as in Figure 1.

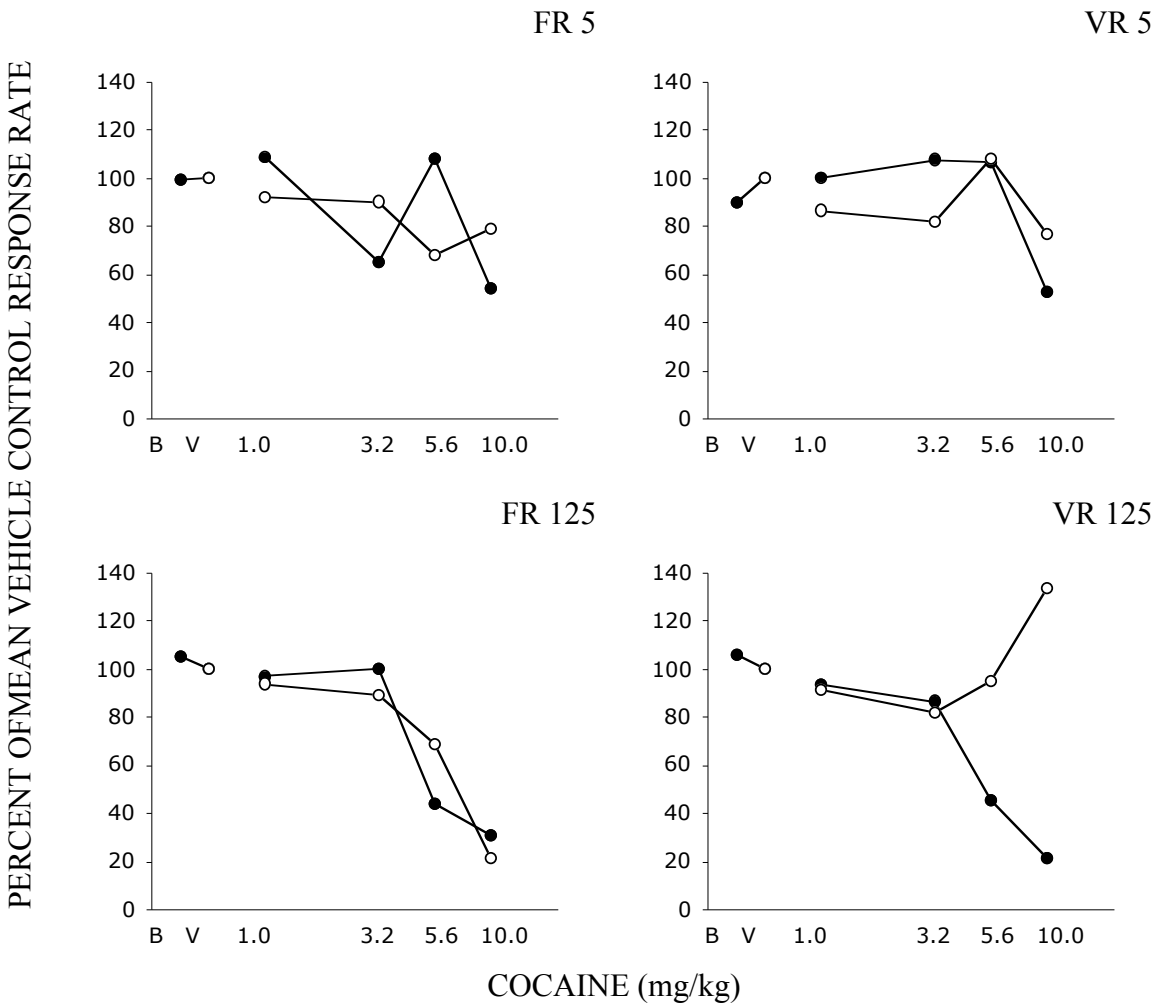

Figure 6. Pre- and postchronic dose-response curves for Tova expressed as percentage of vehicle control. Details are the same as in Figure 1.

whereas for Yovel and Tova, the response rates were similar under doses of 1.0 and 3.2 mg/kg but dropped substantially under the higher doses, with response rates decreased under drug doses for Yovel; the response rates for Tova under zero doses (baseline and vehicle) and low doses (1.0 and 3.2 mg/kg) were similar, whereas there was a substantial drop in response rate of nearly one response per second once drug was introduced for Yovel.

Prechronic performance under VR 5 was generally similar to that under FR 5, with performance under most doses similar to baseline and vehicle performances with a large decline at the 10.0 mg/kg dose. Bluma Shalom's performance dipped moderately at 3.2 mg/kg, whereas that of Yovel regularly declined across doses between 1.0 and 5.6 mg/kg and Tova's responding slightly increased across the same doses.

Under VR 125, there was generally a regular decline in prechronic response rate across increasing doses, the performance resembling that under FR 125. For Bluma Shalom, performance at 1.0 mg/kg was similar to in baseline and vehicle conditions, whereas for Yovel the response rate was slightly higher at this dose. For Tova, the performance across doses was similar to that under FR 125, with performance at 1.0 and 3.2 mg/kg similar to (albeit slightly less than) that under baseline and vehicle conditions, and with a steady decline at higher doses.

Consistently across component schedules the lowest response rates were found in the prechronic phase at the 10.0 mg/kg dose. In Bluma Shalom and Yovel response rates dropped to zero or near-zero, whereas in Tova they were considerably higher, being at approximately 0.5 responses per second under FR 125 and VR 125 and over one response

per second under FR 5 and VR 5. This may reflect individual differences in the sensitivities of the subjects to the drug.

Increases in postchonic response rates were typically observed under FR 5, especially across doses for Bluma Shalom. In Yovel, tolerance was slight under the 3.2 mg/kg dose but not at other doses. Tova did not show tolerance, owing in part to an erratic prechronic dose-response curve. Responding under the vehicle condition was increased for Bluma Shalom and Yovel; adjusting for this difference, tolerance was only found in the highest dose for Bluma Shalom (Figure 4).

Under FR 125, Bluma Shalom showed considerable tolerance, with postchronic response rates elevated across all doses. The postchronic response rates for Tova were also elevated across all doses save for 10.0 mg/kg, but tolerance was not found when rates were adjusted for the shift in the response rate under vehicle (Figure 6). In Yovel, tolerance is most evident in the 10.0 mg/kg dose; a small amount of tolerance under the 1.0 mg/kg dose vanishes when adjusted for an increase in postchronic responding under vehicle (Figure 5).

Evidence of tolerance under VR 5 was inconsistent across subjects. Postchronic response rates increased across all doses including vehicle for Bluma Shalom, similar to the subject's performance under FR 5; adjusting for this shift, tolerance was found clearly at only the 10.0 mg/kg dose (Figure 4). Tova showed a decrease in postchronic response rates across all doses including vehicle; even adjusting for this baseline shift (Figure 6), tolerance was only found at the 10.0 mg/kg dose, though the extreme variability of the performance makes this unclear. In Yovel tolerance was found mostly at the 3.2 mg/kg dose but with little at other doses; there was little shift in the behavioral baseline.

Under VR 125, all subjects showed a pattern of postchronic responding that included a decrease in the response rate under vehicle and tolerance at the higher doses. Bluma Shalom had relatively stable response rates across drug doses at roughly the same rate as under vehicle; Tova was similar but the postchronic response rate was substantially elevated under the 10.0 mg/kg dose. For Yovel, the postchronic response rate under most doses was similar to that under vehicle but substantially lower under the 10.0 mg/kg dose; moderate tolerance was found at this dose.

Although postchronic performances were similar for FR and VR schedules of the same parameter, an unexpected similarity was found between VR 5 and VR 125, being relatively constant in rate across doses, save for higher rates under the lower ratio. Bluma Shalom performed similarly across doses with a slight decline as dose increased; under VR 5 the response rate was mean of 1.72 responses per second (R/s) higher than under VR 125 with a standard deviation of 0.32 R/s. Tova's performance was also relatively constant across doses; under VR 5, the response rate was a mean of 0.75 R/s higher than under VR 125 with a standard deviation of 0.25. Yovel was the most variable, with responding generally becoming increasingly less frequent with higher doses, with a response rate under VR 5 being a mean of 0.34 R/s higher than under VR 125 with a standard deviation of 0.37 R/s. In this case, the numbers may be misleading as the response rates under 10.0 mg/kg are close to 0; omitting this dose from the calculations results in a mean difference of 0.46 R/s with a standard deviation of 0.29 R/s.

Reinforcement Loss

Table 2 lists the mean proportion of programmed reinforcers earned across conditions. As the rate of reinforcement is directly proportionate to the rate of

Bluma Shalom

	Prechronic				Postchronic			
Dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	1	1	1	1				
	(5)	(5)	(5)	(5)				
V	1	1	1	1	1	1	1	1
	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
1.0	1	1	1	1	1	1	1	1
	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
3.2	1	0.75	1	0.75	1	1	1	1
	(5)	(3.75)	(5)	(3.75)	(5)	(5)	(5)	(5)
5.6	1	0.85	1	0.75	1	1	1	0.98
	(5)	(4.25)	(5)	(3.75)	(5)	(5)	(5)	(4.69)
10.0	0.50	0.45	0.25	0.50	1	1	1	1
	(2.50)	(2.25)	(1.25)	(2.50)	(5)	(5)	(5)	(5)

Yovel

	Prechronic				Postchronic			
Dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	1	1	1	1				
	(5)	(5)	(5)	(5)				
V	1	1	1	1	1	1	1	1
	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
1.0	1	1	1	1	1	1	1	1
	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
3.2	1	0.80	1	1	1	1	1	1
	(5)	(4.00)	(5)	(5)	(5)	(5)	(5)	(5)
5.6	1	0.75	1	0.95	0.97	0.97	0.93	1
	(5)	(3.75)	(5)	(4.75)	(4.86)	(4.84)	(4.63)	(5)
10.0	0	0	0	0.20*	0.50	1	0.55	0.50
	(0)	(0)	(0)	(1)	(2.50)	(5)	(2.75)	(2.50)

Tova

	Prechronic				Postchronic			
Dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	1	1	1	1				
	(5)	(5)	(5)	(5)				
V	1	1	1	1	1	1	1	1
	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
1.0	1	1	1	1	1	1	1	1
	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
3.2	1	1	1	1	1	1	0.95	1
	(5)	(5)	(5)	(5)	(5)	(5)	(4.75)	(5)
5.6	1	0.90	1	1	0.90	1	0.93	1
	(5)	(4.50)	(5)	(5)	(4.52)	(5)	(4.64)	(5)
10.0	0.75	0.65	0.75	0.70	1	0.85	0.75	1
	(3.75)	(3.25)	(3.75)	(3.50)	(5)	(4.25)	(3.75)	(5)

Table 2. Mean proportion of programmed reinforcers earned (top value) and number of programmed ratios per component completed (bottom value in parentheses). Proportions are from a programmed 10 per component per session, averaged across sessions in the prechronic and postchronic phases. Doses are in mg/kg of cocaine. B = baseline, V = vehicle. *The values in this condition are based on a single session due to a computer malfunction.

responding, the measures are closely related; all programmed ratios will be completed and programmed reinforcers earned so long as the subject responds sufficiently rapidly enough to complete the trials before the component-schedule times-out. In the prechronic phase, all programmed reinforcers were earned during baseline, vehicle injections, and a dose of 1.0 mg/kg. Whereas subjects consistently failed to earn substantial proportions of the programmed reinforcers at a dose of 10.0 mg/kg, at doses of 3.2 and 5.6 mg/kg, subjects earned most or all of the programmed reinforcers. For all subjects at these doses, all programmed reinforcers were earned under FR 5 and VR 5, whereas there were small reductions (≤25%) under FR 125 and to a lesser extent VR 125. During the postchronic phase, all or almost all programmed reinforcers (in excess of 90%) were earned at all doses except 10.0 mg/kg; at 10.0 mg/kg, all reinforcers were earned by Bluma Shalom and between half and all earned by Yovel and Tova.

Discussion

Although the forms of the postchronic functions are suggestive of a schedule difference in tolerance (that postchronic VR 125 performance decreases less across increasing doses than postchronic FR 125 performance), the data do not strongly support this difference. The chronic dose of 10.0 mg/kg was not sufficient to produce a large decrease in response rate (Figures 1 through 3) or proportion of reinforcers in all component schedules (Table 2). Without a demonstrated drug effect at this dose, one cannot demonstrate recovery to a previous level of responding. Thus the necessary

requirements for producing tolerance or its putative determinant are not fulfilled sufficiently or uniformly for all subjects.

While the chronic dose used here did not produce tolerance across all subjects and component schedules, the same did in other similar published studies (e.g., Hoffman et al., 1987). The difference in the initial drug effect may reflect individual differences between subjects. Although not uniformly reported, subjects may vary in their responses in tolerance studies; for example, two out of six subjects in Yoon and Branch (2004), Experiment 3, failed to develop tolerance under the same 5.6 mg/kg dose that otherwise produced such in the remaining subjects.

CHAPTER IV

EXPERIMENT 2

Instead of the same chronic dose for all subjects, an alternative strategy would be to set the set the chronic individually based on how specific doses affect responding during acute exposure. The desired chronic dose should sufficiently decrease response rate and proportion of reinforcers earned such that the necessary conditions for tolerance to be identified are regularly produced in all subjects. By individualizing the chronic dose, this criterion was satisfied in Experiment 2.

Method

Subjects

The subjects were four adult female White Carneau pigeons (*Columba livia*): Ariel, Golda, Lumpkin Rachel, and Grumpy Torah. The subjects were obtained from the same source and maintained in the same manner as those in Experiment 1 and naïve previous to their participation in the study. (An additional six subjects began the study but were dropped for relative slowness in autoshaping or expediency.)

Apparatus

The same apparatus was used as in Experiment 1.

Procedure

The procedure was substantially identical to that in Experiment 1. Subjects were similarly trained to keypeck and perform under increasingly larger ratios before being switched to the same mult FR 5 FR 125 VR 5 VR 125 schedule. The subjects performed under the multiple schedule for several sessions until performance was determined stable by visual inspection over five sessions; this occurred after 55 sessions for Ariel, 47 sessions for Golda, 55 for Lumpkin Rachel, and 54 for Grumpy Torah. In addition to the measures recorded in Experiment 1 (duration, number of responses, and number of reinforcements), an additional measure, latency to first response after the trial begins, was recorded to examine changes in postreinforcement pausing that might occur.

The subjects' performance was measured in the same two phases. The prechronic phase was similar to that in Experiment 1 with the exception of the largest drug dose in the acending series. For Golda, the series had drug doses of 1.0, 3.2, 5.6, and 10.0 mg/kg. Based on the responses of the subjects to the drugs being insufficient to substantially reduce response rate and proportion of reinforcers earned at the higher doses, the series for the remaining subjects included a 17.8 mg/kg dose; this was to ensure that there be at least one dose where there was substantial drop in response rate and reinforcement earned across component schedules.

The chronic dosing was similar to that in Experiment 1 except for the individualized chronic dosing. For Ariel the chronic dose was 17.8 mg/kg, 5.6 mg/kg for Golda, and 10.0 mg/kg for Grumpy Torah. Lumpkin Rachel was begun on 17.8 mg/kg but responding dropped to almost zero; as it did not recover, the dose was reduced to a

lower intermediate dose (13.3 mg/g) after 9 sessions. Grumpy Torah's performance was judged stable by visual assessment (lacking trend and of consistent variability) over five sessions after 60 sessions with chronic doses, after which postchronic dosing began (below). The remaining subjects failed to achieve these criteria and for them postchronic dosing began after 65 sessions.

As in Experiment 1, postchronic dose-effect curves were determined similarly to those in prechronic testing. Baseline (no injection) and vehicle sessions or sessions of another drug dose (1.0, 3.2, 5.6, and 10.0 mg/kg for Ariel; 1.0, 3.2, and 10.0 for Golda; 1.0, 3.2, 5.6, 10.0, and 17.8 mg/kg for Lumpkin Rachel; 1.0, 3.2, 5.6, and 17.8 mg/kg for Grumpy Torah) were substituted for the chronic dose every third session in ascending order. Once the highest dose was reached, the next substitution was vehicle and the cycle repeated a second time.

Ariel died during the first postchronic substitution series just after the 5.6 mg/kg dose; although incomplete, the existing data is presented for comparison. Due to procedural error, one chronic dose during the second postchronic substitution series (just previous to the baseline substitution) was omitted for Golda, with the subject not being run; a similar error was made for the chronic dose following the last 5.6 mg/kg substitution for Grumpy Torah. There is no evidence that these affected the results.

Results

Prechronic versus Postchronic Performance

Baseline rates of responding are listed in Table 3. Consistent with the previous literature, the response rates under FR 5 were higher than those under FR 125 for three of four subjects (cf. Felton & Lyon, 1966; Hoffman et al., 1987, Figure 3); the exception being Golda. In contrast, the response rates under VR 5 were not consistently higher or lower than those under VR 125 across subjects. Response rates under VR 125 were consistently higher than those under FR 125, whereas there was no such consistent difference across subjects between response rates under FR 5 and VR 5.

	Component Schedule			
Subject	FR 5	VR 5	FR 125	VR 125
Ariel	2.70 (0.34)	2.33 (0.11)	1.03 (0.14)	1.14 (0.14)
Golda	2.92 (0.13)	3.47 (0.33)	4.30 (0.42)	6.70 (0.42)
Lumpkin Rachel	2.78 (0.34)	3.46 (0.39)	1.21 (0.52)	3.27 (0.29)
Grumpy Torah	3.46 (0.33)	3.27 (0.62)	1.94 (0.23)	4.59 (0.84)

Table 3. Mean baseline response rates in responses per second. Means (and standard deviations) are derived from the last five sessions before drug testing.

Pre- and postchronic dose-respone curves are shown in Figures 7 through 10. The postchronic response rates under baseline and vehicle doses were typically shifted downwards relative to the prechronic response rates. The same data are shown in Figures 11 through 14 as percentages of vehicle control response rates. The subject Ariel died just before completing the last dose (10.0 mg/kg) in the first ascending postchronic series, so the postchronic data for this subject (Figures 7 and 11) was based on a single series and allows for only limited comparisons with the other subjects.

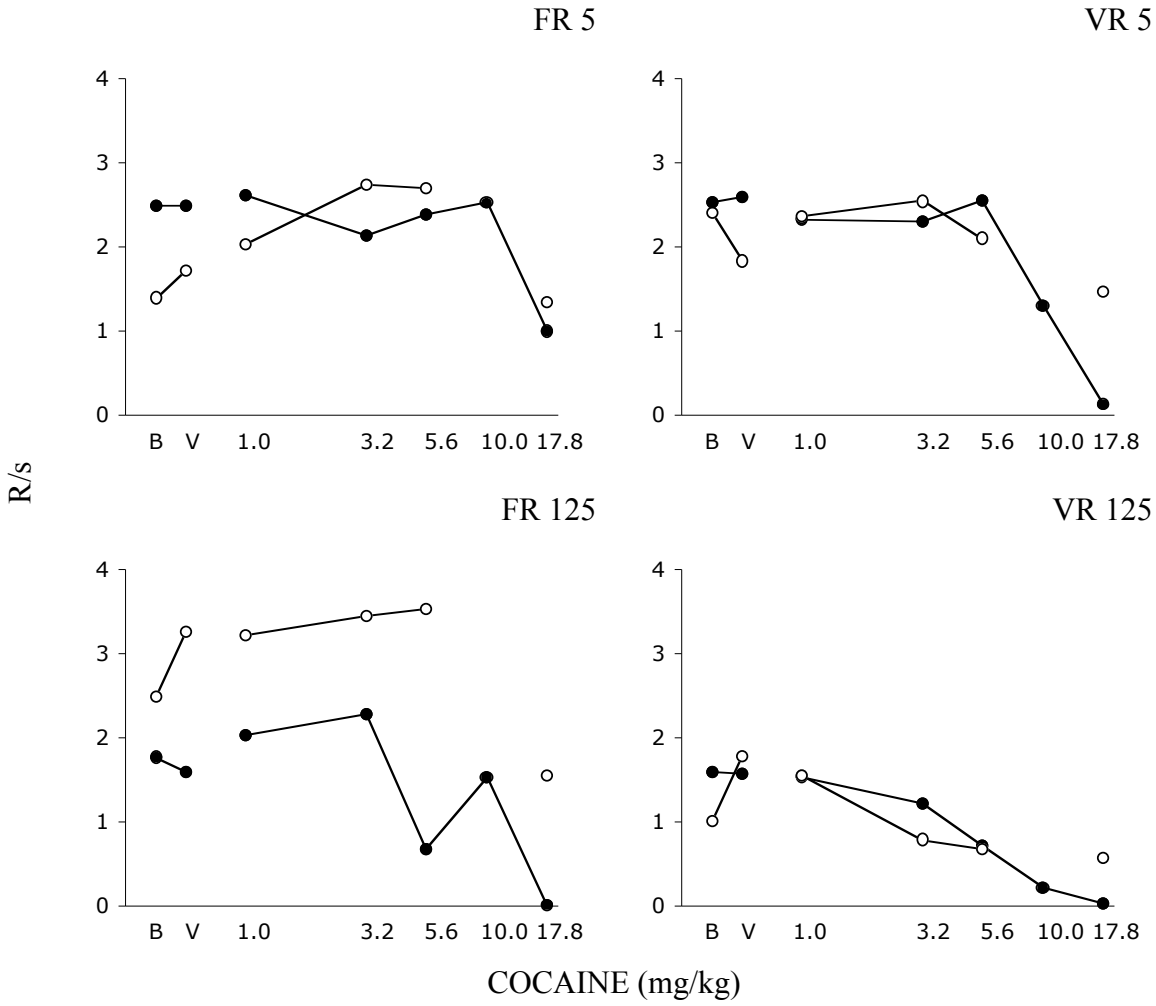

Figure 7. Pre- and postchronic dose-response curves for Ariel. Mean prechronic response rates are represented by filled circles and postchronic by open circles. B = baseline, V = vehicle. Points for baseline and vehicle in prechronic and chronic dose in postchronic are means across all such sessions in those phases; points for drug doses in prechronic and vehicle and substitution doses in postchronic are means of their occurrences in the two ascending series. Values for ranges are listed in Appendix B.

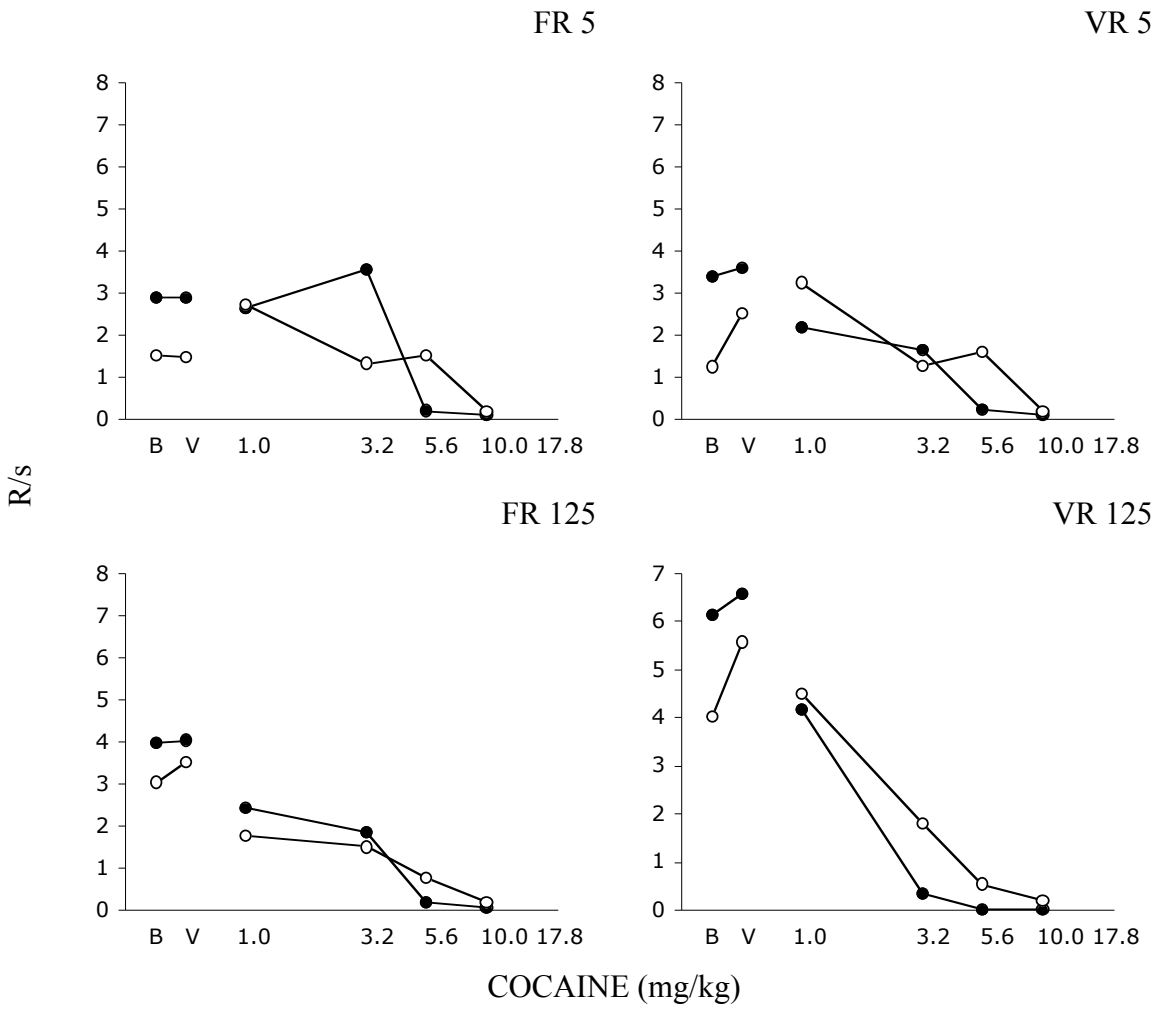

Figure 8. Pre- and postchronic dose-response curves for Golda. Details are the same as in Figure 7.

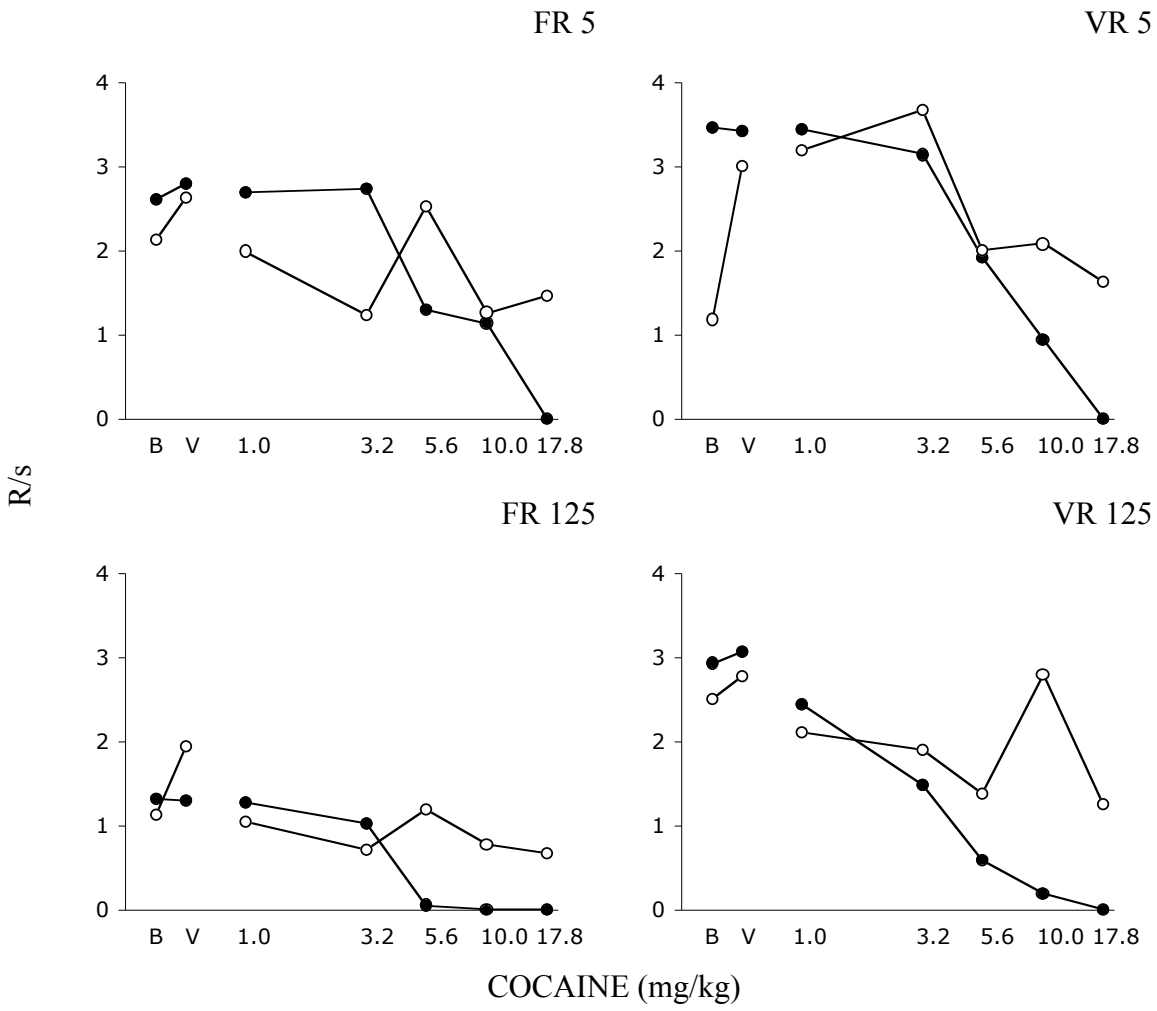

Figure 9. Pre- and postchronic dose-response curves for Lumpkin Rachel. Details are the same as in Figure 7.

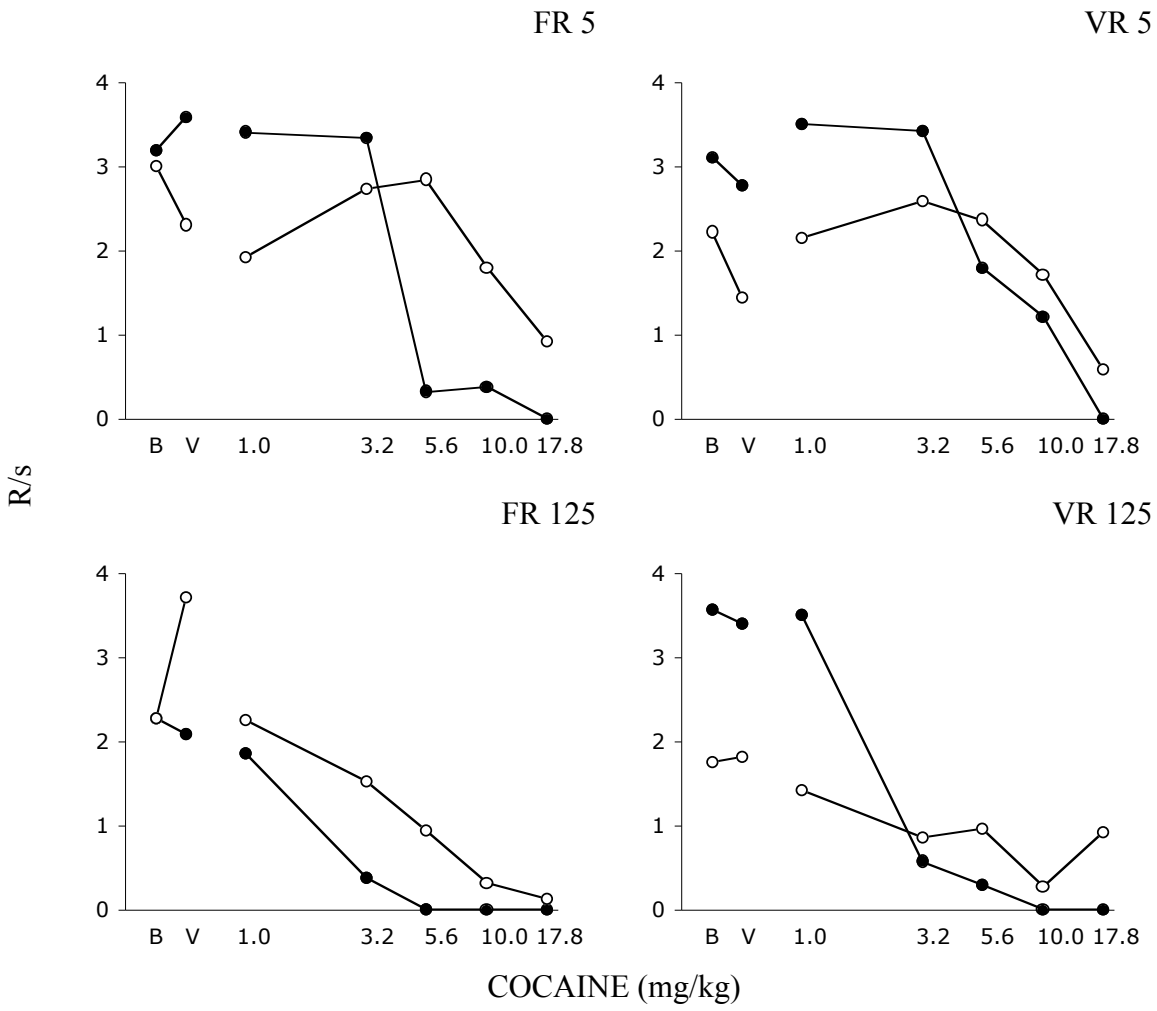

Figure 10. Pre- and postchronic dose-response curves for Grumpy Torah. Details are the same as in Figure 7.

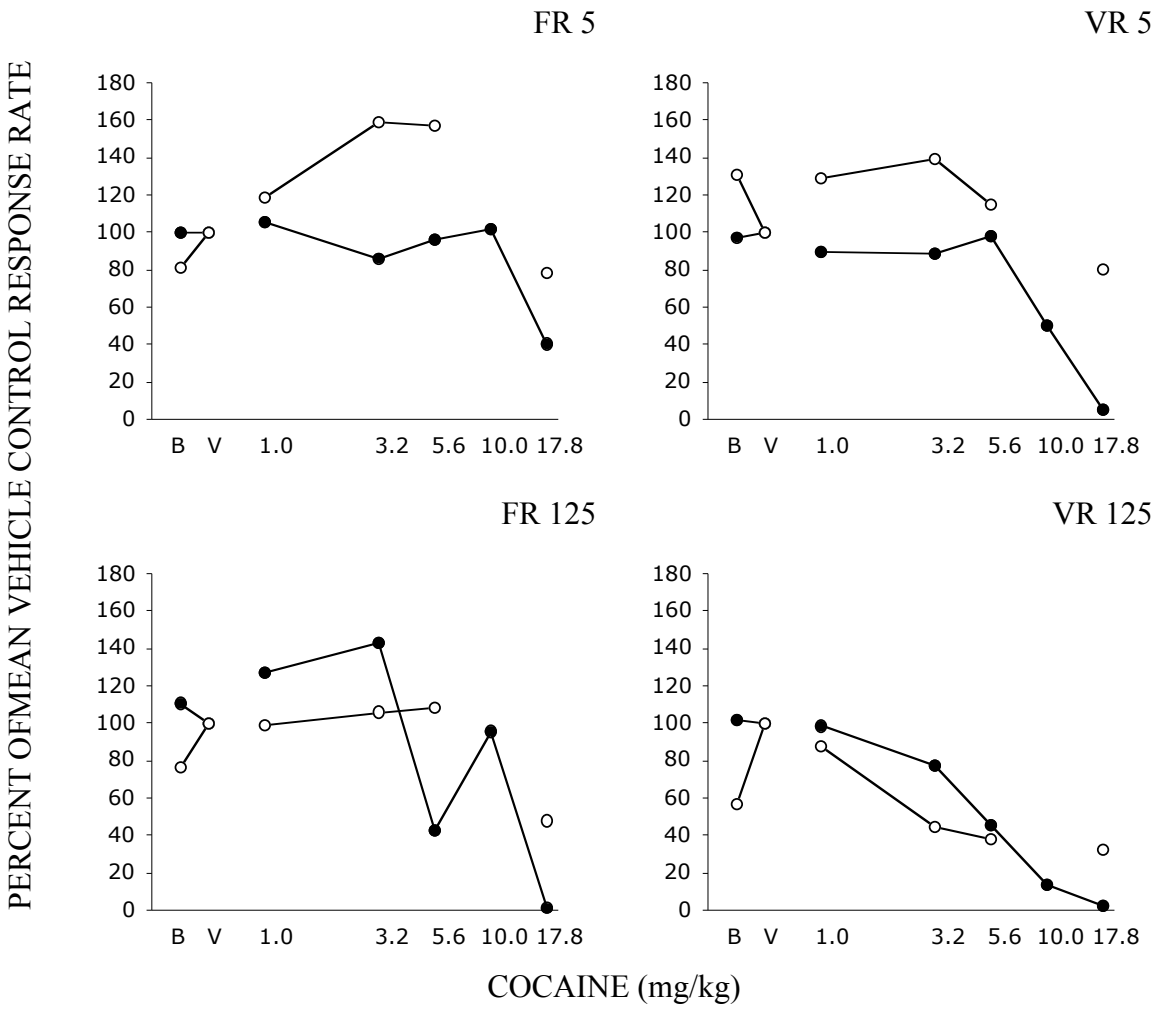

Figure 11. Pre- and postchronic dose-response curves for Ariel expressed as percentage of vehicle control. Details are the same as in Figure 7.

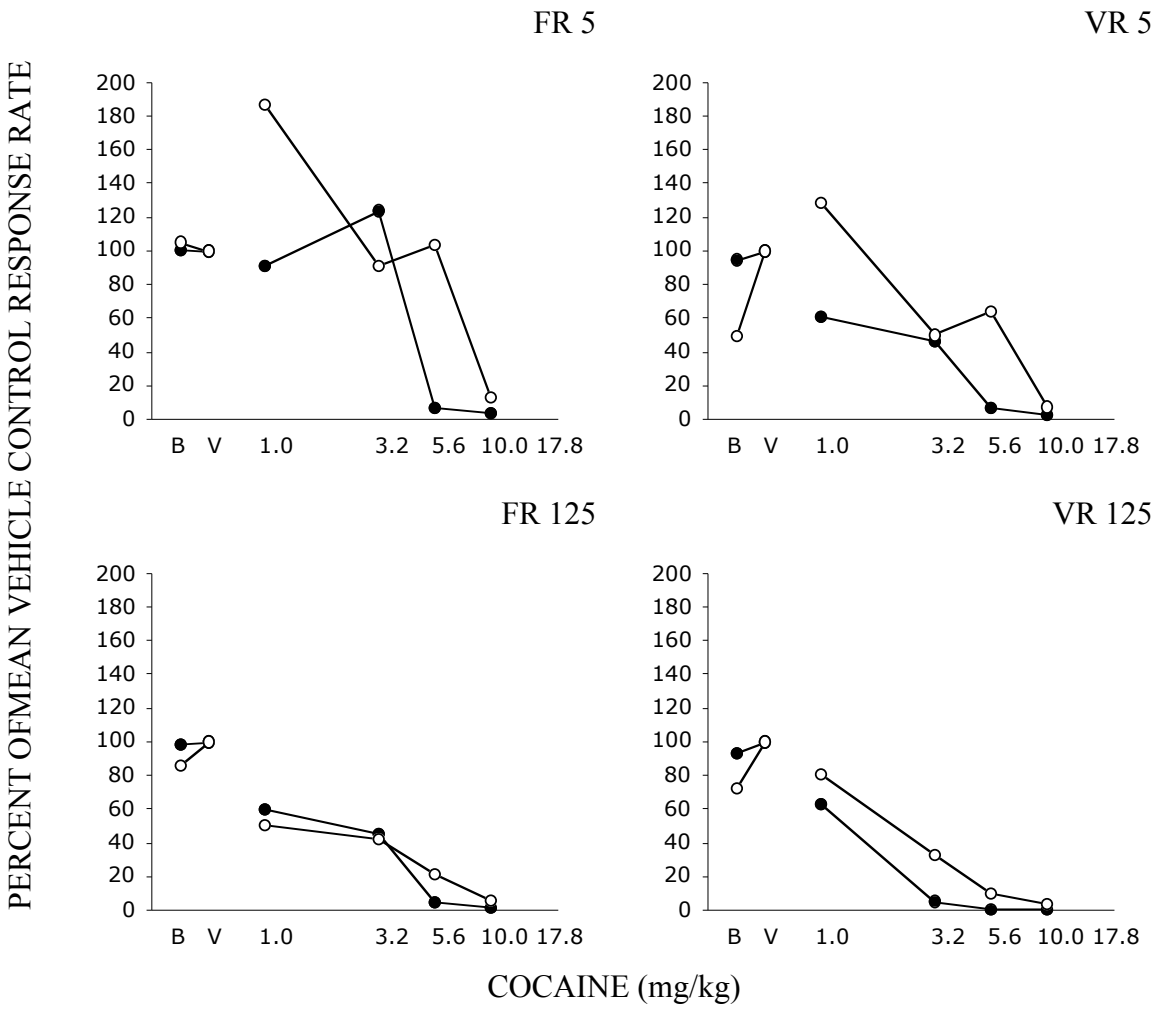

Figure 12. Pre- and postchronic dose-response curves for Golda expressed as percentage of vehicle control. Details are the same as in Figure 7.

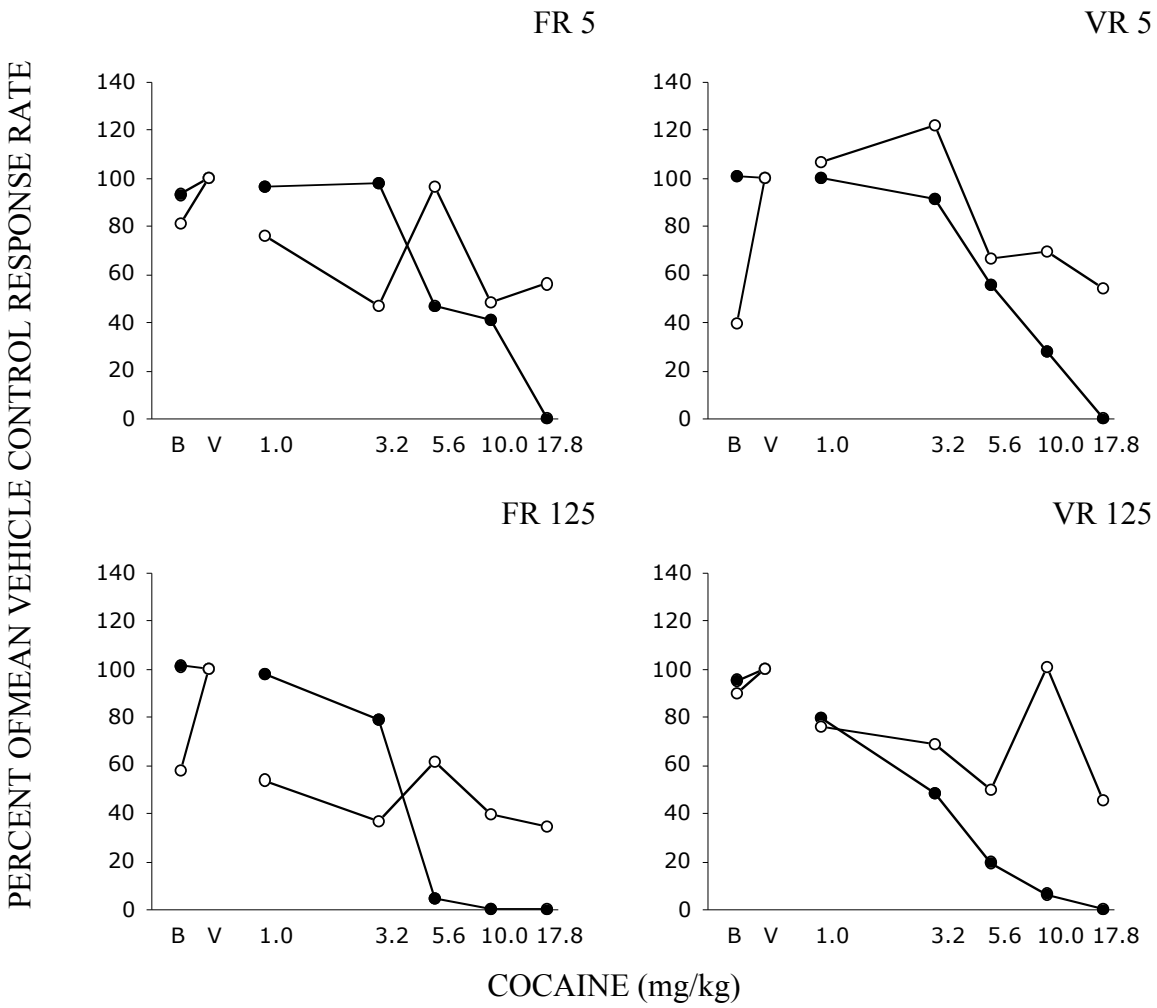

Figure 13. Pre- and postchronic dose-response curves for Lumpkin Rachel expressed as percentage of vehicle control. Details are the same as in Figure 7.

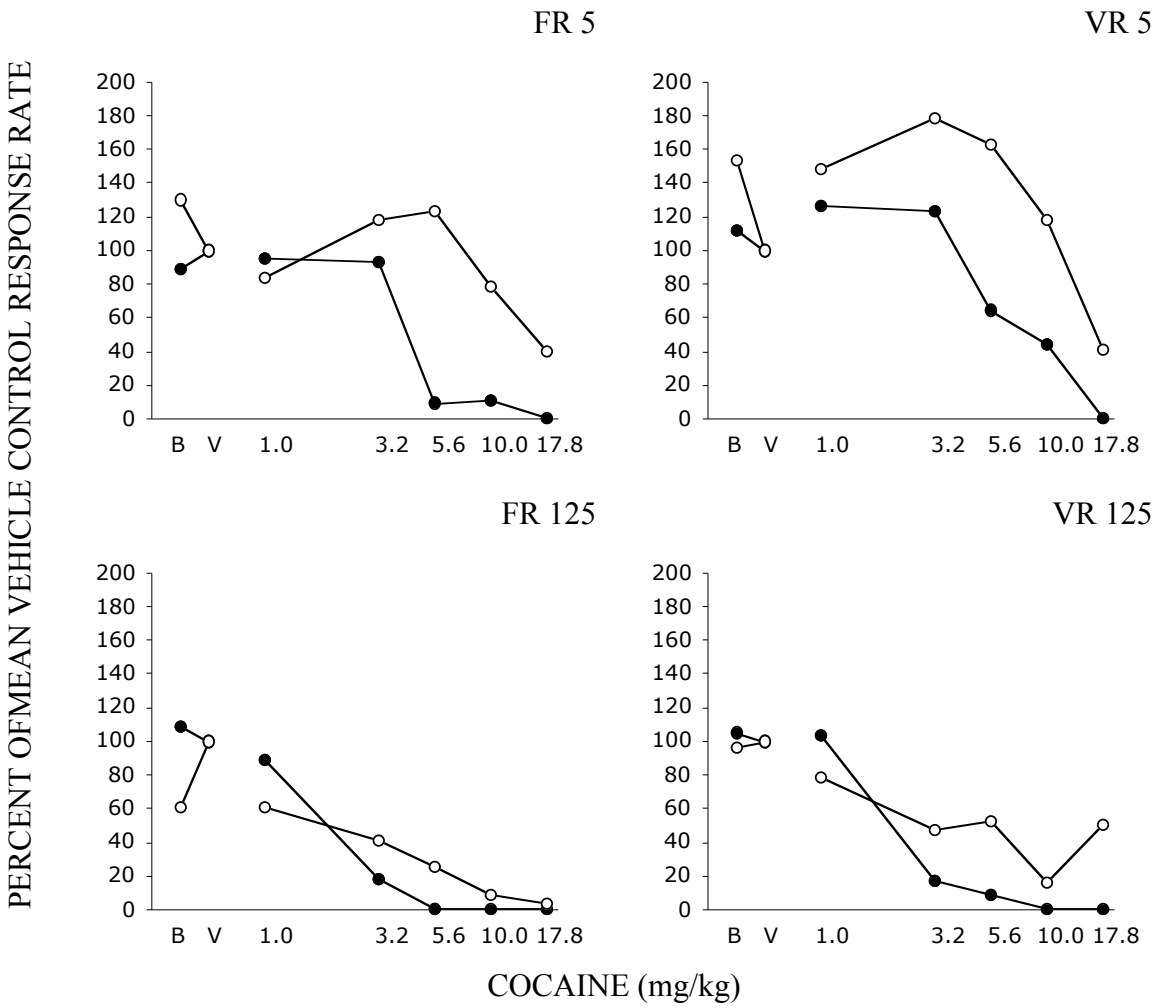

Figure 14. Pre- and postchronic dose-response curves for Grumpy Torah expressed as percentage of vehicle control. Details are the same as in Figure 7.

The prechronic responding under FR 5 across subjects was generally relatively stable, with little decline save for under the highest dose or doses, at which there was a precipitous decline. For Golda (Figures 8 and 12) and Grumpy Torah (Figures 10 and 14) the transition was abrupt and responding at the highest doses approached zero; for Ariel (Figures 7 and 10), responding was stable across most doses (between approximately 2 and 2.5 R/s), dropping to less than half (approximately 1.0 R/s) suddenly at the 17.8 mg/kg dose. For Lumpkin Rachel (Figures 9 and 13) the response rate at the 5.6 and 10.0 mg/kg doses was less than half that the rates at lower doses, the rate at the 17.8 mg/kg dose reaching zero.

The prechronic effects of the drug were less consistent across subjects on FR 125 performance. For Golda (Figures 8 and 12), the response rate declined regularly as the dose increased, whereas for Lumpkin Rachel (Figures 9 and 13) and Grumpy Torah (Figures 10 and 14) the transition was more abrupt in the midrange doses. For Ariel (Figures 7 and 10), the general trend across increasing doses was downward but performance was erratic.

The prechronic performance under VR 5 was generally similar to the performance under FR 5 across subjects, though with Golda (Figures 8 and 12) and Lumpkin Rachel (Figures 9 and 13), the transition from relatively steady state rates across doses to near zero occurs more gradually. This also occurs for Grumpy Torah (Figures 10 and 14), with an additional increase in response rates at the 1.0 and 3.2 mg/kg doses. For Ariel (Figures 7 and 11), the transition remains relatively abrupt but occurs at a lower dose (10.0 mg/kg instead of 17.8 mg/kg), with the rate approaching zero at the 17.8 mg/kg dose.

Under VR 125, there was generally decreasing responding with increasing doses. For Grumpy Torah (Figures 10 and 14) responding transitioned abruptly between the 1.0 and 3.2 mg/kg doses whereas the other subjects (Figures 7 through 9 and 11 through 13) transitioned more gradually across several doses.

Overall across component schedules the lowest response rates were found in the prechronic phase at the highest dose (17.8 mg/kg) and sometimes at lower doses, usually near or at zero (the major exception being Ariel under FR 5, Figures 7 and 11). That different doses were required across subjects to produce the same reduction may reflect individual differences in sensitivities to the drug.

Increases in postchronic response rates were typically observed under FR 5 under higher doses, with often decreases in response rates under baseline, vehicle, and sometimes low drug doses. For Golda (Figure 8) a postchronic increase was only particularly evident under the 5.6 mg/kg dose, and when expressed as a proportion of the rate of the vehicle control (Figure 12), tolerance is evident under the 1.0 mg/kg dose as well. Lumpkin Rachel (Figures 9 and 13) only showed increases under the 5.6 and 17.8 mg/kg doses. Grumpy Torah (Figure 10) showed large increases under the 5.6, 10.0, and 17.8 mg/kg doses, with 3.2 mg/kg also having an increase when adjusted for changes in the vehicle control rate (Figure 14). The incomplete data for Ariel (Figures 7 and 11) suggest tolerance at the 3.2, 5.6, and 17.8 mg/kg doses.

Postchronic FR 125 performance was less consistent across subjects. Golda (Figures 8 and 12) and Grumpy Torah (Figures 10 and 14) showed a pattern of baseline responding being lower than vehicle responding and regular decreases in responding between vehicle and the highest dose. Tolerance was not evident for Golda; for Grumpy

Torah, the increases in response rate at the 3.2 and 5.6 mg/kg doses were diminished when adjusted for changes in the vehicle control rate. Lumpkin Rachel (Figures 9 and 13) showed an increase under vehicle and the 5.6, 10.0, and 17.8 mg/kg doses, the latter persisting even when adjusted for changes in the vehicle control rate. The incomplete data for Ariel (Figures 7 and 11) suggests an increase across all doses (including baseline and vehicle) which, when adjusted for changes in the vehicle control rate, suggests tolerance at the 5.6 and 17.8 doses.

Postchronic VR 5 performances typically resembled FR 5 performances for the same subject, also typically involving decreased response rates under baseline and vehicle and increased responding under the higher doses. Golda (Figures 8 and 12) had increases under the 1.0 and 5.6 doses, resembling especially the pattern under FR5 as adjusted for changes in the vehicle control rate. Lumpkin Rachel (Figures 9 and 13) had a substantially depressed baseline performance and increased rates under 10.0 and 17.8 mg/kg, with an increase under 3.2 mg/kg as well when adjusted for changes in the vehicle control rate. Grumpy Torah (Figures 10 and 14) had decreased response rates under controls and lower doses and increases under higher doses; when adjusted for changes in vehicle control rates, increases are found at all drug doses and during baseline responding. The incomplete data for Ariel (Figures 7 and 11) suggest a depressed response rate under vehicle and an increase at the 17.8 mg/kg dose.

Under VR 125, subjects typically showed a pattern of postchronic responding that included a decrease in the response rate under baseline and vehicle and increases under larger doses. For Golda (Figures 8 and 12) the pattern of responding was similar to that under FR 125, with responding decreasing under increasing drug doses, approaching zero

at the 10.0 mg/kg dose; increases at the 3.2 and 5.6 mg/kg dose may be more suggestive of tolerance than that under 5.6 mg/kg under FR 125. Lumpkin Rachel (Figures 9 and 13) shows similar patterns under FR 125 and VR 125, with tolerance only at the higher doses but with tolerance more evident at a smaller dose (3.2 vs. 5.6 mg/kg) under VR 125. Grumpy Torah (Figures 10 and 14) has a gentler slope across doses under VR 125 than under FR 125, the former showing tolerance under the highest (17.8 mg/kg) dose whereas under the latter it does not. The incomplete data for Ariel (Figures 7 and 11) suggest depressed responding under baseline but not vehicle, no tolerance at low drug doses, and tolerance under 17.8 mg/kg.

To examine similarities in the postchronic performances, Wilcoxon signed-rank tests (Wilcoxon, 1945; Ott, 1993, pp. 297-299) were used; a nonparametric test was used as the sample size was small enough and the variance sufficiently large enough to underpower parametric tests such as *t* and *F*. Means for response rate in component schedules at all drug doses were expressed as percent of vehicle response rates; comparisons were made between all pairs of component schedules pooled across all doses and subjects to obtain a sufficient sample size. The results of the comparisons are listed in Table 4. Whereas comparisons between component schedules with different ratio values were regularly discriminated by the test (p between .002 and <.001), with the same ratio value the results were not statistically significant (p = .264 for FR 5 vs. VR 5, p = .250 for FR 125 vs. VR 125). As visual inspection indicated that there was no reliable difference in tolerance between high and low ratio values for Lumpkin Rachel, the tests were also done omitting data for this subject. In this situation, although the p values were still very low for dislike-parameter comparisons, for the like-parameter

All subjects (n = 18)

Schedules	T	z	p
FR 5 vs. FR 125	0	-3.724	<.001
FR 5 vs. VR 5	71	-0.631	.264
FR 5 vs. VR 125	21	-2.809	.002
FR 125 vs. VR 5	0	-3.724	<.001
FR 125 vs. VR 125	70	-0.675	.250
VR 5 vs. VR 125	9	-3.332	<.001

All subjects except Lumpkin Rachel (n = 13)

Schedules	T	z	p
FR 5 vs. FR 125	0	-3.180	.001
FR 5 vs. VR 5	47	-0.105	.458
FR 5 vs. VR 125	3	-2.970	.001
FR 125 vs. VR 5	0	-3.180	.001
FR 125 vs. VR 125	43	-0.175	.431
VR 5 vs. VR 125	2	-3.040	.001

Table 4. Pairwise comparisons of postchronic performance using the Wilcoxon signed-rank test. Data is pooled from means (expressed as percent of vehicle response rate) for drug sessions across all subjects. The conversion to z for calculating probability is after Ott (1993, p. 299). All tests are two-tailed using an α of .05.

comparisons the p value was substantially increased (p = .458 for FR 5 vs. VR 5, p = .431 for FR 125 vs. VR 125). Not being discriminated by the test, this strongly supports the contention that FR and VR performance with the same ratio parameter are similar.

Reinforcement Loss

Table 5 lists the mean programmed reinforcers earned and trials completed across conditions. As the rate of reinforcement is directly proportionate to the rate of responding, the measures are closely related; all programmed ratios will be completed and programmed reinforcers earned so long as the subject responds rapidly enough to complete the trials before the component schedule times out. In the prechonic phase, nearly all programmed reinforcers were earned during baseline, vehicle, and the 1.0

Ariel

	Prechronic				Postchronic			
Dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)
V	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)
1.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)
3.2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)
5.6	1.00	0.75	1.00	0.85	1.00	1.00	1.00	1.00
	(5.00)	(3.75)	(5.00)	(4.25)	(5.00)	(5.00)	(5.00)	(5.00)
10.0	1.00	0.75	1.00	0.45	*	*	*	*
	(5.00)	(3.75)	(5.00)	(2.25)				
17.8	0.75	0.00	0.45	0.05	0.92	1.00	0.86	0.92
	(3.75)	(0.00)	(2.25)	(0.25)	(4.60)	(5.00)	(4.30)	(4.60)

Golda

	Prechronic				Postchronic			
Dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	1.00	1.00	1.00	1.00	0.75	1.00	0.75	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(3.75)	(5.00)	(3.75)	(5.00)
V	1.00	1.00	1.00	1.00	0.80	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(4.00)	(5.00)	(5.00)	(5.00)
1.0	1.00	1.00	0.83	0.83	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(4.17)	(4.17)	(5.00)	(5.00)	(5.00)	(5.00)
3.2	0.75	0.75	0.50	0.40	0.75	0.75	0.75	0.75
	(3.75)	(3.75)	(2.50)	(2.00)	(3.75)	(3.75)	(3.75)	(3.75)
5.6	0.50	0.25	0.55	0.00	0.82	0.69	0.83	0.34
	(2.50)	(1.25)	(2.75)	(0.00)	(4.08)	(3.47)	(4.16)	(1.71)
10.0	0.25	0.10	0.25	0.00	0.50	0.00	0.75	0.25
	(1.25)	(0.50)	(1.25)	(0.00)	(2.50)	(0.00)	(3.75)	(1.25)

Table 5. Mean proportion of programmed reinforcers earned (top) and number of programmed ratios per component completed (bottom). Proportions are from a programmed 10 per component per session, averaged across sessions in the prechronic and postchronic phases. Doses are in mg/kg of cocaine. B = baseline, V = vehicle, * = subject died before completing any sessions in this condition. (Continued below.)

Table 5 continued

Lumpkin Rachel

	Prechronic				Postchronic			
Dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	0.98	0.98	1.00	0.98	1.00	1.00	1.00	1.00
	(4.88)	(4.92)	(5.00)	(4.92)	(5.00)	(5.00)	(5.00)	(5.00)
V	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)
1.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)
3.2	1.00	1.00	1.00	1.00	0.85	0.95	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(4.25)	(4.75)	(5.00)	(5.00)
5.6	0.75	0.10	0.50	0.75	1.00	1.00	0.80	1.00
	(3.75)	(0.50)	(2.50)	(3.75)	(5.00)	(5.00)	(4.00)	(5.00)
10.0	0.50	0.00	0.50	0.50	1.00	1.00	0.80	1.00
	(2.50)	(0.00)	(2.50)	(2.50)	(5.00)	(5.00)	(4.00)	(5.00)
17.8	0.00	0.00	0.00	0.00	0.75	0.80	0.75	0.85
	(0.00)	(0.00)	(0.00)	(0.00)	(3.75)	(4.00)	(3.75)	(4.25)

Grumpy Torah

	Prechronic				Postchronic			
Dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)
V	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)
1.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)	(5.00)
3.2	1.00	0.50	1.00	0.75	1.00	1.00	1.00	0.95
	(5.00)	(2.50)	(5.00)	(3.75)	(5.00)	(5.00)	(5.00)	(4.75)
5.6	0.75	0.00	1.00	0.50	1.00	0.75	1.00	0.75
	(3.75)	(0.00)	(5.00)	(2.50)	(5.00)	(3.75)	(5.00)	(3.75)
10.0	0.50	0.00	0.55	0.00	0.85	0.50	0.91	0.48
	(2.50)	(0.00)	(2.75)	(0.00)	(4.26)	(2.50)	(4.57)	(2.41)
17.8	0.00	0.00	0.00	0.00	0.95	0.25	0.90	0.00
	(0.00)	(0.00)	(0.00)	(0.00)	(4.75)	(1.25)	(4.50)	(0.00)

mg/kg dose. The proportion of reinforcers earned decreased as dose increased, though there were substantial variations across subjects and component schedules. The largest dose tested for Golda (10.0 mg/kg) substantially decreased the proportion of reinforcers earned (between 0.00 and 0.25), whereas for the same dose in Lumpkin Rachel and Grumpy Torah produced reductions which ranged as high as 0.55; for these latter two subjects, a 17.8 mg/kg dose was required to consistently reduce the proportion of reinforcers earned to zero. However, for Ariel, even at the highest dose (17.8 mg/kg) the proportion under VR 5 was only 0.45 and under FR 5 was 0.75, possibly reflecting an individual difference in drug sensitivities.

During the postchronic phase, all subjects showed variable degrees of recovery, generally with a smaller proportions earned for higher doses. The incomplete data for Ariel has significant recovery (between 0.86 and 1.00) at the 17.8 mg/kg doses. Lumpkin Rachel recovered at the 17.8 mg/kg dose to a relatively limited range of proportions across component schedules (0.75 to 0.85), whereas for Golda (at 10.0 mg/kg) and Grumpy Torah (at 17.8 mg/kg) the range was much larger (between 0.00 and 0.75 for Golda, 0.00 and 0.95 for Grumpy Torah. For all subjects other than Lumpkin Rachel, performance at higher doses recovered more under FR 5 and VR 5 than under FR 125 and VR 125; there was no consistent difference in recovery across subjects between fixed- and variable-ratio schedules of the same parameter value.

Postreinforcement Pausing

As an indicator of postreinforcement pausing, latencies to the first response made in each component schedule were recorded; the values are displayed in Table 6. The data, particularly at zero and low doses, are generally consistent with previous work on

Ariel

	prechronic				postchronic			
dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	1.05	26.16	0.80	1.77	2.34	6.35	0.98	1.12
	(0.59)	(22.61)	(0.31)	(1.72)	(2.93)	(8.70)	(0.13)	(0.28)
V	1.01	33.78	0.77	2.35	1.44	10.30	1.25	1.14
	(0.52)	(27.96)	(0.22)	(2.40)	(0.77)	(6.30)	(0.77)	(0.16)
1.0	0.90	14.77	0.78	1.82	1.37	7.81	0.98	1.00
	(0.26)	(11.65)	(0.10)	(2.77)	(0.48)	(6.15)	(0.48)	(0.19)
3.2	0.89	13.76	0.85	0.94	0.88	5.21	0.76	0.95
	(0.30)	(6.75)	(0.40)	(0.14)	(0.23)	(3.84)	(0.09)	(0.37)
5.6	1.02	42.22	0.75	0.91	0.86	2.78	1.18	0.88
	(0.44)	(125.03)	(0.15)	(0.15)	(0.08)	(1.52)	(1.03)	(0.14)
10.0	0.98	6.43	1.24	6.61	***	***	***	***
	(0.21)	(10.62)	(0.41)	(11.79)				
17.8	10.90	1.78	14.49	144.27	2.54	29.00	2.35	20.85
	(29.87)	*	(26.88)	(45.29)	(2.73)	(51.17)	(3.75)	(54.25)

Golda

	prechronic				postchronic			
dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	0.91	9.47	1.40	2.35	0.97	30.79	14.97	8.93
	(0.28)	(8.56)	(1.51)	(3.32)	(0.20)	(35.82)	(34.01)	(13.87)
V	0.89	10.25	0.94	1.51	6.05	13.03	7.31	4.72
	(0.22)	(9.41)	(0.20)	(0.62)	(12.77)	(8.96)	(19.91)	(6.41)
1.0	0.91	23.57	1.05	5.46	0.92	60.42	0.95	7.91
	(0.18)	(48.04)	(0.24)	(9.37)	(0.13)	(146.93)	(0.20)	(18.58)
3.2	1.15	14.35	0.98	81.76	5.99	22.03	1.54	4.82
	(0.44)	(19.64)	(0.15)	(127.71)	(12.55)	(11.99)	(0.820	(4.76)
5.6	1.10	402.49	1.34	1294.92	1.92	39.88	5.17	57.56
	(0.35)	(35.42)	(0.22)	*	(2.59)	(53.07)	(9.47)	(117.29)
10.0	0.88	27.86	1.67	1.02	1.68	496.60	13.50	81.10
	(0.040	(25.90)	(0.50)	*	(0.49)	*	(37.99)	(113.72)

Table 6. Latencies to first response in seconds. Values are means (top) and standard deviations (bottom). Doses are in mg/kg of cocaine. B = baseline, V = vehicle. * = Cells with values derived from a single session out of two due to a lack of responding in one. ** = No responding in any session in this cell. *** = Subject died before completing any sessions in this condition. (Continued below.)

Table 6 continued

Lumpkin Rachel

	prechronic				postchronic			
dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	0.75	29.49	0.69	1.28	1.25	25.47	1.94	3.42
	(0.25)	(54.14)	(0.21)	(0.64)	(0.32)	(39.33)	(1.76)	(6.25)
V	0.79	22.42	0.74	1.12	1.03	8.09	1.01	1.85
	(0.37)	(40.09)	(0.30)	(0.39)	(0.38)	(6.57)	(0.52)	(1.63)
1.0	0.89	15.39	0.62	1.59	1.45	15.12	0.84	2.44
	(0.34)	(15.38)	(0.17)	(1.99)	(1.20)	(10.99)	(0.19)	(3.14)
3.2	0.78	14.32	0.78	1.32	1.85	37.21	0.75	8.06
	(0.21)	(13.13)	(0.28)	(1.17)	(1.84)	(69.94)	(0.23)	(10.67)
5.6	0.81	12.08	0.70	130.69	4.74	12.65	8.86	20.23
	(0.30)	(12.53)	(0.17)	(290.86)	(11.93)	(9.52)	(20.03)	(54.97)
10.0	0.89	3.30	1.69	10.00	14.02	58.24	2.40	3.57
	(0.20)	(3.49)	(2.37)	(13.49)	(34.38)	(109.26)	(3.35)	(5.60)
17.8	**	**	**	**	0.86	98.48	0.85	64.40
					(0.27)	(161.56)	(0.21)	(144.06)

Grumpy Torah

	prechronic				postchronic			
dose	FR 5	FR 125	VR 5	VR 125	FR 5	FR 125	VR 5	VR 125
B	0.89	18.06	0.77	3.33	0.91	17.97	1.01	7.35
	(0.44)	(11.71)	(0.18)	(5.25)	(0.24)	(18.00)	(0.43)	(16.19)
V	0.71	20.82	1.82	3.70	1.72	5.65	2.23	6.38
	(0.20)	(11.22)	(3.72)	(5.47)	(0.80)	(3.79)	(1.16)	(5.13)
1.0	0.75	14.75	0.66	3.03	2.07	19.16	1.04	6.53
	(0.21)	(16.07)	(0.14)	(1.73)	(3.74)	(20.65)	(0.90)	(9.83)
3.2	0.94	6.07	0.67	12.91	0.95	38.12	0.81	39.29
	(0.30)	(9.71)	(0.24)	(29.80)	(0.51)	(61.26)	(0.19)	(115.00)
5.6	4.97	189.20	7.94	25.09	1.00	30.46	0.85	54.35
	(12.12)	(194.44)	(19.56)	(56.79)	(0.29)	(11.35)	(0.20)	(124.61)
10.0	21.77	**	43.73	188.43	5.07	129.74	4.53	86.54
	(40.25)		(0.19)	(75.49)	(11.09)	(103.98)	(11.10)	(169.42)
17.8	**	**	**	589..213	32.03	1.90	21.50	601.92
				(159.11)	(36.33)	(1.01)	(56.77)	*

schedule performance, with latencies under FR 5 generally being brief (circa 1 s) and much shorter than those under FR 125 (which typically varied between 10 and 20 s and was sometimes much greater). Latencies under VR 125 also tended to be greater than those under VR 5, though the differences were less dramatic (i.e., latencies for the former tended to vary between about 1 and 4 s). Latencies under VR 125 tended to be smaller than those under FR 125, consistent with previous work indicating that postreinforcement pausing tends to be less in the former than the latter (cf. Ferster & Skinner, 1957, p. 391). The patterns of latencies varied considerably across both subjects and component schedules. Prechronic responding typically involved relatively stable, brief latencies across most doses with a very large latency (or no responding, which amounts to a latency longer than the time before the component times out) at a large or the largest dose with the shift in values beng abrupt. Lumpkin Rachel under FR 5 and VR 5 showed relatively stable latencies at most doses and no responding under the 17.8 mg/kg dose, an essentialy similar pattern. However, counterexamples exist; for example, Ariel and Lumpkin Rachel have responding that generally decreases across doses under FR 125. Golda had relatively stable, small latencies across doses with one unusually high value under FR 125 and two raised values under VR 125 other than the highest dose (10.0 mg/kg).

Postchronic responding also typically had a similar pattern of relatively stable latencies with an abrupt increase at a high or the highest dose, but again there were variants. Relatively flat distributions occurred sometimes (Golda under FR 5), or decreases at a high dose after an increase across doses (Lumpkin Rachel under FR 5 and VR 5), and even high latencies under baseline and vehicle and increasing latencies under

increasing doses (Golda under VR 5). Latencies under the highest doses that did not completely suppress responding were smaller for postchronic than prechronic performance for Ariel (except under FR 5) and Grumpy Torah, but the relation was not regular at lower doses, nor did it consistently appear in all subjects. For Lumpkin Rachel, the reverse relationship was found at the 10.0 mg/kg dose under all component schedules except VR 125.

Discussion

Consistent the previous literature, performance under FR schedules varied systematically with schedule parameter; performance under FR 5 recovered more than under FR 125 in Golda, Grumpy Torah, and perhaps Ariel; only Lumpkin Rachel did not show a clear difference. Similarly, under VR schedules, the lower parameter value was associated with greater recovery in all subjects (cf. Branch, 1990); again, only Lumpkin Rachel did not show a clear difference. Tolerance under FR and VR schedules of the same parameter appeared to be generally similar, though for some subjects the data is suggestive of greater tolerance under VR 125 than FR 125. This data is generally consistent with the response-strength hypothesis. As previously discussed, greater tolerance is predicted (and found) under small ratios than large ones. As seen in Figures 7 through 10, the prechronic baseline response rates for FR 5 and VR 5 were generally similar across subjects, with any difference favoring VR 5. Under FR 125 and VR 125 the differences were often larger (circa two responses per second for Golda and Lumpkin

Rachel); as reinforcement rate increases under a ratio schedule as the response rate increases, greater tolerance would be expected with an increase in response rate.

Consistent with other studies using the mult-FR paradigm, data obtained were problematic for the reinforcement-loss hypothesis; greater tolerance was consistently associated with those component schedules with the least reinforcement loss. As listed in Table 5, the proportion of reinforcers earned during the prechronic series typically were higher under FR 5 than under FR 125 (1.00 for FR 5 versus 0.75 for FR 125 at 10.0 mg/kg for Ariel, 0.50 versus 0.25 at 5.6 mg/kg for Golda, 0.50 versus 0.00 at 10.0 mg/kg for Lumpkin Rachel and Grumpy Torah). Essentially the same relationship was found for VR 5 and VR 125 (1.00 for VR 5 versus 0.45 for VR 125 at 10.0 mg/kg for Ariel, 0.55 versus 0.00 at 5.6 mg/kg for Golda, 0.55 versus 0.00 at 10.0 mg/kg for Grumpy Torah; Lumpkin Rachel, however, was 0.50 versus 0.50 at 10.0 mg/kg). Differences between performances under FR and VR schedules were unsystematic across subjects except that, for the same parameter value, VR performances tended to have higher baseline response rates than FR performances.

The latency data strongly support control of the behavior by the reinforcement schedules. The latency data generally followed the expected patterns for postreinforcement pausing for the relevant component schedules; thus the results cannot be attributed to a lack of schedule control across different component schedules. Thelatency data do not strongly support a role for changes in postreinforcement pausing in tolerance; changes in latencies did not systematically reflect overall response rates. The tendency for large latencies in the higher doses may not necessarily reflect changes in pausing per se, but rather a general slowing or suppression of responding in general. A

more detailed recording of the performance may be warranted to determine what actually occurs under these conditions. In principle, the time of every response might be recorded and a cumulative record reconstructed; some recent studies have used cumulative records (e.g., Pinkston & Branch, 2004b), though without a cumulative recorder or the proper data management tools, the enormous amount of data might become unwieldy. An alternative would be to divide time into a number of "bins" of a fixed length and record the number of responses occurring in successive bins.

The lack of differences in tolerance across ratio parameters for Lumpkin Rachel (FR 5 vs. FR 125; VR 5 vs. VR 125), in exception to the data from the other subjects, almost certainly can be related to the change in the chronic dose. Although the dosage was changed as the initial drug effect was too large (suppressed too much responding), reducing it may have interrupted the relationship between the injection procedure and drug effect. Whereas under the usual chronic dosing procedure the administration regularly predicts a particular drug dose, by changing the dose, the predictive power of the administration as an antecedent is interrupted, possibly partly extinguishing its behavioral effects; thus as the subject habituates to the drug, performances under large ratios might recover more fully than they would otherwise. Previous work using a chronic administration procedure in which the dose varied across adminstrations (the injection procedure failing to predict a specific dose) failed to produce differences in tolerance across schedule parameters (Yoon & Branch, 2004).

CHAPTER V

GENERAL DISCUSSION

Although Experiment 1 produced some results suggesting that tolerance under VR schedules was less related to the schedule parameter than under FR schedules, when the problems of the study were corrected in Experiment 2, the contrary result was found, that is, they in fact performed similarly. The difference is likely due to the procedures; whereas in Experiment 2 the chronic doses were adjusted to sufficiently reduce responding enough to produce tolerance, this did not occur uniformly in Experiment 1.

The similarity of performances under FR and VR schedules of the same ratio parameter has important implications. As discussed above, such a result favors the response-strength hypothesis as greater tolerance is associated with a greater rate of reinforcement. While decreases in tolerance with increasing ratio requirements have been found in RR schedules (Branch, 1990), the results of Experiment 2 suggest that the tolerance produced by ratio schedules of differing variability (FR versus VR) is actually comparable. Such a result makes sense if the overall rate of reinforcement is the controlling factor.

An equally important implication of this is that the molecular-level pattern of behavior produced by the schedule may not be related to the level of tolerance it produces. These results are reminiscent of those of Pinkston and Branch (2004b), who, by adding a small tandem FR requirement to FI schedules of different interval parameters, produced patterns of responding similar to those produced by FR schedules;

nevertheless, the tolerance that developed across the tand FI FR schedule components was similar across interval parameters, as typically occurs in FI alone. In both cases, the pattern of responding itself does not appear to be critical to the development of tolerance. This provides additional support for molar-level hypotheses, such as the response-strength hypothesis.

Although these studies examined how ratio variability alters the effects of reinforcement rate on tolerance, several avenues have yet to be explored. The response-strength hypothesis would predict that two responses with the same reinforcement rate would have the same tolerance even if the schedules are different. By altering the rate of response through pacing contingencies, the rate of reinforcement under ratio schedules could be manipulated to provide direct tests of this hypothesis. For example, the response rate of an FR 25 component could be increased to be five times that of an FR 5 component; since the reinforcement rate under these two components would be identical, the response strength hypothesis would predict they would have similar tolerance. Alternatively, a standard FR component might be compared with FR components that have been paced; a slowed-down component should have less tolerance than an unpaced component of the same ratio, whereas a sped-up component should have more. An additional direction without pacing contingencies would be to supplement the reinforcers by providing additional reinforcers independently of responding; according to the response-strength hypothesis, this increased rate of reinforcement would increase response strength (and thus tolerance) above a similar schedule without the supplementation.

Another direction concerns a consistent difference reported in the literature. As previously discussed, whereas ratio schedules produce decreasing tolerance with increasing ratio requirements, there is no similar reliable change in tolerance under FI schedules with different interval requirements. As the interval of an FI schedule increases, the rate of reinforcement decreases; under these circumstances the response-strength hypothesis would predict that tolerance should decrease with increasing intervals.

The resolution of this apparent contradiction may result from the discriminative-stimulus functions inherent in the schedules, aside from those specifically programmed (usually key-light colors in the above-reviewed research). In a ratio schedule, responding may occur at any rate and result in reinforcement so long as the proper number of responses have occurred; save for the schedule timing out, the passage of time has no discriminative function. In contrast, in an FI schedule, the passage of time has a discriminative function; once the programmed interval has expired, the first response is reinforced, whereas before then all responses are extinguished (cf. Ferster & Skinner, 1957, pp. 134-135). An FI schedule thus includes an inherent discriminative function that interacts with the rate of reinforcement for control on responding. Time-related discriminative stimuli, of course, are present in FR schedules, where the delivery of a reinforcer acts as a discriminative stimulus for the absence of reinforcement for responding (op. cit., pp. 39-40); however, the suppressive intervals involved may be comparatively short (postreinforcement pausing) and have little effect on the overall result. Thus the response-strength hypothesis may be essentially correct but incomplete. During an FI schedule, in the time leading up to the end of the interval a discriminative

stimulus suppressing responding is in effect; only at the end of the interval is this not the case, at which point the schedule is effectively a small ratio schedule. Hence similar tolerance is observed across FI schedules of different interval durations, the requirements across schedule parameters is effectively similar.

There are several approaches to examining this hypothesis. In an FR schedule, the suppressive effects of the reinforcer as a discriminative stimulus are relatively short; thus control by schedule-correlated stimuli predominates and tolerance is similar to that observed in a VR schedule with the same parameter. A similar relationship would not be expected between FI and VI. Whereas the passage of time has a discriminative function in FI schedules, in VI schedules there is no discriminative stimulus for a regular period of extinction occurring before responding is reinforced (cf. op. cit., p. 326). Hence under VI there would be no period where responding is regularly suppressed and decreases in tolerance would be expected with increasing mean interval parameters. A simple examination of this hypothesis would be examining tolerance under a mult VI schedule (e.g., mult VI 5-s VI 30-s VI 180-s), though one might also directly compare VI schedule components with FI for a control comparison (e.g., mult FI 5-s FI 180-s VI 5-s VI 180-s). A different approach would be to contrive a stimulus to take the place of the passage of time under FI. An arbitrary stimulus could be associated with extinction; this stimulus could then be superimposed over an FR 1 schedule, the occurrence of the stimulus being yoked to the intervals where responding would not be reinforced in a FI schedule; if the above hypothesis is correct, the tolerance that develops under the two schedules should be similar.

Another issue regards the degree to which tolerance is affected by antecedent stimuli. Some suggestion of this comes from several examples in Experiment 2 (Figures 7 through 10) where the postchronic response rates in the baseline and vehicle conditions differed. If the drug effects alone were effective, they arguably should have been identical; however, drug or vehicle administration inevitably involves stimuli that are not present in baseline conditions, even if no actual drug is administered. Additionally, as described above, the change in the chronic dose for Lumpkin Rachel may have disrupted the effectiveness of the administration itself as an antecedent. A direct parallel occurs in Yoon and Branch (2004), where a variable chronic dosing procedure resulted in a failure of tolerance to develop. Arguably then the injection procedure may acquire some control over the behavior which will occur even during vehicle administrations. The particular antecedent stimulus relationship is arguably a conditioned eliciting stimulus as the effects above described seem tied to the ability of the administration procedure to predict a specific drug dosage; once cued, the subject produces compensatory responses, presumably physiological, which counter the unconditioned drug effect (cf. Siegel et al., 1982). (The effect being due to habituation is unlikely as the postchronic baseline sessions should have been equally affected as the vehicle sessions.) A simple test of this hypothesis would be to replace the manual injections to administration through an indwelling catheter; this would eliminate the need to physically handle the subject during administration and minimize or eliminate any antecedent stimuli related to the administration procedure. Catheter administration would allow arbitrary stimuli to be used as an "injection" preceding particular events. For example, if tolerance depends on the administration procedure becoming an effective antecedent to a specific chronic dose,

then a variable-dosing procedure might be used to produce tolerance if the "injection" stimulus only occurs when a particular dose is injected. Finally, if the compensatory responses can be sufficiently specified, their occurrence may be directly measured in relation to other events of interest, such as putative discriminative stimuli or motivating operations.

Limitations of the Study

These studies had certain limitations. Tolerance research does not always replicate previous results, sometimes resulting from arbitrary procedural variations (e.g., the variable dosing procedure in Yoon and Branch [2004]). As not all factors affecting tolerance may be well known, understood, or even previously documented, it is difficult if not impossible to design studies without arbitrary features with the potential to affect the outcome, this study being no exception. For example, the baseline and vehicle sessions during the prechronic series and the chronic sessions during the postchronic series act as "buffers" to maintain experience with the schedule while isolating the effects of particular doses; presumably in this or other research, the number of sessions between these probes was sufficient that there was little or no carryover of effects. The number of chronic sessions between probe sessions in Experiment 2 was smaller than in many other studies (e.g., Hoffman et al., 1987). Had the results been, for example, that there were systematic differences across subjects between tolerance under FR and VR schedules, one might have argued that the results were affected by the procedure that allowed for carryover during the postchronic series. Given the results were not unexpectedly different from previous research, one may argue that the number of buffer sessions

between was sufficient to prevent carryover, though logically there is no reason to judge the issue in either direction.

Several other features of these studies may be similarly criticized. For example, although the duration of chronic dosing was determined by the visual stability of the data for all subjects in Experiment 1 and for one subject (Golda) in Experiment 2, for the remaining subjects, in part for expediency, a set number of sessions was chosen. These variants in part may be responsible for the observed intrasubject variability in this study as, dependent on the subjects, some may have not received the same effective exposure. The simplest procedural variation for standardizing the chronic dose would be to select an arbitrary number of sessions. Such a procedure allows the chronic dosing phase to be determined in relatively simple, direct terms (i.e., a set number of sessions), making it relatively easy to replicate. However, as occurred in these experiments, different subjects may not have the same sensitivity to the same drug dose. Alternatively, a procedure could be used where the length of the chronic phase is determined by the stability, defined either visually or mathematically, of the subject's performance. While this might produce more consistent performance, the length of the chronic dosing would depend on the subject's behavior, with the potential for it to be greatly extended, perhaps indefinitely.

Details of the schedules used might also be relevant. For the VR schedules, an arithmetic distribution was used, similar to that described by Ferster and Skinner (1957, p. 392-293), this being relatively simple to generate. Some other research, however, has used other distributions, such as one based on that described by Fleshler and Hoffman (1962) for intervals in variable-interval schedules (e.g., Herrnstein & Heyman, 1979;

Webbe et al., 1974). Since a quasi-Fleshler-Hoffman distribution would specifically favor ratios within particular ranges relative to a flat distribution as in an arithmetic VR, the choice of distribution might affect the outcome. Thus, if short ratios engender greater tolerance, one might argue that one would find greater tolerance under a quasi-Fleshler-Hoffman VR than under an arithmetic VR. Similar criticisms might be made for different kinds of distribution (e.g., geometrical) or variations within the same distribution (e.g., a VR composed of ten ratios versus one of the same overall ratio parameter but with twenty ratios). Ultimately these questions are empirical ones and must be explored thusly.

The use of latency to first response as a measure of postreinforcement pausing in Experiment 2 is also subject to criticism. The validity of this measure is supported by prechronic performance under baseline and vehicle conditions, in which the values vary as expected for the component schedules (particularly FR 125 being much larger than both FR 5 and VR 125). However, the use of the measure depends on responding to adhere to a break-and-run pattern where, once begun, responding occurs regularly. It is possible that the subject could continue to pause after making one response and that responding could occur irregularly through the trial. Again, the question is empirical and requires a finer-grained investigation of the subjects' performances.

Additional Directions for Future Research

Although these studies did not directly test the reinforcement-loss hypothesis, the data was relevant as this hypothesis was not supported. Although there was

reinforcement loss associated with the presence of drug, greater reinforcement loss (large ratios) was associated with less tolerance than less reinforcement loss (small raios; Table 5). To make this hypothesis consistent with data from this and other mult-FR paradigm studies would require that the degree of tolerance must be inversely related to the amount of reinforcement loss; hence, less tolerance would develop in responding under large ratios, which experience large reinforcement losses, as opposed to responding under small ratios, which experience less loss in reinforcement. This modified hypothesis might be tested specifically through manipulating the delivery of reinforcers. For example, an FR component might be compared with an FR component of the same ratio parameter but for which the reinforcer deliveries are supplemented to maintain the reinforcement rate even when the response rate drops due to drug effects; according to the reinforcement-loss hypothesis, responding under the supplemented FR should not develop tolerance.

Tolerance research using multiple schedules has typically involved visual stimuli for programmed discriminative stimuli, but this does not necessarily have to be so. Mauro and Mace (1996) examined behavioral momentum in rats using multiple schedules, comparing the persistence of responding once the schedules were changed to extinction. When the multiple schedule used visual discriminative stimuli, resistance to change was related to the previous schedule experienced in each component; however, when auditory discriminative stimuli were used, no such relationship was found. Similarly, although there is no a-priori reason to believe the modality of the discriminative stimuli should affect the results, this may not be the case, and future research should investigate how discriminative stimulus characteristics affect tolerance.

The topic may be of particular relevance as tolerance outside the laboratory arguably may involve discriminative stimuli that may involve nonvisual modalities or be complex.

Another possible direction would be to systematically investigate the effects of using different kinds of consequences on tolerance. As mentioned above, some failures to find tolerance under FI schedules may be related to negatively reinforcing behavior with electric shock or positively reinforcing behavior with electric brain stimulation. These differences may in part be related to differences in motivating operations. Whereas food's effectiveness as a reinforcer decreases with repeated exposure if the reinforcements occur closely enough (it acts as its own abolishing operation), this is not the case with shock, which acts as its own establishing operation. Behavior reinforced with electrical brain stimulation is known for not only occurring at high rates, but for being so persistent that subjects will respond for it to the exclusion of everything else (e.g., Olds & Milner, 1954), suggesting a lack of habituation, saturation, or abolishing operations. Changes in the effectiveness of consequences were not addressed by the hypotheses reviewed here. Whether or not this is specific to FI schedules or occurs more generally is unknown, and a comparison across schedules would be warranted. Additionally, the effects of manipulating motivating operations might be investigated to isolate whether any differences in tolerance observed are due to the particular reinforcers themselves or how they change due to of repeated exposure.

APPENDIX A

MEANS AND RANGES FOR DATA IN EXPERIMENT 1

B = baseline, V = vehicle, pre = mean prechronic performance, post = mean postchronic performance, min = minimum value, max = maximum value. All response rates are expressed in responses per second. All doses are expressed in mg/kg of cocaine.

Bluma Shalom (response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	3.21	2.18	4.03	3.67	3.19	4.21
	V	3.46	2.99	3.80	4.19	3.82	4.55
	1.0	3.16	2.97	3.34	4.10	3.30	4.90
	3.2	2.83	2.81	2.85	3.12	3.05	3.18
	5.6	2.90	2.87	2.92	3.54	2.12	5.01
	10.0	0.20	0.19	0.20	3.17	2.91	3.43
FR 125	B	3.85	2.33	4.79	3.22	2.31	4.00
	V	3.63	2.93	4.51	3.28	2.81	3.76
	1.0	3.03	2.66	3.40	3.87	3.38	4.36
	3.2	1.81	0.25	3.38	2.97	2.95	2.99
	5.6	0.95	0.55	1.35	2.01	1.23	3.02
	10.0	0.27	0.20	0.35	0.92	0.68	1.15
VR 5	B	3.01	1.69	5.69	3.39	3.02	3.72
	V	3.04	2.58	3.44	4.30	3.83	4.76
	1.0	2.82	2.68	2.95	3.83	3.23	4.43
	3.2	2.36	1.93	2.79	3.94	3.01	4.87
	5.6	2.73	2.73	2.73	3.73	1.94	5.42
	10.0	0.08	0.00	0.16	3.00	2.40	3.60
VR 125	B	3.64	2.33	4.76	3.37	1.95	3.91
	V	3.58	2.46	4.53	2.19	2.12	2.26
	1.0	3.59	2.90	4.29	2.38	2.33	2.43
	3.2	1.56	0.36	2.77	1.98	1.97	2.00
	5.6	1.04	0.37	1.72	1.99	0.38	2.82
	10.0	0.24	0.24	0.25	1.66	1.49	1.82

Bluma Shalom (expressed as percentage of vehicle response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	92.69	67.73	125.10	87.74	76.34	100.48
	V	100.00	92.76	118.15	100.00	91.20	108.80
	1.0	91.13	92.26	103.93	98.04	78.96	117.12
	3.2	81.72	87.24	88.68	74.45	72.85	76.05
	5.6	83.58	89.29	90.65	84.65	50.56	119.71
	10.0	5.70	5.95	6.32	75.82	69.58	82.05
FR 125	B	105.97	64.15	132.06	98.04	70.36	121.88
	V	100.00	80.80	124.20	100.00	85.45	114.55
	1.0	83.45	73.26	93.64	117.79	102.88	132.71
	3.2	49.91	6.77	93.06	90.44	89.76	91.12
	5.6	26.15	15.08	37.22	61.08	37.51	92.02
	10.0	7.56	5.48	9.63	27.88	20.63	35.12
VR 5	B	99.07	55.62	187.62	78.97	70.42	86.64
	V	100.00	84.88	113.22	100.00	89.25	110.75
	1.0	92.76	88.38	97.13	89.09	75.10	103.07
	3.2	77.79	63.61	91.97	91.70	70.00	113.40
	5.6	89.91	89.90	89.92	86.87	45.20	126.25
	10.0	2.63	0.14	5.12	69.85	55.95	83.75
VR 125	B	101.89	65.22	132.99	153.73	88.71	178.08
	V	100.00	68.67	126.53	100.00	96.79	103.21
	1.0	100.50	81.12	119.89	108.46	106.15	110.78
	3.2	43.67	9.99	77.35	90.43	89.91	90.96
	5.6	29.16	10.23	48.09	90.57	17.18	128.46
	10.0	6.79	6.59	6.99	75.53	68.08	82.98

Yovel (response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	2.06	1.33	2.53	2.43	2.14	2.62
	V	2.18	1.45	2.56	2.57	2.34	2.79
	1.0	2.44	2.37	2.51	2.37	2.19	2.55
	3.2	1.67	1.31	2.02	2.95	2.54	3.36
	5.6	1.94	1.40	2.48	2.18	0.20	3.34
	10.0	0.00	0.00	0.00	0.19	0.19	0.19
FR 125	B	1.89	1.17	2.61	1.87	1.63	2.21
	V	1.91	1.06	2.24	2.26	2.16	2.35
	1.0	1.02	0.67	1.38	1.28	0.92	1.64
	3.2	1.11	0.44	1.79	1.10	0.84	1.37
	5.6	0.54	0.26	0.81	0.94	0.38	1.62
	10.0	0.00	0.00	0.00	0.79	0.73	0.85
VR 5	B	1.99	1.31	2.49	2.07	1.39	2.50
	V	2.18	1.25	2.56	2.14	1.35	2.94
	1.0	2.14	1.77	2.52	2.40	2.28	2.52
	3.2	1.91	1.71	2.10	2.64	2.51	2.78
	5.6	1.80	1.46	2.14	1.97	0.16	2.92
	10.0	0.00	0.00	0.00	0.21	0.19	0.23
VR 125	B	2.45	1.96	3.19	2.08	1.87	2.20
	V	2.25	1.66	2.73	2.03	1.78	2.27
	1.0	2.78	2.34	3.21	1.90	1.49	2.30
	3.2	1.91	0.99	2.83	1.82	1.39	2.26
	5.6	0.69	0.66	0.72	1.57	0.87	2.39
	10.0	0.14	0.14	0.14	0.35	0.34	0.37

Yovel (expressed as percentage of vehicle response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	94.65	61.11	116.06	94.86	83.28	102.14
	V	100.00	66.39	117.31	100.00	91.19	108.81
	1.0	111.97	108.80	115.13	92.29	85.25	99.33
	3.2	76.56	60.34	92.79	114.92	98.87	130.97
	5.6	89.00	64.35	113.65	84.99	7.62	130.35
	10.0	0.00	0.00	0.00	7.53	7.52	7.55
FR 125	B	98.89	61.40	136.58	82.71	72.11	98.89
	V	100.00	55.46	117.22	100.00	95.80	100.00
	1.0	53.65	35.00	72.30	56.62	40.80	53.65
	3.2	58.30	22.98	93.62	48.88	37.06	58.30
	5.6	28.20	13.75	42.64	41.64	16.81	28.20
	10.0	0.00	0.00	0.00	34.80	32.13	0.00
VR 5	B	91.44	60.06	114.09	96.39	64.91	116.69
	V	100.00	57.38	117.35	100.00	62.96	137.04
	1.0	98.34	81.02	115.66	112.01	106.52	117.51
	3.2	87.40	78.44	96.37	123.30	116.94	129.65
	5.6	82.59	66.88	98.31	91.87	7.38	136.52
	10.0	0.19	0.19	0.19	9.75	8.71	10.78
VR 125	B	108.70	80.24	130.62	102.77	92.13	108.79
	V	100.00	67.87	111.55	100.00	88.04	111.96
	1.0	123.52	95.83	131.44	93.71	73.77	113.65
	3.2	84.84	40.33	115.77	89.94	68.36	111.52
	5.6	30.62	26.85	29.50	77.63	43.00	117.78
	10.0	6.00	5.52	5.52	17.41	16.77	18.06

Tova (response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	2.18	1.66	2.59	2.29	2.07	2.56
	V	2.19	1.54	2.56	2.29	2.06	2.53
	1.0	2.38	2.27	2.49	2.12	1.42	2.81
	3.2	1.42	0.92	1.92	2.07	0.19	2.30
	5.6	2.36	2.20	2.52	1.56	0.19	2.89
	10.0	1.19	0.19	2.19	1.81	1.75	1.88
FR 125	B	1.47	0.98	2.00	1.39	1.12	1.67
	V	1.39	0.75	2.06	1.87	1.83	1.91
	1.0	1.35	0.93	1.76	1.76	1.58	1.94
	3.2	1.39	1.39	1.39	1.67	0.37	1.72
	5.6	0.61	0.53	0.69	1.29	0.70	1.73
	10.0	0.43	0.31	0.55	0.40	0.36	0.44
VR 5	B	2.00	1.22	2.68	2.14	1.53	2.48
	V	2.22	1.42	2.52	1.87	0.81	2.93
	1.0	2.23	2.02	2.45	1.62	0.70	2.54
	3.2	2.40	2.13	2.66	1.54	0.15	2.73
	5.6	2.37	2.24	2.51	2.02	0.15	2.97
	10.0	1.17	0.18	2.16	1.44	0.24	2.65
VR 125	B	2.14	1.63	2.59	1.82	1.48	2.07
	V	2.02	1.62	2.45	1.20	1.15	1.25
	1.0	1.89	1.78	2.00	1.10	1.10	1.10
	3.2	1.75	1.25	2.25	0.98	0.69	1.06
	5.6	0.92	0.90	0.93	1.14	0.69	1.46
	10.0	0.44	0.28	0.60	1.60	1.56	1.64

Tova (expressed as percentage of vehicle response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	99.60	75.91	118.65	99.62	90.06	111.59
	V	100.00	70.57	116.89	100.00	89.76	110.24
	1.0	108.79	103.88	113.69	92.23	61.88	122.58
	3.2	65.01	42.18	87.84	90.42	8.19	100.39
	5.6	108.03	100.63	115.42	67.92	8.19	125.76
	10.0	54.44	8.77	100.11	79.04	76.34	81.75
FR 125	B	105.61	70.90	144.08	74.38	60.00	89.33
	V	100.00	54.24	148.40	100.00	97.91	102.09
	1.0	97.08	67.16	127.00	94.08	84.52	103.64
	3.2	100.08	99.84	100.33	89.41	19.84	91.86
	5.6	43.90	38.41	49.39	68.80	37.59	92.19
	10.0	30.88	22.23	39.54	21.30	19.04	23.56
VR 5	B	90.11	54.87	120.53	114.17	81.74	132.54
	V	100.00	63.99	113.27	100.00	43.30	156.70
	1.0	100.49	90.78	110.21	86.61	37.50	135.73
	3.2	107.88	96.10	119.65	82.21	7.94	146.03
	5.6	106.80	100.80	112.80	108.02	7.94	158.72
	10.0	52.67	7.97	97.38	77.17	12.57	141.76
VR 125	B	106.06	76.25	120.94	151.88	123.13	172.47
	V	100.00	75.47	114.28	100.00	95.48	104.52
	1.0	93.44	82.97	93.22	91.61	91.42	91.81
	3.2	86.74	58.45	105.11	81.97	57.72	88.56
	5.6	45.35	41.90	43.63	95.21	57.72	121.61
	10.0	21.73	12.95	28.04	133.59	130.16	137.01

APPENDIX B

MEANS AND RANGES FOR DATA IN EXPERIMENT 2

Details are the same as in Appendix A.

Ariel (response rate)

schedule	dose	pre	min	max	post*
FR5	B	2.48	1.04	3.35	1.39
	V	2.48	1.26	3.06	1.72
	1.0	2.61	2.58	2.64	2.03
	3.2	2.14	1.74	2.54	2.73
	5.6	2.39	2.18	2.59	2.70
	10.0	2.52	2.39	2.66	
	17.8	1.00	1.00	1.82	1.34
FR 125	B	1.77	1.10	2.61	2.50
	V	1.60	0.93	1.98	3.26
	1.0	2.03	1.68	2.37	3.22
	3.2	2.28	1.87	2.69	3.45
	5.6	0.68	0.34	1.02	3.54
	10.0	1.52	0.27	2.78	
	17.8	0.02	0.01	0.03	1.55
VR 5	B	2.53	1.65	3.08	2.40
	V	2.60	2.41	2.91	1.83
	1.0	2.33	2.28	2.38	2.36
	3.2	2.30	2.01	2.59	2.54
	5.6	2.55	2.54	2.57	2.10
	10.0	1.30	0.64	1.95	
	17.8	0.13	0.10	0.15	1.46
VR 125	B	1.59	1.18	1.95	1.01
	V	1.57	1.41	1.71	1.77
	1.0	1.54	1.52	1.56	1.55
	3.2	1.21	0.73	1.70	0.79
	5.6	0.72	0.55	0.89	0.68
	10.0	0.21	0.08	0.34	
	17.8	0.03	0.01	0.06	0.57

*Due to subject death, postchronic values are based on a single session.

Ariel (expressed as percentage of vehicle response rate)

schedule	dose	pre	min	max	post*
FR5	B	100.01	41.98	134.79	81.21
	V	100.00	50.81	123.16	100.00
	1.0	105.13	103.95	106.31	118.51
	3.2	86.06	70.02	102.10	159.01
	5.6	96.00	87.73	104.27	157.37
	10.0	101.56	96.01	107.10	
	17.8	40.16	40.16	73.42	78.15
FR 125	B	110.56	68.58	163.32	76.67
	V	100.00	58.45	124.19	100.00
	1.0	126.91	105.38	148.44	98.91
	3.2	142.73	116.82	168.65	105.89
	5.6	42.60	21.30	63.90	108.62
	10.0	95.45	16.96	173.94	
	17.8	0.99	0.38	1.61	47.69
VR 5	B	97.21	63.59	118.51	130.87
	V	100.00	92.87	112.08	100.00
	1.0	89.73	87.84	91.61	129.06
	3.2	88.60	77.37	99.83	138.83
	5.6	98.28	97.65	98.92	114.75
	10.0	49.88	24.57	75.20	
	17.8	4.82	3.69	5.95	79.87
VR 125	B	101.42	75.09	124.49	56.73
	V	100.00	90.02	108.93	100.00
	1.0	98.39	97.09	99.70	87.45
	3.2	77.49	46.36	108.62	44.57
	5.6	45.69	34.85	56.54	38.10
	10.0	13.47	5.11	21.83	0.00
	17.8	2.03	0.32	3.75	31.89

*Due to subject death, postchronic values are based on a single session.

Golda (response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	2.88	2.07	3.77	1.53	0.19	2.87
	V	2.88	2.56	3.17	1.46	0.23	2.68
	1.0	2.62	2.26	2.95	2.73	2.55	2.90
	3.2	3.56	2.09	5.04	1.33	0.21	2.45
	5.6	0.20	0.19	0.20	1.50	0.17	2.51
	10.0	0.10	0.00	0.19	0.18	0.18	0.19
FR 125	B	3.98	1.83	4.95	3.04	1.50	4.57
	V	4.03	1.32	5.24	3.52	3.30	3.75
	1.0	2.42	1.30	3.76	1.78	0.93	2.62
	3.2	1.84	0.21	3.47	1.49	0.35	2.63
	5.6	0.18	0.04	0.32	0.75	0.26	2.80
	10.0	0.04	0.00	0.09	0.18	0.18	0.19
VR 5	B	3.39	0.49	4.12	1.25	0.15	2.35
	V	3.58	3.07	3.90	2.52	2.05	2.99
	1.0	2.19	0.17	3.34	3.25	3.23	3.27
	3.2	1.66	0.00	3.31	1.26	0.15	2.36
	5.6	0.24	0.22	0.25	1.61	0.12	2.96
	10.0	0.09	0.01	0.16	0.18	0.18	0.19
VR 125	B	6.14	2.89	7.42	1.25	2.51	5.57
	V	6.58	5.50	7.21	2.52	4.51	6.64
	1.0	4.17	0.48	6.25	3.25	2.37	6.62
	3.2	0.34	0.00	0.67	1.26	0.47	3.15
	5.6	0.00	0.00	0.00	1.61	0.00	4.03
	10.0	0.00	0.00	0.00	0.18	0.18	0.19

Golda (expressed as percentage of vehicle response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	100.05	71.78	130.99	105.11	13.26	196.97
	V	100.00	89.01	110.20	100.00	16.10	183.90
	1.0	91.08	78.39	102.28	187.34	175.54	199.14
	3.2	123.74	72.65	174.82	91.33	14.43	168.23
	5.6	6.82	6.72	6.92	103.37	11.71	172.45
	10.0	3.37	0.00	6.74	12.67	12.45	12.90
FR 125	B	98.55	45.27	122.68	86.20	42.58	129.81
	V	100.00	32.68	129.94	100.00	93.51	106.49
	1.0	59.95	32.22	93.18	50.43	26.44	74.42
	3.2	45.56	5.19	85.94	42.38	10.05	74.70
	5.6	4.46	0.93	7.98	21.31	7.52	79.56
	10.0	1.06	0.00	2.12	5.23	5.14	5.33
VR 5	B	94.63	13.62	115.04	49.48	5.98	92.97
	V	100.00	85.62	108.82	100.00	81.38	118.62
	1.0	61.09	4.80	93.14	128.87	128.12	129.63
	3.2	46.23	0.00	92.45	49.87	6.03	93.71
	5.6	6.60	6.24	6.96	63.89	4.57	117.37
	10.0	2.40	0.23	4.56	7.31	7.18	7.44
VR 125	B	93.20	43.96	112.67	72.45	45.03	99.87
	V	100.00	83.55	109.47	100.00	80.91	119.09
	1.0	63.27	7.35	94.90	80.59	42.54	118.65
	3.2	5.11	0.01	10.20	32.47	8.49	56.46
	5.6	0.01	0.00	0.02	9.74	0.00	72.26
	10.0	0.01	0.00	0.01	3.31	3.25	3.37

Lumpkin Rachel (response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	2.61	0.20	3.31	2.13	2.00	2.27
	V	2.80	2.25	3.10	2.63	2.47	2.79
	1.0	2.70	2.47	2.93	2.00	1.50	2.49
	3.2	2.75	2.29	3.20	1.24	0.29	2.19
	5.6	1.31	0.19	2.42	2.53	2.32	2.74
	10.0	1.14	0.00	2.29	1.27	0.23	2.31
	17.8	0.00	0.00	0.00	1.47	0.19	2.75
FR 125	B	1.33	0.22	2.42	1.13	0.94	1.32
	V	1.31	0.67	1.91	1.95	1.94	1.96
	1.0	1.28	1.02	1.55	1.05	0.98	1.12
	3.2	1.03	0.98	1.09	0.71	0.53	0.90
	5.6	0.06	0.00	0.12	1.19	1.00	1.39
	10.0	0.00	0.00	0.00	0.78	0.50	1.05
	17.8	0.00	0.00	0.00	0.68	0.32	1.03
VR 5	B	3.47	2.75	4.23	1.18	1.01	1.36
	V	3.43	2.92	4.10	3.00	2.34	3.67
	1.0	3.44	3.03	3.86	3.20	3.19	3.21
	3.2	3.14	2.69	3.60	3.67	3.62	3.73
	5.6	1.92	0.00	3.84	2.01	0.21	3.80
	10.0	0.95	0.00	1.90	2.08	0.84	3.33
	17.8	0.00	0.00	0.00	1.64	0.23	3.04
VR 125	B	2.94	2.23	3.58	2.50	2.13	2.88
	V	3.08	2.71	3.66	2.78	2.67	2.88
	1.0	2.45	2.41	2.50	2.12	2.11	2.13
	3.2	1.49	1.35	1.63	1.91	1.28	2.53
	5.6	0.60	0.25	0.95	1.39	0.77	2.00
	10.0	0.20	0.19	0.22	2.80	2.35	3.25
	17.8	0.00	0.00	0.00	1.26	0.60	1.91

Lumpkin Rachel (expressed as percentage of vehicle response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	93.36	6.99	118.30	81.27	76.01	86.54
	V	100.00	80.30	110.96	100.00	93.93	106.07
	1.0	96.54	88.36	104.72	76.01	57.11	94.91
	3.2	98.15	81.94	114.36	47.16	10.96	83.36
	5.6	46.73	6.94	86.52	96.42	88.39	104.44
	10.0	40.90	0.00	81.81	48.23	8.61	87.86
	17.8	0.00	0.00	0.00	56.13	7.35	104.90
FR 125	B	101.32	16.93	184.99	58.05	48.24	67.87
	V	100.00	50.87	145.84	100.00	99.70	100.30
	1.0	97.86	77.62	118.09	53.83	50.34	57.32
	3.2	78.91	74.95	82.87	36.49	26.98	45.99
	5.6	4.53	0.00	9.06	61.30	51.28	71.32
	10.0	0.13	0.00	0.25	39.93	25.80	54.06
	17.8	0.00	0.00	0.00	34.70	16.52	52.89
VR 5	B	101.19	80.04	123.43	39.43	33.69	45.16
	V	100.00	85.25	119.51	100.00	77.90	122.10
	1.0	100.39	88.19	112.59	106.66	106.27	107.05
	3.2	91.67	78.43	104.91	122.41	120.66	124.15
	5.6	55.94	0.00	111.87	66.81	7.12	126.50
	10.0	27.72	0.00	55.43	69.33	27.83	110.83
	17.8	0.00	0.00	0.00	54.47	7.77	101.18
VR 125	B	95.46	72.36	116.19	90.16	76.57	103.76
	V	100.00	87.97	118.77	100.00	96.29	103.71
	1.0	79.63	78.17	81.09	76.31	75.83	76.79
	3.2	48.46	43.90	53.02	68.66	46.09	91.23
	5.6	19.49	8.07	30.92	49.90	27.68	72.11
	10.0	6.52	6.06	6.99	100.69	84.46	116.91
	17.8	0.00	0.00	0.00	45.21	21.63	68.80

Grumpy Torah (response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	3.20	1.76	3.94	3.01	2.77	3.25
	V	3.59	2.91	4.13	2.31	1.49	3.14
	1.0	3.42	3.05	3.78	1.93	1.36	2.50
	3.2	3.35	2.32	4.39	2.74	2.37	3.10
	5.6	0.33	0.20	0.47	2.85	2.37	3.34
	10.0	0.38	0.10	0.66	1.81	0.19	3.65
	17.8	0.00	0.00	0.00	0.92	0.34	1.49
FR 125	B	2.28	1.44	3.64	2.28	2.15	2.40
	V	2.10	1.57	2.75	3.72	3.50	3.93
	1.0	1.86	0.85	2.87	2.26	2.15	2.38
	3.2	0.38	0.37	0.39	1.53	1.49	1.56
	5.6	0.01	0.00	0.01	0.95	0.35	1.56
	10.0	0.00	0.00	0.00	0.31	0.00	0.73
	17.8	0.00	0.00	0.00	0.13	0.00	0.26
VR 5	B	3.11	2.05	3.89	2.23	1.67	2.78
	V	2.78	0.39	3.95	1.45	1.04	1.87
	1.0	3.51	3.28	3.74	2.16	2.11	2.20
	3.2	3.43	2.99	3.87	2.59	2.21	2.98
	5.6	1.79	1.43	2.15	2.37	2.18	2.57
	10.0	1.22	0.01	2.43	1.72	0.12	3.27
	17.8	0.00	0.00	0.00	0.60	0.31	0.89
VR 125	B	3.58	2.49	5.48	1.76	1.60	1.91
	V	3.40	2.22	4.17	1.82	1.03	2.61
	1.0	3.51	3.34	3.68	1.43	1.26	1.59
	3.2	0.58	0.40	0.76	0.86	0.50	1.22
	5.6	0.31	0.17	0.45	0.96	0.27	1.65
	10.0	0.00	0.00	0.00	0.29	0.13	0.63
	17.8	0.00	0.00	0.00	0.92	0.34	1.49

Grumpy Torah (expressed as percentage of vehicle response rate)

schedule	dose	pre	min	max	post	min	max
FR5	B	89.21	49.06	109.90	130.14	119.68	140.61
	V	100.00	81.04	115.07	100.00	64.25	135.75
	1.0	95.29	85.09	105.50	83.51	58.83	108.18
	3.2	93.50	64.66	122.34	118.41	102.59	134.24
	5.6	9.22	5.45	12.99	123.31	102.34	144.27
	10.0	10.59	2.91	18.27	78.17	8.30	158.08
	17.8	0.00	0.00	0.00	39.64	14.74	64.55
FR 125	B	108.76	68.59	173.77	61.20	57.93	64.47
	V	100.00	74.68	130.88	100.00	94.21	105.79
	1.0	88.81	40.70	136.92	60.86	57.78	63.94
	3.2	18.16	17.51	18.82	41.10	40.17	42.03
	5.6	0.34	0.16	0.52	25.63	9.32	41.95
	10.0	0.00	0.00	0.00	8.41	0.01	19.61
	17.8	0.00	0.00	0.00	3.54	0.00	7.07
VR 5	B	111.76	73.85	140.13	153.33	115.00	191.66
	V	100.00	14.04	142.28	100.00	71.34	128.66
	1.0	126.41	118.12	134.70	148.65	145.56	151.74
	3.2	123.32	107.44	139.20	178.55	152.10	205.00
	5.6	64.47	51.40	77.55	163.40	149.86	176.94
	10.0	43.90	0.30	87.51	118.24	8.11	225.16
	17.8	0.00	0.00	0.00	41.43	21.65	61.22
VR 125	B	105.23	73.12	161.13	96.45	87.79	105.11
	V	100.00	65.39	122.74	100.00	56.48	143.52
	1.0	103.36	98.36	108.35	78.39	69.39	87.39
	3.2	17.06	11.85	22.26	47.30	27.58	67.02
	5.6	8.99	4.87	13.12	52.78	15.08	90.48
	10.0	0.05	0.02	0.09	15.66	7.34	34.55
	17.8	0.05	0.02	0.09	50.31	18.70	81.93

APPENDIX C

IACUC APPROVAL LETTER

The IACUC approval letter is on file at the Graduate College.

BIBLIOGRAPHY

Branch, M. N. (1979). Consequent events and determinants of drug effects on schedule-controlled behavior: Modification of effects of cocaine and *d*-amphetamine following chronic amphetamine administration. *The Journal of Pharmacology and Experimental Theraputics*, *210*, 354-360.;

Branch, M. N. (1990). Cocaine tolerance: Interactions among random-ratio and random-interval reinforcement-schedule parameters and repeated exposure to cocaine. *Drug Development Research*, *20*, 19-30.

Brady, J. V., Griffiths, R. R., Hienz, R. D., Ator, N. A., Lukas, S. E., & Lamb, R. J. (1987). Assessing drugs for abuse liability and dependence potential in laboratory primates. In M. A. Bozarth (Ed.), Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag, pp. 45-85.

Brown, P. L., & Jenkins, H. M. (1968). Auto-shaping of the pigeon's key-peck. *Journal of the Experimental Analysis of Behavior*, *11*, 1-8.

Cassens, G., Actor, C., Kling, M., & Schildkraut, J. J. (1981). Amphetamine withdrawal: Effects on threshold of intracranial reinforcement. *Psychopharmacology*, *73*, 318-322.

Catania, A. C. (1998). *Learning* (4th Ed.). Upper Saddle River, NJ: Prentice Hall.

Chen, C. S. (1968). A study of the alcohol-tolerance effect and an introduction of a new behavioural technique. *Psychopharmacologia*, *12*, 433-440.

Cohen, S. L. (1986). A pharmacological examination of the resistance-to-change hypothesis of response strength. *Journal of the Experimental Analysis of Behavior*, *46*, 363-379.

Corfield-Sumner, P. K., & Stolerman, I.P. (1978). Behavioral tolerance. In D. E. Blackman & D. J. Sanger (Eds.), *Contemporary research in behavioral pharmacology*. New York: Plenum Press, pp. 391-448.

D'Amour, F. E., & Smith, D. L. (1941). A method for assessing loss of pain sensation. *Journal of Pharmacology and Experimental Theraputics*, *72*, 74-79.

Demellweek, C., & Goudie, A. J. (1983). An analysis of behavioural mechanisms involved in the acquisition of amphetamine anorectic tolerance. *Psychopharmacology*, *80*, 287-307.

Dews, P. B. (1955). Studies on behavior: I. Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward. *Journal de Pharmacologie*, *113*, 393-401.

Dews, P. B. (1978). Behavioral tolerance. In N. A. Krasnegor (Ed.), *Behavioral tolerance: Research and treatment implications*, NIDA Research Monograph 18. Washington, DC: U. S. Government Printing Office, pp. 18-26.

Dews, P. B., & Wenger, G. R. (1977). Rate dependency of the behavioral effects of amphetamine. In T. Thompson & P. B. Dews (Eds.), *Advances in behavioral pharmacology, Vol. 1*. New York: Academic Press, pp. 167-227.

Felton, M., & Lyon, D. O. (1966). The post-reinforcement pause. *Journal of the Experimental Analysis of Behavior*, *9*, 131-134.

Ferster, C. B., & Skinner, B. F. (1957). *Schedules of reinforcement*. New York: Appleton-Century-Crofts.

Fleshler, M., & Hoffman, H. S. (1962). A progression for generating variable-interval schedules. *Journal of the Experimental Analysis of Behavior*, *5*, 529 530.

Foltin, R. W., & Schuster, C. R. (1982). Behavioral tolerance and cross-tolerance to *dl*-cathinone and *d*-amphetamine in rats. *Journal of Pharmacology and Experimental Theraputics*, *222*, 126-131.

Genovese, R. F., Elsmore, T. F., & Witkin, J. M. (1988). Environmental influences on the development of tolerance to the effects of physostigmine. Psychopharmacology, 96, 462-467.

Goudie, A. J., & Demellweek, C. (1986). Conditioning factors in drug tolerance. In S. R. Goldberg & I. P. Stolerman (Eds.), *Behavioral analysis of drug dependence*. Orlando, FL: Academic Press, Inc.

Harris, R. A., & Snell, D. (1980). Effects of acute and chronic administration of phenobarbital and *d*-amphetamine on schedule-controlled behavior. *Pharmacology Biochemistry & Behavior*, *12*, 47 52.

Heifetz, S. A., & McMillan, D. E. (1971). Development of behavioral tolerance to morphine and methadone using the schedule-controlled behavior of the pigeon. *Psychopharmacologia*, *19*, 40 52.

Herrnstein, R. J. (1970). On the law of effect. *Journal of the Experimental Analysis of Behavior*, *13*, 243-266.

Herrnstein, R. J., & Heyman, G. M. (1979). Is matching compatible with reinforcement maximization on concurrent variable interval variable ratio? *Journal of the Experimental Analysis of Behavior*, *31*, 209-223.

Himmelsbach, C. K., Gerlach, G. H., & Stanton, E. J. (1935). A method for testing addiction, tolerance and abstinence in the rat: Results of its application to several morphine alkaloids. *Journal de Pharmacologie*, *53*, 10.

Hodos, W. (1961). Progressive ratio as a measure of reward strength. *Science*, *134*, 943-944.

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

Howell, L. L., & Morse, W. H. (1989). Behavioral effects of chronically administered cocaine in squirrel monkeys. *Psychopharmacology*, *97*, 12-16.

Hughes, C. E., Sigmon, S. C., Pitts, R. C., & Dykstra, L. A. (2005). Morphine tolerance as a function of ratio schedule: Response requirement or unite price? *Journal of the Experimental Analysis of Behavior*, *83*, 281-296.

Hull, C. L. (1943). *Principles of behavior: An introduction to behavior theory*. New York: Appleton-Century-Crofts.

Jarema, K., Macomber, C., Lesage, M., & Poling, A. (1999). Acute and chronic effects of morphine under a progressive-ratio 25 schedule of food delivery. *Pharmacology Biochemisty and Behavior*, *62*, 209-214.

Krank, M. D, Hinson, R. E., & Siegel, S. (1984). Effect of partial reinforcement on tolerance to morphine-induced analgesia and weight loss in the rat. *Behavioral Neuroscience*, *98*, 72-78.

Kransnegor, N. A. (1978). Introduction. In N. A. Krasnegor (Ed.), *Behavioral tolerance: Research and treatment implications*, NIDA Research Monograph 18. Washington, DC: U. S. Government Printing Office, pp. 1-3.

Kuribara, H. (1980). Effects of repeated administration of d-amphetamine on Sidman avoidance responding in rats. *Psychopharmacology*, *71*, 105-107.

LeBlanc, A. E., Poulos, C. X., & Cappell, H. D. (1978). Tolerance as a behavioral phenomenon: Evidence from two paradigms. In N. A. Krasnegor (Ed.), *Behavioral tolerance: Research and treatment implications*, NIDA Research Monograph 18. Washington, DC: U. S. Government Printing Office, pp. 72-89.

Liebman, J. M., & Segal, D. S. (1976). Lack of tolerance or sensitization to the effects of chronic *d*-amphetamine on substantia nigra self-stimulation. *Behavioral Biology*, *16*, 211-220.

Macht, D. I. (1947). Influence of penicillin and streptomycin on the cerebral and neuromuscular reactions of white rats. *Archives Internationales de Pharmacodynamie et de Therapie*, *75*, 126.

Macht, M. B. (1939). Effect of repeated injections of cobra venom and morphine on behavior of rats in a maze. *Proceedings of the Society for Experimental Biology & Medicine*, *42*, 433-436.

Mauro, B. C., & Mace, F. C. (1996). Differences in the effect of Pavlovian contingencies upon behavioral momentum using auditory versus visual stimuli. *Journal of the Experimental Analysis of Behavior*, *65*, 389-399.

Millenson, J. R. (1963). Random interval schedules of reinforcement. *Journal of the Experimental Analysis of Behavior*, *6*, 437-443.

Miller, M. L., Brodkorb, G. W., & Branch, M. N. (2001). Tolerance to the effects of performance under behavior-correlated reinforcement magnitude. *Journal of the Experimental Analysis of Behavior*, *76*, 217-234.

Nevin, J. A., Mandell, C., & Atak, J.R. (1983). The analysis of behavioral momentum. *Journal of the Experimental Analysis of Behavior*, *39*, 49 59.

Nickel, M., Alling, K., Kleiner, M., & Poling, A. (1993). Fixed-ratio size as a determinant of tolerance to cocaine: is relative or absolute size important? *Behavioural Pharmacology*, *4*, 471-478.

Nickel, M., & Poling, A. (1990). Fixed-ratio size as a determinant of the development of tolerance to morphine. *Behavioural Pharmacology*, *4*, 471-478.

Olds, J., & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology*, *47*, 419-427.

Ott, R. L. (1993). *An introduction to statistical methods and data analysis* (4th Ed.). Belmont, CA: Duxbury Press.

Pickens, R. W., & Crowder, W. F. (1967). Effects of CS-US interval on conditioning of drug response, with assessment of speed of conditioning. *Psychopharmacologia*, *11*, 88-94.

Picker, M., Blakely, E., & Poling, A. (1986). Effects of anticonvulsant drugs under automaintenance and negative automaintenance procedures. *Pharmacology, Biochemistry and Behavior*, *24*, 555 560.

Picker, M., Grossett, D., Sewell, R., Zimmermann, B., & Poling, A. (1982). The development of tolerance to morphine under discrete-trial fixed-ratio, automaintenance, and negative automaintenance procedures. *Bulletin of the Psychonomic Society*, *19*, 249 252.

Pinkston, J. W., & Branch, M. N. (2004a). Repeated post- or presession cocaine administration: Roles of dose and fixed-ratio schedule. *Journal of the Experimental Analysis of Behavior*, *81*, 169-188.

Pinkston, J. W., & Branch, M. N. (2004b). Effects of cocaine on performance under fixed-interval schedules with a small tandem ratio requirement. *Journal of the Experimental Analysis of Behavior*, *82*, 293-310.

Poling, A., Byrne, T., Christian, L., & Lesage, M. G. (2000). Effects of cocaine and morphine under mixed-ratio schedules of food delivery. *Pharmacology Biochemistry and Behavior*, *66*, 313-321.

Powell, R. W. (1968). The effect of small sequential changes in fixed-ratio size upon the post-reinforcement pause. *Journal of the Experimental Analysis of Behavior*, *11*, 589-593.

Rees, D. C., Wood, R. W., & Laties, V. G. (1985). The roles of stimulus control and reinforcement frequency in modulating the behavioral effects of *d*-amphetamine in the rat. *Journal of the Experimental Analysis of Behavior*, *43*, 243-255.

Sanger, D. J., & Blackman, D. E. (1976). Rate-dependent effects of drugs: A review of the literature. *Pharmacology, Biochemistry and Behavior*, *4*, 73-83.

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

Schama K. F., & Branch, M. N. (1994). Tolerance to cocaine's rate-increasing effects upon repeated administration. *Journal of the Experimental Analysis of Behavior*, *62*, 45 56.

Schuster, C. R., Dockens, W. S., & Woods, J. H. (1966). Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia*, *9*, 170-182.

Schuster, C. R., & Zimmerman, J. (1961). Timing behavior during prolonged treatment

with *dl*-amphetamine. *Journal of the Experimental Analysis of Behavior*, *4*, 327-330.

Searle, L. V., & Brown, C. W. (1938). The effect of subcutaneous injections of benzedrine sulphate on the activity of white rats. *Journal of Experimental Psychology*, *22*, 480-490.

Siegel, S. (1984). Pavlovian conditioning and heroin overdose: Reports by overdose victims. *Bulletin of the Psychonomic Society*, *22*, 427-430.

Siegel, S., Hinson, R. E., Krank, M. D., & McCully, J. (1982). Heroin "overdose" death: Contribution of drug-associated environmental cues. *Science*, *216*, 436-437.

Simon, A. K., & Eddy, N. B. (1935). Studies of morphine, codeine, and their derivatives: V. The use of maze-trained rats to study the effect on the central nervous system of morphine and related substances. *American Journal of Psychology*, *47*, 597-613.

Skinner, B. F. (1953). *Science and human behavior*. New York: The Free Press.

Smith, J. B. (1986a). Effects of chronically administered *d*-amphetamine on spaced responding maintained under multiple and single-component schedules. *Psychopharmacology*, *88*, 296-300.

Smith, J. B. (1986b). Effects of fixed-ratio length on the development of tolerance to decreased responding by *l*-nantradol. *Psychopharmacology*, *90*, 259-262.

Smith, J. B. (1990). Effects of fixed-ration requirement on observed tolerance to decreased responding by clonidine. *Pharmacology Biochemisty & Behavior*, *36*, 993-995.

Thompson, T. (1981). Behavioral mechanisms and loci of drug dependence: An

overview. In T. Thompson & C. E. Johanson, *Behavioral pharmacology of human drug dependence*. Washington, DC: US Government Printing Office, pp. 1-10.

van Haaren, F., & Anderson, K. G. (1994). Behavioral effects of acute and chronic cocaine administration in male and female rats: effects of fixed-ratio schedule parameters. *Behavioural Pharmacology*, *5*, 607-614.

Webbe, F. M., DeWeese, J., & Malagodi, E. F. (1974). Induced attack during multiple fixed ratio, variable ratio schedules of reinforcement. *Journal of the Experimental Analysis of Behavior*, *22*, 197-206.

Weiner, H. (1981). Contributions of reinforcement schedule histories to our understanding of drug effects in human subjects. In T. Thompson & C. E. Johanson, *Behavioral pharmacology of human drug dependence*. Washington, DC: US Government Printing Office, pp. 90-104.

Wilcoxon, F. (1945). Individual comparisons by ranking methods. *Biometrics*, *1*, 80-83.

Williams, D. R., & Williams, H. (1969). Automaintenance in the pigeon: Sustained pecking despite contingent non-reinforcement. *Journal of the Experimental Analysis of Behavior*, *12*, 511 520.

Wolgin, D. L. (1989). The role of instrumental learning in behavioral tolerance to drugs. In A. J. Goudie & M. W. Emmett-Oglesby (Eds.), *Psychoactive drugs: Tolerance and sensitization*, pp. 17-114. Clifton, NJ: Humana Press.

Woolverton, W. L., Kandel, D., & Schuster, C. R. (1978). Tolerance and cross-tolerance to cocaine and d-amphetamine. *Journal of Pharmacology and Experimental Therapeutics*, *205*, 525 535.

Yoon, J. H., & Branch, M. N. (2004). Interactions among unit-price, fixed-ratio value, and dosing regimen in determining effects of repeated cocaine administration. *Behavioural Processes*, 67, 363-381.