EXAMINATION OF RELATIONSHIPS BETWEEN RESPONSE TOPOGRAPHY AND THE DEVELOPMENT OF BEHAVIORAL TOLERANCE TO EFFECTS OF COCAINE WITH RATS AND PIGEONS

By

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TABLE OF CONTENTS

page

ACKNOWLEDGMENTS 4

LIST OF TABLES 7

LIST OF FIGURES 9

ABSTRACT 10

CHAPTER

1 GENERAL INTRODUCTION 12

2 EXPERIMENT 1 27

Method 29
Subjects 29
Apparatus 29
Procedure 30
Results and Discussion 37

3 EXPERIMENT 2 51

Method 54
Subjects 54
Apparatus 54
Procedure 56
Results and Discussion 59

4 GENERAL DISCUSSION 82

LIST OF REFERENCES 98

BIOGRAPHICAL SKETCH 104

LIST OF TABLES

Table		page
2-1	Total variance accounted (r^2) for by the local and global models fit to dose-response functions from the Acute and Chronic Drug Treatment Phases.	41
2-2	Acute phase mean rate of responding, minimum and maximum session response rates, standard deviations, and number of injections per dose for all subjects.	42
2-3	Chronic phase mean rate of responding, minimum and maximum session response rates, standard deviations, and number of injections per dose for all subjects.	43
2-4	Estimate Effective Dose 50 (mg/kg) values for the group means and individual animals for all phase.	44
2-5	Model Comparisons using Akaike's Corrected Information Criterion.	45
3-1	Total variance accounted (r^2) for by the local and global models fit to dose-response functions from the Acute and Chronic Drug Treatment Phases.	65
3-2	Total variance accounted (r^2) for by the local and global models fit to dose-response functions from the Acute and Abstinence Drug Treatment Phases.	66
3-3	Total variance accounted (r^2) for by the local and global models fit to dose-response functions from the Chronic and Abstinence Drug Treatment Phases.	67
3-4	Acute phase mean rate of responding, minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the After group.	68
3-5	Acute phase mean rate of responding, minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the Before group.	69
3-6	Chronic phase mean rate of responding, minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the After group.	70
3-7	Chronic phase mean rate of responding, minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the Before group.	71
3-8	Abstinence phase mean rate of responding, minimum and maximum session response rates, standard deviations, and number of injections per dose per dose for subjects in the After group.	72

3-9 Abstinence phase mean rate of responding, minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the Before group. 73

3-10 The estimated Effective Dose 50 (mg/kg) values for the group means and individual animals for all phases.. 74

3-11 Model Comparisions using Akaike's Corrected Information Criteria. 75

LIST OF FIGURES

Figure page

2-1 Hill-slope fits to the session-average responses per minute for the acute, and chronic drug phases as a function of cocaine dose for two individuals. 46

2-2 Session-average responses per minute for the acute and chronic drug phases as a function of cocaine dose for individuals in the After group. 47

2-3 Session-average responses per minute for the acute and chronic drug phases as a function of cocaine dose for individuals in the Before group. 48

2-4 Group Aggregate dose-response functions are presented on panels for both the Before and After groups 49

2-5 Between group comparison of dose-response functions are presented on panels for the Acute and Chronic treatment phases. 50

3-1 Photograph of the custom-built operant-conditioning chamber used in Experiment 2 76

3-2 A close-up photograph of the treadle plate and hopper opening for the custom-built operant-conditioning chamber. 77

3-3 Between group comparison of dose-response functions are presented on panels for the Acute, Chronic, and Abstinence treatment phases. 78

3-4 Session-average responses per minute for the acute, chronic and abstinence drug phases as a function of cocaine dose for individuals in the Before group. 79

3-5 Session-average responses per minute for the acute, chronic and abstinence drug phases as a function of cocaine dose for individuals in the After group. 80

3-6 Group Aggregate Dose response functions are presented on individually labeled panels. Response rates are presented as percent of vehicle control. 81

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Tolerance is the attenuation of drug effects after repeated administration. The phenomenon of tolerance is multifaceted and closely related to the problems of substance abuse and substance dependence. The development of tolerance to behavioral effects is dependent on physiological and behavioral factors. A need for behavioral mechanisms to account for tolerance is illustrated through the Before-After Test of Tolerance. In this test two groups are subjected to the same experimental contingencies and drugs, however, the Before group receives the drug prior to experimental contingencies and the After group receives the drug following the contingencies. Typically, only the Before group develops tolerance, and this outcome shows that tolerance is contingent on a learning history while under the influence of drug. The finding, known as contingent tolerance, has been replicated using a variety of drugs, experimental arrangements, and animal species. Interestingly, contingent tolerance has not been exhibited in pigeons. This species difference may be a result of using species-typical responses to test for tolerance. In contrast, similar studies using rats and non-human primates included species-arbitrary responses, and contingent tolerance has been the typical result.

This dissertation addresses the role of response topography in the development of tolerance to the rate-decreasing effects of cocaine with two experiments using the Before-After Test of Tolerance. Experiment 1 required rats to use species-typical licking responses in a procedure similar to that previously had resulted in tolerance for both Before and After groups of pigeons. Experiment 2 employed pigeons and a species-arbitrary treadle-pressing response, an arrangement similar to those that have led to contingent tolerance when rats were used. Experiment 1 resulted in tolerance for both the Before and After groups, which is consistent with the idea that response topography may influence the development of tolerance. Experiment 2 resulted in tolerance for both the Before and After groups, which is inconsistent with the idea that response-topography was the confounding variable in development of contingent tolerance. The outcome, however, was consistent with previous pigeon experiments. It was therefore concluded that factors other than the operantly maintained response topography must be influencing the species differences in development of tolerance to effects of cocaine.

CHAPTER 1
GENERAL INTRODUCTION

Tolerance to effects of a drug is often characterized by three features: it occurs after repeated or continuous use, it is revealed as a loss of potency relative to the initial drug effect, and more of the drug is usually required to obtain an earlier effect (Carlton, 1983). An important area of tolerance research is Behavioral Tolerance, which may be conceptualized in descriptive or theoretical terms. In the former case, observable behavior of an animal is used to show tolerance, and no further explanatory emphasis is place on the behavioral mechanisms that may contribute to the development of tolerance. When behavioral tolerance is used as a theoretical explanation, however, tolerance is often conceptualized as a learned compensation that counteracts some disruptive drug effects, and thus emphasizes the environmental and behavioral interactions that account for learning. Furthermore, behavioral tolerance can be discussed in terms of either operant or classical conditioning. In the case of operant conditioning, mechanisms of behavioral tolerance are discussed via the Reinforcement-Loss hypothesis. This hypothesis, which is also referred to as the Reinforcer-Density hypothesis, states that tolerance will occur when the initial effect of the substance decreases the amount of reinforcement. The loss of reinforcers leads to novel behavior or the suppression of the disruptive effects of the drug, in either case learning allows the animal to obtain the lost reinforcers (Schuster, Dockens, & Woods, 1966). Reinforcement loss is thought to be a key behavioral mechanism through which tolerance develops.

In the area of Behavioral Tolerance a goal of research is to elucidate and further explain the development of tolerance through the careful arrangement and observation of environment-behavior interactions. The current series of experiments focused on Contingent Tolerance, a phenomenon that has shown the importance of behavioral mechanisms, like reinforcement loss,

in the development of tolerance. Contingent tolerance is said to be evident when the attenuation to the behavioral effects of a drug is dependent on the particular behavior occurring while the organism is under the influence of a drug. That is, tolerance is contingent on the relationship of time of drug ingestion or administration and when performance of behavior occurs.

Contingent tolerance has most often been studied by an experimental preparation known as the Before-After (B-A) Test of Tolerance (e.g., Branch & Sizemore, 1988; Bowen, Fowler, & Kallman, 1993; Carlton & Wolgin, 1971; Campbell & Seiden, 1973; Chen, 1968; Smith, 1990; Tang and Falk, 1978; Wenger, Tiffany, Bombardier, Nicholls, & Woods, 1981; Woolverton, Kandel, & Schuster, 1978; for discussion see Carlton, 1983 pp. 126-128 & 133-138). The B-A design typically calls for baseline measurements of a target response and for repeated drug administration to two groups. In this test, animals are assigned to a Before group or an After group**.** The Before group receives a chronic (usually daily) dose of drug prior to the experimental-test session. The After group receives the chronic dose of drug following the session. In tolerance-testing sessions groups are given identical pre-session administrations of drug. The resulting behavioral output is compared to baseline output, and the results are also compared between groups. The comparison to baseline output determines if drug treatment has engendered tolerance and the comparison across groups determines the role of drugging regimen. A major advantage of the B-A design is that the number of drug injections and experience with the test environment is held constant for both groups. Thus, the key independent variable is the relationship between time of administration and access to the experimental-test conditions. The group comparison determines if tolerance is dependent on experimental exposure while the organism was under the drug's influence. If this occurs only the Before group will show evidence of tolerance and the After group will not show evidence, or at least less, when tested.

In this case, principles of operant conditioning are likely contributors to tolerance development, and tolerance is said to be dependent or contingent on the interaction between drug and the environment, thus the term "contingent tolerance." On the other hand, if tolerance develops regardless of the relationship between injection and experimental condition then non-operant, most notably physiological factors, may be more significant contributors to the process. It may be prudent to note that physiological and behavioral mechanisms are likely to be affecting behavior in the B-A Test of Tolerance. The contingent tolerance outcome shows that the phenomenon cannot be reduced only to enzyme induction, down-regulation of receptors, or other physiological mechanism of tolerance (Rang, Dale, Ritter, & Moore, 2003). That is, the importance of behavioral history is shown through the B-A Test of Tolerance and this helps to create a complete characterization of the phenomenon of tolerance. It is therefore, important to indentify and describe environmental, historical, and subject-related conditions that lead to the situations in which the effects of behavioral and physiological mechanisms may be identified through behavioral research.

The initial study showing contingent tolerance provides an example of typical findings when the B-A Test of Tolerance is employed. Chen (1968) studied the development of behavioral tolerance of two groups of six rats. The behavioral task involved two turns around a circular maze, with spaghetti bits serving as reinforcers. Daily sessions consisted of 30 trials, and all animals had previously satisfied a maze running criterion. The experimental treatment was carried out in blocks that included three daily sessions. The total experiment consisted of four repetitions of the blocks. The first session was a control when saline was injected prior to the session. Session two was the alcohol session and session three was a no treatment session. On alcohol-session days, subjects in the Behavioral group (i.e. Before group) were injected with

ethanol ten minutes prior to the task, while the Physiological group (i.e., After group) was injected two minutes after the task. The first alcohol session for the Behavioral group showed significant decreases in performance when compared to control sessions, however tolerance developed by the fourth alcohol session. On the fourth alcohol session, the Physiological group received the ethanol injection prior to the session and showed no evidence of tolerance. This led the author to conclude that tolerance was not completely dictated by physiological mechanisms. Rather, experience with the behavioral task while under the influence of drug was required. In subsequent studies, the phenomenon of contingent tolerance to ethanol has been replicated (Wenger, et al., 1981), and generalized to pentobarbital (Tang and Falk, 1978) and psychomotor stimulants, including amphetamines (Carlton & Wolgin, 1971; Campbell & Seiden, 1973; Woolverton, et al., 1978) and cocaine (Branch & Sizemore, 1988; Smith, 1990; Woolverton, et al., 1978).

The contingent tolerance outcome has also generalized across experimental procedures that can be distinguished by whether they have involved "trained operants" (Branch & Sizemore, 1998; Chen, 1968; Campbell & Seiden, 1973; Smith, 1990) or "untrained operants" (Bowen, et. al., 1993; Carlton & Wolgin, 1971; Wenger, et al., 1981; Woolverton, et al., 1978). The delineation between operant types can be made on the basis of differences in procedures, while acknowledging that similar operant processes are likely responsible for the production of behavior. In the case of "trained-operant" procedures, researchers shaped a response class that in turn, was a necessary component for a programmed schedule of reinforcement. The trained behavior allowed the researcher to observe animal behavior and to quantify responding as it occurred through time. The effects of the drug were observed through decreases in response rates and tolerance was observed when response rates recover following a repeated-drug

treatment phase. A key aspect of "trained-operant" arrangements is that the measured response did not directly lead to reinforcers, but rather served to complete a schedule of reinforcement, which then led to access to a consumable commodity. For instance, Campbell and Seiden (1973), exposed rats to a schedule of reinforcement that arranged for reinforcement of any inter-response times longer than 17.5 s (Inter-Response Time [IRT]>17.5-s schedule of reinforcement) and followed the B-A paradigm. This schedule was arranged for a lever-press response that had been shaped by the researcher. The initial effect of 1.5 mg/kg amphetamine increased responding, which in turn, led to a loss of reinforcers when compared to baseline. Following chronic pre- or post-session administration, the authors reported outcomes consistent with a previous contingent tolerance study that had employed the "untrained-operant" method (Carlton & Wolgin, 1971). That is, experience with the task while under the influence of drug was necessary for tolerance to develop to the reinforcer decreasing drug effects.

Procedures categorized as using "untrained-operants" (Bowen, et al., 1993; Carlton &Wolgin, 1971; Wenger, et al., 1981; Woolverton, et al., 1978) did not involve response shaping prior to experimental examination, and the response directly resulted in the animal obtaining a reinforcer. Often the dependent variable has been an indirect measure of behavior, such as the amount of a commodity consumed during an allotment of time. For example, Carlton and Wolgin (1971) performed a B-A experiment in which rats freely consumed sweetened milk for 30 minutes each day, the amount consumed was the major dependent variable. This experiment included three groups, referred to as the A-S, S-A, and S-S, with the "A" signifying amphetamine and "S" representing the saline vehicle. The A-S and S-A groups were analogous to the Behavioral and Physiological groups of Chen (1968). The S-S group controlled for the effects of time and injections. The initial drug-effect screen consisted of one pre-session

administration of amphetamine, and showed that the ability to consume milk had been disrupted. Following the amphetamine screening session, all animals whose intakes decreased by 50% were divided into the three previously mentioned groups. The authors reported that the rats in the A-S group reached a consumption level equal to, or greater then control between two and nine days with an average of 4.4 days. The S-A group did not show evidence of tolerance when probed with a pre-session amphetamine injection after seven days. Following this test of tolerance, the S-A group's drugging regimen was changed and duplicated the A-S group regimen. Following the change in drug regimen the S-A group showed a comparable pattern of tolerance to the original A-S group, with subjects becoming tolerant to the consumption decreasing effects between day nine and fifteen, with an average of 3.6 days. The control group never illustrated tolerance. This outcome is an instance of contingent tolerance.

To this date, consistent with the results of the two studies just described, there have not been notable differences in the outcomes obtained using "trained" or "untrained" operants, and the variation in methods has helped to illustrate further the generality of the effect. The potential influence of these different methods however, has not been exhaustively examined. The choice of response topography with regards to the experimental arrangement may have influenced the development of tolerance. In that, trained operants may require species-arbitrary response topographies, while untrained-operants procedures may not. That is, contingent tolerance has been reliably observed in trained-operant procedures that included responses that have not appeared to be biologically prepared to be associated with a specific reinforcer. On the other hand, untrained-operants do not appear to require such an arbitrary response topography because species-typical response topographies have been used in such procedures. The current dissertation will attempt to address the use of species-typical and species-arbitrary responses in

trained-operant procedures.

Contingent Tolerance has also been shown to occur across species, specifically, with non-human primates (Branch & Sizemore, 1988) and rats (Bowen, et al., 1993; Campbell & Seiden, 1973; Carlton & Wolgin, 1971; Chen, 1968; Smith, 1990; Wenger, et al., 1981; Woolverton, et al., 1978). Recent studies involving pigeons, however, have yielded an apparent species limitation to the generality of the effect. Specifically, research conducted by Branch and colleagues using the B-A Test of Tolerance have found that pigeons in both the Before and After groups are likely to form tolerance to the rate decreasing effects of cocaine (Marusich, 2008; Pinkston & Branch, 2004).

Pinkston and Branch (2004) first found this atypical outcome in a B-A experiment that subjected pigeons to a Multiple schedule that required either five or 100 key-pecks to attain three-seconds access to food (a multiple Fixed-ratio [FR] 5, FR 100 schedule). All subjects were exposed to a determination of acute (i.e., administrations spaced by one week) cocaine effects and to three phases of chronic (i.e., daily) drug administration: 1) "small" drug dose post-session, 2) "small" dose pre-session and 3) "large" dose post-session. The order of chronic drug administration phases varied among animals. The dose designations were determined by the acute effects of the cocaine doses, specifically, the "small" doses did not substantially disrupt responding, but the "large" doses eliminated or severely decreased responding. The authors found that tolerance was the predominant outcome for both pre- and post-session injections of "small" doses. That is, tolerance was not contingent on the pigeons having access to the behavioral test while under the influence of cocaine. As noted previously, this is an outcome that is not consistent with similar arrangements when rats or non-human primates were used. The authors concluded that factors other than learning in the experimental conditions likely

accounted for the development of tolerance.

The Pinkston and Branch (2004) design included two notable departures from other studies in the contingent tolerance literature. The first was the use of a multiple schedule, which have sometimes yielded tolerance outcomes inconsistent with those seen with simple schedules (Branch, 1991; Hoffman, Branch & Sizemore, 1987; Hughes, Sigmon, Pitts, & Dykstra, 2005; Nickel, Ailing, Kliener, & Poling, 1993; Pinkston & Branch, 2004b; Schama & Branch, 1989; van Haaren & Anderson, 1994; Weaver & Branch, 2008; Yoon & Branch, 2004). The second departure was the use of pigeons, not rats or non-human primates, which along with physiological differences involve subtle differences in testing methodology.

A series of experiments by Marusich (2008) addressed the various roles of multiple schedules, post-session drug regimens, and pharmacological tolerance in the atypical outcome reported by Pinkston and Branch (2004). Marusich (2008) systematically replicated the earlier pigeon experiments by exposing the subjects to one chronic dose of cocaine under a simple FR 20 schedule of reinforcement. The value of chronic dose varied across subjects, but it consistently decreased responding by at least 50% and did not completely suppress responding. This experiment also resulted in tolerance that did not appear to be contingent upon exposure to the behavioral test. It was therefore assumed that the use of a multiple schedule in the previous pigeon study (Pinkston & Branch, 2004) was not responsible for the atypical tolerance outcome (i.e., non-contingent tolerance).

The outcomes of the studies with pigeons therefore suggest that the development of contingent tolerance to drug effects on operant behavior depends on species. The source of the apparent species difference, however, deserves further inquiry. That is, are the anomalous outcomes caused by fundamental differences in species physiology, or could differences in

methodology across species be the source of the anomaly? The current dissertation focuses on the latter possibility. More specifically, the potential influence of response topography is examined.

The experimental analysis of behavior (EAB) involves the study of the dynamic functional relationship between the behavior of an organism and its controlling environment (including the organism's environmental history). In basic laboratory practice this has led to the use of controlled environments and measurable, easily repeated responses. The response form is preferably arbitrary, in the sense that it is chosen to be relatively free of phylogenetic specialization or limitation. It is hoped that by observing relations involving arbitrary responses a description of the learning process that has wide applicability will emerge. A quote by B.F. Skinner helps to clarify the type of response that is valued in the operant paradigm:

> The general topography of operant behavior is not important, because most if not all specific operants are conditioned. I suggest that the dynamic properties of operant behavior may be studied with a single reflex (*or at least with only as many as are needed to assure the general applicability of the results*) (Skinner, 1938, pp. 45-46, emphasis added).

The value of an arbitrary-response topography in the study of behavior analysis is apparent, however, the identification of such a response may be tricky in practice, because of species-typical response susceptibilities.

The autoshaping procedure can serve as a metric to test the "arbitrariness" of response topographies. Autoshaping has been the focus of considerable research with both pigeons and rats, and has shown that some response classes are susceptible to non-operant conditioning. Pigeon autoshaping studies have shown that a transilluminated-key that reliably predicts the

presentation of food, or water, will lead to pecking of the key. Likewise, rat autoshaping studies have shown that retractable levers that reliably predict the presentation of primary reinforcers lead to lever contacts. In both cases the topography of the responses evoked by the autoshaping arrangement resembled those that would have been directed at the primary reinforcer. Furthermore, operant conditioning has proven to be inadequate in describing the development and maintenance of responding in the autoshaping literature. It is therefore, assumed that autoshaping arrangements can differentially identify species-typical and species-arbitrary response topographies. That is, responses that are generated during autoshaping trials are considered species-typical. Conversely, responses that do not occur in autoshaping arrangements, but can be shaped by successive approximations to researcher defined standards are considered species-arbitrary. Further discussion of the variations of the autoshaping arrangement may help to clarify the use of autoshaping as a metric of response topographies.

The original autoshaping work of Brown and Jenkins (1968) showed that key-pecking of pigeons was subject to more than operant conditioning. In this now classic procedure, a key was transilluminated for period eight seconds and once the key light was terminated grain was presented. After a period of four seconds the access to grain via a hopper was removed and an inter-trial interval, of a varying duration that averaged 60 seconds occurred, and then another trial began. Pecking of the lit key also resulted in the termination of the key-light and the presentation of hopper grain. The authors also tried several other arrangements of key-lights, hopper lights, and grain presentation. They found that forward pairing of the key light with food was an effective means to engender key-directed responding. In fact, the authors reported that all 36 animals that were subjected to the forward pairing pecked the key within 119 trials. Some responded as early as the 6^{th} trial, and the group average was 45 trials. This arrangement was by

far the most effective of the manipulations reported. The mechanism(s) controlling the emergence of pecking remained unclear, however, because the arrangement included aspects common to both operant and classical conditioning. That is, the forward pairing arrangement was typical of procedures used in classical conditioning, but the immediate food presentation resulting from the key-directed response may have led to operant conditioning, or possibly the maintenance of responding once the association between key light and grain had led the animal to make the first response. Extensions of the original studies, addressing various parameters helped to elucidate the behavioral mechanisms responsible for autoshaping and automaintenance.

Research directed at relations between type of unconditioned stimulus (i.e., water or grain) and the topography of the unconditioned response (i.e. drinking or eating) with pigeons has shown that the type of unconditioned stimulus influenced the topography of the response (Wolin, 1968; Jenkins & Moore, 1973). Examination of motion pictures and photographs showed that key pecking maintained by water was similar in form to untrained drinking directed at water. For instance the water-maintained key-directed pecks were described as longer, closed beaked, and consisting of slow pushing motions, which are all characteristics of drinking by pigeons. Likewise, food-maintained pecking directed at the key was described as short, rapid, open beaked pecks that are like those made towards food (Wolin, 1968). Jenkins and Moore (1973) performed a series of studies that illustrated that the type of unconditioned stimulus, rather than the state of deprivation (i.e. establishing operation) was responsible for the topographical differences in responding. That is, regardless of experimentally imposed deprivations (i.e., food- or water-deprivation), the response-form of the key-peck was judged to be formally similar to the response appropriate for consuming either food or water. This outcome favored an interpretation of autoshaping as a classical-conditioning paradigm because

pairing of key light with food or water resulted in pecks that were similar in form to the pecks that were elicited when eating food or drinking water. That is, the unconditioned stimulus (US), food (or water), elicited the unconditional response (UR) of eating (or drinking) in the pigeon. Following repeated pairings of the conditioned stimulus (CS), key light, with the US the key became predictive of the US, which in turn elicited the conditioned response (CR) of food- (or water-) appropriate pecking. Thus, the key-light may be described as a substitute for whichever reinforcing stimulus was predicted through prior classical conditioning.

The classical-conditioning explanation of autoshaping was further supported by an experiment by Gamzu and Williams (1971) involving a variant of the "truly-random" control (Rescorla, 1967). Gamzu and Williams (1971) examined the association between food presentations and key-light in two conditions. Both conditions included trials with 8.6 seconds of a transilluminated key as the CS, four-seconds access to grain as the US, and variable inter-trial interval that averaged of 30-second. The delivery of grain was independent of animal responding. The conditions differed in the degree to which the grain presentations were associated to the CS. In the "Differential" condition the grain-US was presented according to a 0.03 probability for each second within the 8.6 seconds of key-light CS, and the presentation of grain coincided with the termination of the key light and house light. In the "Truly-Random" condition the US could occur at any time, with a probability of .03 each second, even during the darkened periods between CS presentations. As a control, US presentations were programmed according to the same rates for both conditions. Thus, food presentation occurred only in conjunction with key-light transillumination for the Differential Condition, and at random times, irrespective of key-light transillumination in the Non-Differential condition. The authors reported that key-directed responding occurred more often during the "Differential" condition

than the "Truly-Random" condition. Therefore, responding was better maintained by a class of stimulus (i.e. transilluminated-key) that was predictive of food presentation. This differential outcome is indicative of classical conditioning.

A final illustration of the effects of classical conditioning on key pecking was illustrated by Williams and Williams (1969), who arranged what is commonly referred to as negative-automaintenance or omission training. Key-directed responding in this variation of autoshaping cancelled the delivery of the grain US that otherwise would have occurred at the end of a six-second transilluminated-key CS presentation. The authors included animals with various histories of reinforcement, including; FR 1 Timeout, negatively-correlated autoshaping, positively-correlated autoshaping, and hand shaping (i.e. a method of differential reinforcement of the terminal response). The authors found that, regardless of history, the classical association between the key and food would elicit responding, even at the expense of reinforcer density. Operant theory would have predicted that response-induced loss of reinforcement would have led the subjects cease responding on the negatively associated trials. A decrease in responding directed toward the negatively correlated key was only observed when an alternative key that was irrelevant to the arrangement of food was concurrently available. In this concurrent arrangement key pecking was directed toward the irrelevant key, however, it was also predictive of food, because its termination coincided with the arrival of food. Therefore, a final test the included a continuous illumination of the irrelevant key resulted in a decrease in the number of responding directed toward it during the time when the negatively correlated alternative was available and an increase in pecks directed toward the negatively-associated alternative was available. The continued responding exemplified the influence of classical conditioning on the pecking response, in that it can be induced and maintained by stimuli negatively correlated with

responding.

Analogous rat autoshaping experiments introduce a lever into the environment for some amount of time, then upon its removal food is presented, and the inter-trial interval follows food presentation (Kearns & Weiss, 2007; Locurto, Terrace, & Gibbon, 1976; Peterson, Ackilt, Frommer, & Hearst, 1972; Stiers & Siblerberg, 1974; for review see Schwartz & Gamzu, 1977). The choice of a lever is consistent with most operant-conditioning experiments, which typically rely on shaped-lever pressing to complete schedules of reinforcement (Ator, 1991). Autoshaping experiments however report the number of lever contacts, rather then lever presses. Presumably the reporting of contacts rather than presses was the result of the topography engendered by the experimental arrangement. Specifically, autoshaping arrangements elicited responses described as licking, pawing, nose contact, and biting (Locurto, et al., 1976; Stiers & Siblerberg, 1974). All of the described behavior would typically be directed toward primary reinforcers, like food or water. To further the parallel between rat and pigeon autoshaping procedure, research has shown that negative automaintenance can occur with rats and the lever contacts (Stiers & Silberberg, 1974; Locurto, et al., 1976). That autoshaping in rats occurs is important because it shows responses like biting and licking are susceptible to non-operant sources of control. Thus, the sources of control for biting and licking in the rat appear to be similar to those that control pecking in the pigeon. The rat autoshaping experiments also show that lever pressing is not as susceptible to non-operant sources of control, because it was not reported to occur in the autoshaping procedures examined so far. In both the rat and pigeon autoshaping experiments species-typical responses are identified by the fact that they occur, while species-arbitrary response are identified by the fact that they do not occur, or at least fail to be maintained.

The results of autoshaping experiments in both rats and pigeons point to a potential

confound in the manner that previous contingent-tolerance experiments were conducted. Namely, it appears that the propensity of the rat experiments to show contingent tolerance may be due to the researcher's measurement of species-arbitrary responses like the lever-press responses in "trained-operant" arrangements. It is true that rat studies using species-typical responses (e.g., drinking milk) have resulted in contingent tolerance, however, those studies are examples of the use of "untrained-operants," and there are no parallel pigeon experiments. The failure of pigeon experiments to replicate contingent tolerance may be a result of species-typical responses being used in "trained-operant" arrangements. It is therefore, the goal of this dissertation to assess the role of response topography in the development of contingent tolerance. The examination was accomplished with two studies, one involving rats and a species-typical response and the other using pigeons and a species-arbitrary response. Both of the experiments involved "trained-operant" arrangements, a strategic choice aimed at adding relevant information pertaining to the relationship between response-form and training procedure.

CHAPTER 2
EXPERIMENT 1

Experiments using rats and psychomotor stimulants to examine effects of the relation between time of drug administration and behavioral testing have typically shown contingent tolerance (Bowen, et al., 1993; Campbell & Seiden, 1973; Carlton & Wolgin, 1971; Smith, 1990; Woolverton et al., 1978). Some of these experiments involved species-typical, "untrained-operant" responses like milk drinking (Bowen, et al., 1993; Carlton & Wolgin, 1971; Woolverton, et al., 1978), while others used species-arbitrary, "trained-operant" responses, like food maintained lever-pressing (Campbell & Seiden, 1973; Smith, 1990). Experiments using pigeons in contingent-tolerance arrangements have resulted in tolerance regardless of the relationship between time of drug administration and experimental test (Pinkston & Branch, 2004; Marusich, 2008). That is, pigeons typically exhibit tolerance that is not contingent on the drug-experimental test relationship. Besides using pigeons, these studies have used "trained-operant" response classes, specifically pecking. Perhaps importantly, the conditioned response class can be described as species-typical. That is, pecking occurs in many circumstances in which a researcher/scientist has not explicitly shaped it to occur, for example, in autoshaping arrangements (Brown & Jenkins, 1968; Gamzu & Williams, 1970; Jenkins & Moore, 1973; Schwartz & Gamzu; 1977; Williams & Williams, 1969) and response-independent schedules of food presentation (Staddon, 1977; Staddon & Simmelherg, 1971; Fenner, 1980). The purpose of Experiment 1 was to see if use of a species-typical response-class topography in a B-A Test of Tolerance experiment with rats would result in the observation of contingent tolerance, or if it would lead to results similar to those seen so far with pigeons. To achieve this goal, a systematic replication of a typical "trained-operant" contingent-tolerance experiment was performed with rats, instead of pigeons.

Experiment 1 involved the operant conditioning of sipper-tube licking. That is, a species-typical response was used in a "trained-operant" arrangement that was analogous to the previous pigeon tests that revealed non-contingent tolerance. Sipper-tube licking was chosen for two reasons; first, it is known to be susceptible to autoshaping contingencies, and, second, it bears a formal similarity to pigeon "trained-operant" experiments. With regards to autoshaping, lever-directed contacts, often licking, are engendered by autoshaping procedures designed for rats (Kearns & Weiss, 2007; Locurto, Terrace, & Gibbon, 1976; Peterson, 1972; for review see Schwartz and Gamzu, 1977) and these procedures parallel those first applied to pigeons (Brown & Jenkins, 1968; Gamzu & Williams, 1970; Jenkins & Moore, 1973; Williams & Williams, 1969; for review see Schwartz & Gamzu; 1977). In both species, autoshaping procedures include trials that introduced a conditioned stimulus (CS) into the environment for a period of time, then the CS is removed and an unconditioned stimulus (US) is presented, and then an inter-trial interval of variable length occurs before the start of a new trial. The responses engendered by the autoshaping arrangement can be conceptualized as conditioned responses (CR) and the topography of the response is similar to the unconditioned response (UR). Furthermore, the responses can be considered species-typical because they are reliably elicited by evolutionarily-relevant unconditioned stimuli, such as food and water, and stimuli that have been associated with said stimuli. The fact that autoshaping procedures engender licking in rats and pecking in pigeons provides evidence that licking and pecking are susceptible to the similar non-operant sources of control. Therefore, licking and pecking are conceptualized as two functionally similar species-typical response topographies.

To maintain a formal similarity between experiments on contingent tolerance with pigeons and the current experiment with rats a species-typical response, licking, was directed to a novel

stimulus, an empty sipper tube, and was maintained through access to consumable primary reinforcer, water. In conventional experiments on pigeon the researcher shapes pecking of a transilluminated key, and, once established, key pecking is maintained according to a schedule of reinforcement. Once the schedule requirement(s) is satisfied, the subject is given access to food-grain that it then pecks to consume (Ator, 1991; Ferster & Skinner, 1957). Experiment 1 required water-deprived rats to lick an empty sipper-tube, according to a schedule of reinforcement, to gain access to a water-filled sipper, which then could be licked to attain reinforcers. For the sake of clarity, the respective sipper tubes will be referred to hereafter as the "response sipper" and "reinforcer sipper."

Method

Subjects

Subjects were six experimentally naive male Long Evans rats (*Rattus norvegicus*). The experiment was designed to include eight subjects. The deaths of two subjects during the experiment limited the number to six. All subjects were 120 days old at the beginning of baseline. Subjects were housed in individual home cages with pine shavings for bedding, in a windowless colony room. Light in the colony room was maintained under a 12 hour light-dark cycle, with light beginning at 6:00 a.m. Subjects were maintained on a 22 hour / day water deprivation regimen, plus a possible 100 seconds of access to water earned during the session. While in their home cages the animals had free access to lab Diet 5001 Rodent Diet (PMI Nutrition International, Brentwood, MO).

Apparatus

All experimental sessions occurred daily, in one 30.5 cm x 24.1 cm x 29.2 cm operant-conditioning chamber (ENV-007; Med Associates, St. Albans, VT). The experimental chamber included a ceiling and three walls made of translucent acrylic glass, one stainless steel wall, a

stainless steel rod floor, and a stainless steel waste pan. The stainless steel wall served as the intelligence panel and included two retractable sipper tubes (ENV-252M, Med Associates, St. Albans, VT) which were available through individual 2.5- x 1.2-cm holes. The bottom edges of the holes were located approximately 1 cm for the grid floor. The waterless response-sipper was located 19 cm from the chamber door and 3 cm from the wall opposite the door. To avoid recording non-lick responses the response tube was permanently recessed 0.5 cm from an access hole. Licks on the response sipper were counted by a drinkometer (ENV-250, Med Associates, St. Albans, VT). The water filled reinforcer sipper was located 3 cm from the chamber door. The reinforcer sipper was out of the chamber until the schedule of reinforcement was satisfied and then it was moved via motor driven platform into the chamber for 2.5 s. When out of the chamber the tip of the reinforcer-sipper was recessed 2 cm and when in the chamber it protruded 0.5 cm from the panel. A 28-V, white house light was centrally located, 2 cm from the ceiling on the wall opposing the intelligence panel.

The operant conditioning chamber was enclosed in a 41 x 56 x 47 cm (internal dimensions) sound-attenuating cubicle (Coulbourn Industries, Whitehall, PA). Extraneous sounds were masked by a fan located on the back wall of the enclosure and a second fan located within the laboratory room surrounding the chamber. Experimental events were arranged and recorded by Med-PC software contained on a personal computer located in the same room as the chamber.

Procedure

Training. All subjects were experimentally naive and required training (i.e., "magazine training") to lick the reinforcer tube. Magazine training consisted of repeated presentations of the reinforcer sipper for variable amounts of time, between 20 to 3 seconds until the subjects reliably approached the sipper upon presentation. The terminal contingency required the animal

to lick an empty response sipper under an FR 20 schedule of reinforcement for two and a half seconds access to the water filled reinforcer sipper. Following magazine training, all animals were exposed to an FR 1 with nine seconds access to water for each lick on the response tube. In some cases no further training was required, for the others licking the response-sipper was shaped via the differential reinforcement of successive approximations of the terminal response. Once responding on the FR 1 was established, the access to water was systematically decreased from nine seconds to two and half seconds over a period of five daily sessions that lasted for 40 water presentations. After the decrease in water access per presentation, the response requirement was gradually increased to 20. The incremental steps from one to 20 varied across subjects and were determined by the inter-reinforcement intervals (IRI) collected in the previous session. The process of increasing the FR requirement occurred over 14 sessions for all subjects except 290, for which 22 sessions were required.

Baseline. As noted, the final schedule was an FR 20. The terminal schedule was chosen to replicate the schedule of reinforcement used in a previous study that included pigeons and key-pecking (Marusich, 2008). Sessions occurred once daily for each rat at roughly the same time, and experimental procedures began after a ten minute black-out. During the black-out no responses were recorded and no programmed stimuli were presented. The blackout was designed to approximate the reported maximal distribution of intraperitoneally (i.p.) injected cocaine (Pan & Hedaya, 1998). Sessions were terminated following the presentation of the 40th reinforcer or after 20 minutes of exposure to the experimental contingencies. Baseline conditions were in effect for 50 sessions.

Drug Regimen. Following baseline, the acute effects of cocaine on responding were determined by probe-drug administrations that occurred every five days. The initial range

included cocaine doses of: 30.0, 17.0, 10.0, 3.0 and 0 mg/kg (Vehicle). The initial range was administered twice and in a fixed, descending order. The fixed order of doses was used to detect systematic effects following repeated drug administrations (Sidman, 1960). No trends or systematic effects were observed during the acute assessment. Following the initial-range assessment some doses were repeated and doses of 1.0 and 0.1 mg/kg were administered as needed to characterize the dose-response functions.

Following the acute determination of cocaine effects subjects were paired, and the pairs were divided into two groups. The divided pairs had dose-response functions with similar response-rate ranges and drug sensitivities. The pairs were then assigned to one of two groups that were differentiated by the relationship between drug administration and exposure to the experimental session. Subjects in the Before group received an injection of 17.0 mg/kg cocaine immediately prior to the beginning of each experimental session. Following the session they were returned to the home cage and received a vehicle injection after 25 minutes. They were given one hour access to water via a licking tube ten minutes after the injection. Two subjects in the Before group died before the completion of this phase, therefore, the data for these subjects are not presented. The After-group subjects received an injection of vehicle immediately before the experimental session. Subjects in the After group were returned to their home cages immediately after the session, 25 minutes later they received an injection of 17.0 mg/kg cocaine, after ten more minutes they received water access via a licking tube for one hour. The delay to post-session injections was a tactic used to prevent within-session response suppression that has accompanied post-session drug administration when it occurs immediately after sessions (Glowa & Barrett, 1983; Pinkston & Branch, 2004). The introduction of water to the home cage was delayed by ten minutes to allow for the distribution of i.p. injected cocaine to occur. During

acute assessment, the daily-administered dose of 17.0 decreased responding by more than sixty percent, but did not completely suppress responding. Access to water was provided by stainless steel water tubes were between 3- and 4-cm long, 0.8-cm wide, and had an opening of 0.4 cm for water access.

The effects of cocaine were reexamined following the 30th consecutive day of administration the 17.0mg/kg chronic dose. The reassessment, or chronic assessment, was conducted in the same manner as the acute assessment, except that the chronic dose was administered on the four days between probe doses. Plus, the dose of 42.0 mg/kg was necessary to complete the characterization of the dose-response functions for all subjects. The experiment was completed after the chronic drug assessment.

Drug Procedure. Cocaine Hydrochloride (obtained from the National Institute on Drug Abuse) was dissolved in 0.9% saline for the first 184 session, which included the acute assessment, the 30 days of the chronic dosing regimen, and a portion of the chronic reassessment. After the 184th session cocaine hydrochloride was dissolved in 0.1-mol/L solution of sodium phosphate. The change was made because injections of 30.0 mg/kg were followed by skin abscesses at the site of injections for some subjects. The change to sodium phosphate solution resulted in no further abscesses. Daily doses were determined by the weight of cocaine salt and injections volume was 1 ml/kg. Doses were administered by an intraperitoneal (i.p.) injection. During chronic administration, the site of injection was alternated between the two sides of the abdomen.

Data Analysis. The main dependent variable was the session average rate of response-sipper licking. More specifically, one session's total number of responses was divided by the total time needed to complete the session. Response rates are presented as percent of vehicle

response rate. For construction of dose-response functions for each phase (i.e., acute, chronic, abstinence), the value for each dose was calculated by averaging the daily-response rates from all sessions prior to which that dose was administered. The values for the vehicle were similarly calculated. During the chronic phase for the Before group, the value for the chronically administered dose was taken as the average of all administrations that occurred the day before an administration of another dose or vehicle. For each subject the drug-response rates were plotted as a function of dose of cocaine for each phase.

For some analyses, estimates of the dose that decreased response rates by fifty percent, the Effective-Dose 50 (ED_{50}) was used to quantify the difference between pre-chronic and chronic dose assessments. Specifically, ED_{50} values were estimated by fitting (using GraphPad Prism 5.0) a negative-sigmoid logistic function (sometimes referred to as the *Hill equation)* to the dose-response data that had been normalized as percent of saline response rates. The following is the unmodified version of the model used to calculate ED_{50}s (Motulsky & Christopoulos, 2004).

$$Y = Bottom + \frac{Top - Bottom}{1 + \left(\frac{10^{\log ED50}}{10^{X}}\right)^{Hill\ Slope}} \tag{2-1}$$

In this equation Y represents the dependent variable of response rate and X represents the independent variable of cocaine dose. *Bottom*, represents the lowest possible response-rate, *Top* represents the maximum response rate. LogED_{50} represents the logarithm of drug dose that produces responding halfway between the *Top* and *Bottom*. The *Hill slope* is the steepness of the dose-response function.

The use of saline normalized data allowed for the *Top* and *Bottom* parameters to be restricted to 100% and 0% respectively. Vehicle-normalized data were used because rates of responding in sessions following vehicle injections provided a measure of responding that was unaffected by cocaine, and therefore, provided a control measure for all drug regimens. The *Hill*

slope and ED_{50} values were left free to vary and be determined by an iterative process that minimized the sum of squared deviations (GraphPad Prism 5.0®). These limitations allowed for a simplified version of Equation 1 to be employed in this analysis.

$$Y = \frac{100}{1+(10^{\log ED_{50}-X})^{Hill\ Slope}} \quad (2\text{-}2)$$

The analysis and discussion of the effects of the independent variables were directed primarily by visual analysis of graphs of individual-subject data. For some measures supplementary model comparisons using a form of Akaike's Information Criterion (AIC) were determined (Akaike, 1974; Motulsky & Christopoulos, 2004). The AIC characterizes a local and global model, and then determines the likelihood that each model correctly accounts for the data by comparing the goodness-of-fit while correcting for the number of free parameters in the respective models. That is, the previously discussed Hill equation (equation 2) was fit separately to data from the individual treatment phases or groups (Local) and a second identical model is fit to data from all treatment phases (Global). The criterion corrects for the advantage of extra free parameters in the local fits. To determine the AIC for each of the models the following equation is used:

$$AIC = N \times \ln\left(\frac{SS}{N}\right) + 2K \quad (2\text{-}3)$$

where N is the number of observations, K is the number of parameters plus 1, and SS refers to the sum of the square of the vertical distances of the points for the curve.

When the number of observations is small compared to the number of parameters (cf. Motulsky & Christopoulos, 2004) the AIC value is considered too small for interpretation, therefore, the second order, or Corrected version of the AIC must be applied. The current examination involves a relatively small number of observations, therefore, Akaike's Corrected Information Criterion (AIC_C) was used, and thus the equation employed was:

$$AICc = AIC + \frac{2K(K+1)}{N-K-1} \quad (3\text{-}4)$$

where, K, N, and AIC were previously defined in equation 3. Furthermore, Motulsky and Christopoulos (2004) have suggested that the corrected form always be used when comparing models. This is be made because N is located in the denominator of this corrected equation. Therefore, it will have a large impact when N is small, but a trivial impact when the N is sufficiently large (Motulsky & Christopoulos, 2004 pp., 144-145)

The model with the lower AIC_C is more likely to be correct, and the greater the absolute distance, the more confident one can be that the correct model was chosen. Furthermore, the absolute difference between the two model scores is used to determine the evidence ratio. An evidence ratio quantifies how much more likely the preferred model is to be correct relative to the other model. The evidence ratio is defined by the equation

$$Evidence\ ratio = 1/e^{-0.5 \cdot \Delta AICc}, \quad (3\text{-}5)$$

where, the ΔAIC_C refers to the difference between the two AIC_C scores.

As it is used here, an AIC_C evidence ratio that favored the local model would mean that two independent functions fit to data associated with the individual treatment phases or groups would be more likely to account for the data correctly. This type of outcome would support the argument that there is a difference between treatment phases or groups. On the other hand, an AIC_C evidence ratio that favored the global model would mean that one function using all data, regardless of treatment or groups would be more appropriate to account for the data. This type of outcome would support the argument that differences between treatment phases or groups were negligible. Model comparisons using the AIC_C were applied to data from individuals and to group-aggregated dose-response functions.

Results and Discussion

The variances accounted (r^2) for by the local and global models derived from Equation 2 are presented in Table2-1. The total amount of variance is reported for each local model with regards to each treatment phase, and the global models are reported with regards to the each treatment phase, as well as all the data collected for each treatment phases. Under the global heading in the Acute and Chronic columns the amount of variance for by the global fit is presented for the individual treatment phases. The ED_{50} values were also derived from the local logistical fits. Reported in table 2-1 are the r^2 values, which were calculated by the following equation;

$$r^2 = \frac{s_y^2 - s_e^2}{s_y^2} \tag{3-6}$$

with s_y^2 equaling the total variance and s_e^2 equaling the unexplained variance. The r^2 estimates were determined by a computer program (GraphPad Prism 5.0) for each comparison. The r^2 value derived from the computer program took into account all of the data points, not simply the mean. Figure 2-1 presents two subjects' dose-response functions along with their logistical models. Subject 296 had a relatively high r^2, but the value for 289 was relatively low. Both of the graphed logistical fits, however, appear to account for the mean effects of the drug. A potentially important difference between the two subjects is the range of response rates that the various doses of cocaine engendered. Particularly, the dose-response ranges for subject 289 were greater than those seen in 296's dose-response ranges. This difference is dose related response ranges supports that notion that the variability across the effects of one dose may have led to the relative differences in the variance accounted for by the models.

The acute effects of cocaine on responding are present for individual subjects in figures 2-2 and 2-3, and a group aggregates are presented in figure 2-4. A comparison of Before- and After-

group aggregates is presented in figure 2-5. Measures of response rate (responses /s) means, minimum and maximum response rates, standard deviations, and number of injections for each acutely administered dose of cocaine are provided in table 2-2. Individual and aggregated dose-response functions generally exhibited a dose-dependent decrease in responding. Mean response rates under the influence of the 30.0 mg/kg cocaine dose were decreased to less than 5 % of the saline responding for subjects in the After group and to less than 20% for the two remaining Before-group individuals. Mean responding rarely increased above vehicle levels, and never outside the range of control variation. The mean of the lowest dose was less than the vehicle mean, but with the vehicle range overlapped with the range of the lowest dose, for subjects 289, 290, 291, and 292. The two subjects that remained of the Before group were relatively more sensitive to the rate decreasing effects of cocaine than the After group subjects. The sensitivity observed in subjects 292 and 296 required them to be exposed to a dose of 0.1 mg/kg cocaine. It should be noted that the two deceased animals in the Before group had cocaine sensitivities that corresponded with the After-group subjects. That is, their lowest administered dose was 1.0 mg/kg cocaine.

Visual comparisons of Before and After group acute dose-response functions did not reveal systematic differences. The form of the dose-response functions and general range of response rates were relatively consistent across individuals and groups (Figures 2-2, 2-3, & 2-4). Likewise, a comparison of group aggregates did not show between group variations (Figure 2-5). An AIC_C model comparison between the aggregate dose-response functions of Before and After group revealed that the global model was 6.18 times more likely to be correct than the local models. It is therefore, unlikely that there were major differences between the groups prior to chronic drug administration.

After the chronic-dosing regimen there was evidence of tolerance for all subjects and (figures 2-2 & 2-3) and groups (figure 2-4). Evidence of tolerance is provide by the fact that the dose-response function for the chronic assessment (open squares in figures 2-2, 2-3, & 2-4) falls to the right of the acute assessment's dose-response function (closed circles in figures 2-2, 2-3, 2-4). The dose-dependent decreases in the various dose-response functions were retained following the chronic-dosing regimen, however the decreases now began a greater doses. The rightward shift of the dose-response function shows that the overall potency of cocaine had decreased following the chronic dosing regimen. Furthermore, ED_{50} estimates derived from fits of the logistic functions to the chronic dose-response data were greater than the acute counterparts for all subjects (Table 2-4). On average the ED_{50} estimate following the chronic-drugging regimen represented a threefold increase over the acute estimate. An AIC_C comparison of group aggregated dose-response functions found that the local model was preferred for both groups with the evidence ratio equaling 22.04 for the After group and >9999 for the Before group (Figure 2-4). This aggregate outcome was consistent with all individual-subject AIC_C comparisons of dose-response functions (Table 2-5).

Visual comparisons of Before and After group chronic dose-response functions did not reveal systematic differences. The form of the dose-response functions and general range of response rates were relatively consistent across individuals and groups (Figures 2-2, 2-3, & 2-4). Similarly, a comparison of group aggregates did not show between group variations (Figure 2-5). An AIC_C model comparison between the aggregate dose-response functions of the Before and After groups revealed that the global model was 3.596 times more likely to be correct than the local models. It is therefore, unlikely that there were qualitative or quantitative differences between chronic dose-response functions associated with the Before and After groups. In the

case of vehicle responding there was a slight decrease in the mean response rates when compared to the acute phase. The range of chronic and acute response rates overlapped for all subjects except 289 (Table 2-1 & 2-2). For this reason response-rate data were normalized according to the percent of saline responding engendered by each phase.

In light of the current findings it should be assumed that the development of tolerance was controlled by sources other than the relationship between time of drug injection and onset of the experimental procedures. That is, tolerance in this arrangement more closely resembled prior experiments on pigeon and not the typical rat outcome. It is proposed that the use of a species-typical response topography may have led to this outcome but further testing is required to be positive. The implications, limitations of the design, and the outcome of Experiment 1 will be further addressed in the General Discussion (Chapter 4).

Table 2-1. Total variance accounted (r^2) for by the local and global models fit to dose-response functions from the Acute and Chronic Drug Treatment Phases.

		Local		Global		
Group	Subject	Acute	Chronic	Acute	Chronic	All
After	289	0.5744	0.2665	0.4483	0.09676	0.3927
	290	0.4975	0.369	0.377	0.0795	0.3517
	291	0.5303	0.4296	0.3768	0.2406	0.3647
	Mean	0.6609	0.3069	0.5035	0.1697	0.3576
	292	0.4471	0.4517	0.02085	0.1882	0.2496
Before	293	0.691	0.7368	0.589	0.5727	0.6379
	296	0.659	0.4507	0.1316	0.1134	0.2765
	Mean	0.7467	0.7643	0.2173	0.3455	0.4075

Table 2-2. Acute phase mean rate of responding (responses /minute), minimum and maximum session response rates, standard deviations, and number of injections per dose for all subjects.

				Dose of Cocaine				
Subject	Vehicle	0.1	1.0	3.0	10.0	17.0	30.0	42.0
				After Group				
289	232.64	-	159.73	121.87	44.50	95.21	4.55	-
Min	165.49	-	89.80	55.14	22.43	27.44	0.62	-
Max	284.51	-	229.67	188.59	74.99	197.03	14.32	-
StDev	48.56	-	98.90	94.36	22.04	77.51	5.57	-
No.	5	-	2	2	4	4	6	-
290	157.87	-	-	130.43	19.86	64.25	5.07	-
Min	137.63	-	-	118.39	0.00	0.00	0.00	-
Max	176.64	-	-	142.48	58.14	130.16	13.55	-
StDev	13.91	-	-	17.03	22.60	65.89	7.39	-
No.	5	-	-	2	6	6	3	-
291	207.31	-	-	199.75	144.58	86.92	4.76	-
Min	127.86	-	-	189.71	11.33	0.00	0.00	-
Max	235.79	-	-	209.78	224.89	227.05	13.58	-
StDev	41.00	-	-	14.20	116.21	104.88	7.64	-
No.	6	-	-	2	3	6	4	-
293	142.94	-	154.04	96.64	56.05	33.33	0.48	-
Min	113.32	-	133.95	39.38	27.57	9.37	0.00	-
Max	165.75	-	174.13	186.20	90.52	88.22	1.01	-
StDev	21.27	-	28.41	78.56	31.90	37.44	0.51	-
No.	6	-	2	3	3	4	4	-
				Before Group				
292	156.41	126.18	99.43	109.81	98.80	74.16	14.60	-
Min	120.32	85.39	94.25	74.89	24.69	5.11	0.78	-
Max	192.48	166.97	104.62	144.20	160.17	159.22	26.30	-
StDev	29.68	57.70	7.33	34.66	68.63	61.81	12.89	-
No.	4	2	2	3	3	6	3	-
296	199.69	208.87	166.87	148.83	83.65	67.18	34.31	-
Min	193.60	193.34	161.53	137.15	64.15	2.09	1.16	-
Max	215.90	224.41	172.21	160.51	113.54	204.59	86.32	-
StDev	10.82	21.96	7.55	16.52	26.29	71.93	41.06	-
No.	4	2	2	2	3	6	4	-

Table 2-3. Chronic phase mean rate of responding (response / minute), minimum and maximum session response rates, standard deviations, and number of injections per dose for all subjects.

			Dose of Cocaine					
Subject	Vehicle	0.1	1.0	3.0	10.0	17.0	30.0	42.0
				After Group				
289	88.20	-	57.46	63.22	92.27	49.88	34.90	29.76
Min	0.00	-	45.22	54.93	72.85	19.77	15.91	22.43
Max	160.97	-	69.71	75.01	124.61	80.00	53.89	37.09
StDev	41.56	-	17.32	10.48	28.19	42.59	26.86	10.37
No.	14	-	2	3	3	2	2	2
290	109.01	-	-	93.98	72.66	51.69	46.18	52.76
Min	90.76	-	-	87.28	48.20	51.57	0.00	0.00
Max	148.97	-	-	100.67	89.23	44.23	81.12	121.72
StDev	13.96	-	-	9.47	21.62	59.38	41.71	61.09
No.	16	-	-	2	3	4	3	4
291	189.58	-	-	180.92	188.72	149.54	92.73	85.58
Min	136.05	-	-	169.25	183.32	115.54	0.41	0.09
Max	217.87	-	-	188.47	193.11	183.55	174.64	187.90
StDev	18.22	-	-	10.25	4.97	48.09	92.54	98.78
No.	16	-	-	3	3	2	4	4
293	102.39	-	102.08	102.37	103.36	64.91	105.96	0.59
Min	103.04	-	102.08	102.37	107.56	42.06	116.66	0.59
Max	71.05	-	100.07	94.70	93.71	37.90	68.26	0.16
StDev	131.94	-	104.08	110.02	108.82	114.77	132.97	1.03
No.	16	-	2	2	3	3	3	2
				Before Group				
292	99.53	-	138.10	86.81	128.46	90.64	88.01	6.08
Min	88.12	-	125.30	93.87	128.46	83.40	62.80	6.08
Max	110.95	-	150.08	55.53	126.42	45.86	56.45	0.00
StDev	16.15	-	12.41	111.02	130.49	134.02	144.80	12.16
No.	2	-	3	3	2	13	3	2
296	135.08	140.10	130.64	146.98	142.35	126.12	119.95	40.76
Min	125.95	131.74	130.64	146.98	132.74	137.76	119.95	0.00
Max	146.94	148.46	115.69	138.20	121.95	78.65	108.71	81.52
StDev	10.55	11.83	145.60	155.77	172.35	175.16	131.18	57.65

Table 2-4. Estimate Effective Dose 50 (mg/kg) values for the group means and individual animals for all phase.

Group	Subject	Acute	Chronic
After	289	8.284	28.58
	290	6.428	30.72
	291	15.2	35.49
	292	9.552	17.4
	Mean	12.74	30.79
Before	292	14.85	31.45
	296	12.1	38.02
	Mean	12.88	37.13

Table 2-5. Model Comparisons using Akaike's Corrected Information Criterion.

Group	Subject	Preferred Model	ΔAIC_C	Evidence ratio
After	289	Local	5.18	13.33
	290	Local	11.27	280.03
	291	Local	9.68	126.47
	293	Local	12.45	505.00
	Mean	Local	6.19	22.04
Before	292	Local	18.09	8493.94
	296	Local	40.94	>9999
	Mean	Local	24.34	>9999

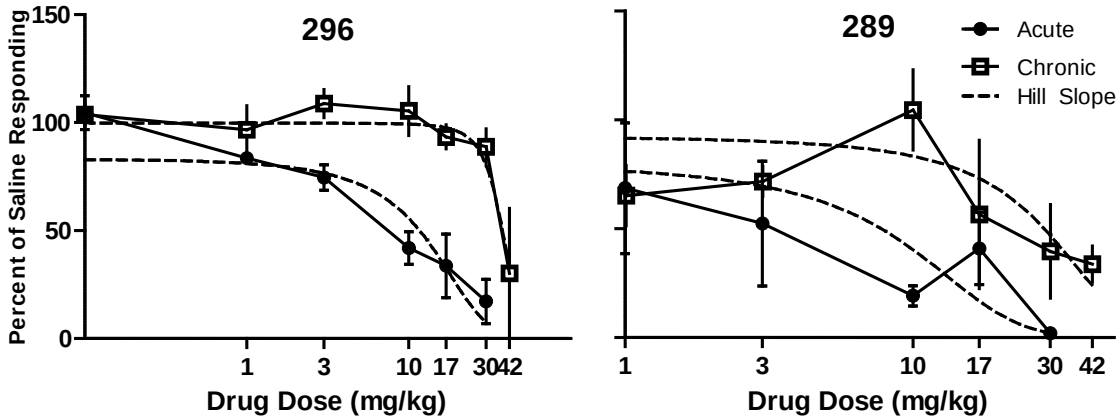

Figure 2-1. Hill-slope fits to the session-average responses per minute for the acute, and chronic drug phases as a function of cocaine dose for two individuals. Session-Average response rates are presented as percent of saline control. Hill-slope fits are presented as dashed lines. Each panel presents data from an individual subject and the subject number is identified at the top of the figure. Black circles represent data collected during the acute-cocaine assessment and white squares represent data collected during the chronic-cocaine assessment.

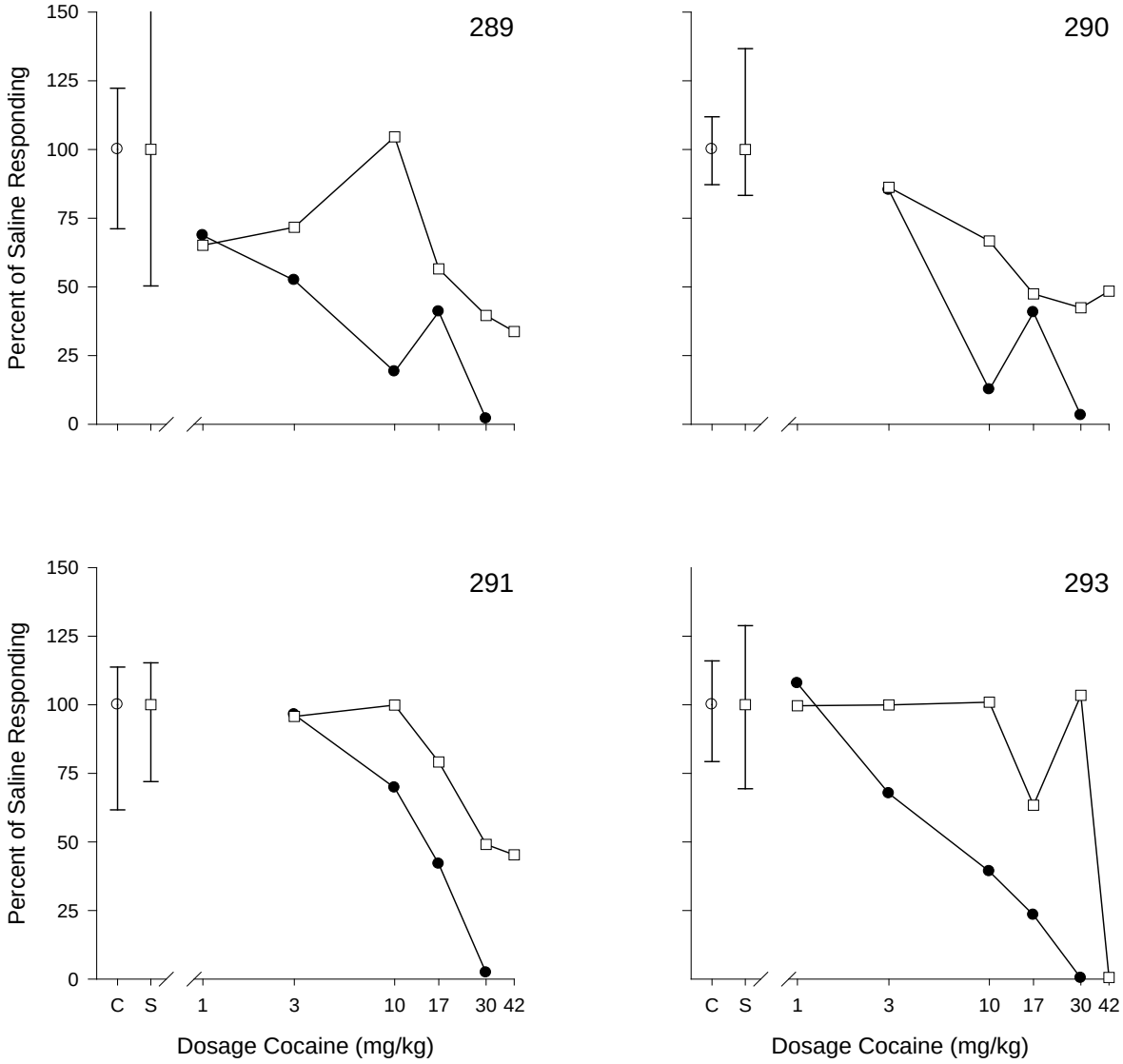

Figure 2-2. Session-average responses per minute for the acute and chronic drug phases as a function of cocaine dose for individuals in the After group. Session-Average response rates are presented as percent of saline control. Each panel presents data from an individual subject and the subject number is identified in the top-right portion of the panel. Black circles represent data collected during the acute-cocaine assessment and white squares represent data collected during the chronic-cocaine assessment. The points and range bars above "A" and "C" correspond to the mean and range of responses rates that occurred following pre-session saline administrations. Please note the first point after the x-axis break is 1.0 mg/kg.

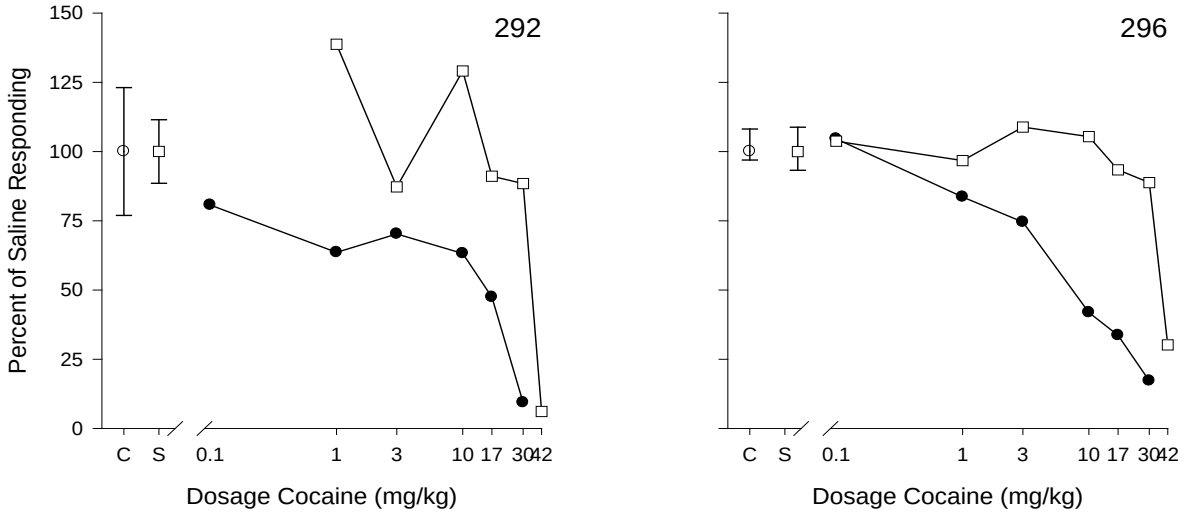

Figure 2-3. Session-average responses per minute for the acute and chronic drug phases as a function of cocaine dose for individuals in the Before group. Session-Average response rates are presented as percent of saline control. Each panel presents data from an individual subject and the subject number is identified in the top-right portion of the panel. Black circles represent data collected during the acute-cocaine assessment and white squares represent data collected during the chronic-cocaine assessment. The points and range bars above "A" and "C" correspond to the mean and range of responses rates that occurred following pre-session saline administrations. Please note the first point after the x-axis break is 0.1 mg/kg and the undefined tick corresponds to 30.0 mg/kg.

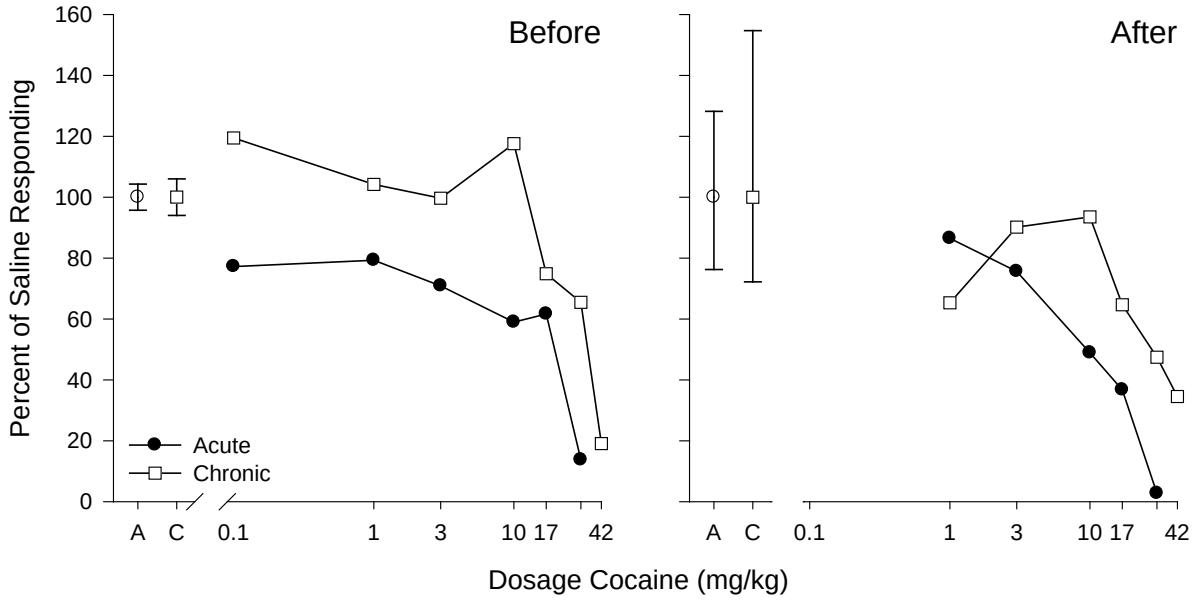

Figure 2-4. Group Aggregate Dose response functions are presented on individually labeled panels for both the Before and After groups Black circles represent data collected during the acute-cocaine assessment and white squares represent data collected during the chronic-cocaine assessment The points and range bars above "A" and "C" correspond to the mean and range of responses rates that occurred following pre-session 0.9% saline administrations Please note the first point after the x-axis break is 0.1 mg/kg and the undefined tick corresponds to 30.0 mg/kg

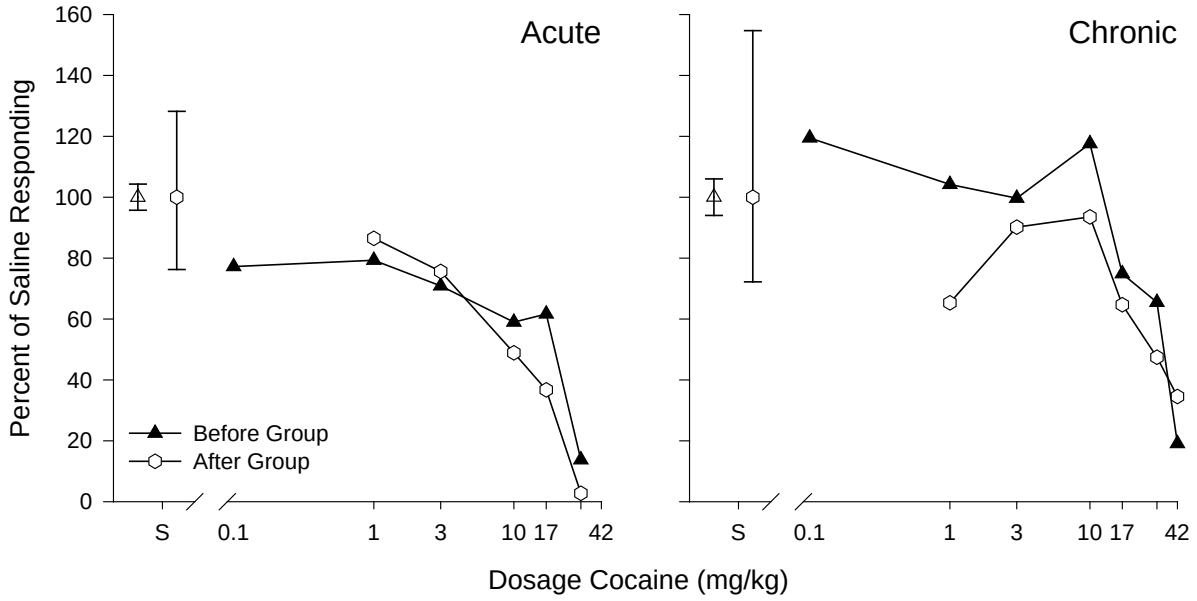

Figure 2-5. Before and After group aggregated response rates as a function of cocaine dose. Panel present data according to treatment phase, which is identified in the top—right corner of the panel. Filled Triangles represent the Before-group aggregate response rates and open hexagons represent the aggregated response rates for the After group. All response rates are presented as a percentage of the response rates observed in sessions following 0.9% saline-vehicle injections. Points and error bars above "S" correspond to the mean and total range of response rates following saline administration. Please note the first point after the x-axis break is 0.1 mg/kg and the undefined tick corresponds to 30.0 mg/kg.

CHAPTER 3
EXPERIMENT 2

Experiments using psychomotor stimulants with rats or monkeys have shown tolerance to be dependent on the drug being administered immediately prior to the experimental test, an outcome referred to as contingent tolerance (Branch & Sizemore, 1988; Bowen, et al., 1993; Campbell and Seiden, 1973; Carlton & Wolgin, 1971; Smith, 1990; Woolverton, et al., 1978). Conversely, experiments designed to analyze contingent tolerance using pigeons reported tolerance that developed regardless of when the drug was given (Pinkston & Branch, 2004: Marusich, 2008). Experiment 2 was designed to address a difference between procedures that use pigeons or other animals, namely that of response topography. Specifically, it is proposed that the operantly maintained key-peck response used in the pigeon studies has species-typical phylogenetic properties and susceptibilities to classically-conditioned associations that may have precluded the development of contingent tolerance.

Typical pigeon operant-conditioning experiments employ key pecking as the reinforced response class (Ator, 1991; Ferster & Skinner, 1957). The species-typical response of pecking is very prevalent in the repertoire of a pigeon and is commonly observed in a variety of situations in which no explicit operant conditioning has occurred, or when the influence of operant conditioning is presumed to be minimal. Such situations include; schedule-induced aggression (e.g., Azrin & Hutchinson, 1967; Azrin, Hutchinson, & Hake, 1966; Kupfer, Allen, & Malagodi, 2008), response-independent schedules (Staddon, 1977; Staddon & Simmelherg, 1971; Fenner, 1980), autoshaping maintained by grain (Brown & Jenkins, 1968; Gamzu &Williams, 1970; Jenkins & Moore, 1973; Schwartz & Gamzu; 1977; Williams & Williams, 1969), autoshaping maintained by water (Jenkins & Moore, 1973; Woodruff & Williams, 1976), and administration of the apomorphine (Graeff & Oliveira, 1975; Pinkston, Madden, & Fowler, 2008). The

propensity of pecking in a variety of non-operant arrangements may illustrate that the pecking-response topography is not arbitrary, or that it is prepared to occur in a number of varied situations. That is, the evidence suggests a predisposition for the pigeon to use its beak in a pecking motion in a variety of situations and be motivated to do so for a number of different reasons (Schwartz & Gamzu, 1977; Seligman, 1970; Timberlake, 1993). The use of the key peck in the experimental arrangement and the wide range of situations under which pecking occurs may have allowed pecking-related tolerance to occur in the home cage. That is, the post-session drugging regimen, may have led to an overall deficit in overall pecking levels, which recovered following repeated exposure. Once tolerance was established in the home cage it may have generalized to the experimental chamber and disrupted the observation of contingent tolerance. Therefore, the species-typical predisposition to peck may have prevented Branch and colleagues (Marusich, 2008; Pinkston & Branch, 2004) from observing contingent tolerance with pigeons. The approach taken to address this problem was to use treadle-press topography, which appears to be more arbitrary than the key peck.

Experiment 2 arranged for food deprived pigeons to attain grain under a schedule of reinforcement that required treadle-pressing. Treadle-press has been successfully used as an operant response in several investigations when pecking led to atypical outcomes that may not have generalized across species (e.g., Graeff & Oliveira, 1975; Hemmes, 1975, 1973; McSweeney, 1982; Smith & Keller, 1970; Richardson & Clark, 1976). The free-operant escape and avoidance literature, in particular the work of Smith and Keller (1970), illustrates that the use of a more-arbitrary response may lead to outcomes consistent with those of other species. Smith and Keller's research followed from the early work in free-operant avoidance and escape, which focused on operantly conditioning pigeons to key-peck to remove shocks This method,

however, proved to be time consuming and only marginally successful (Hoffman & Fleshler, 1959; Rachlin & Hineline, 1967). Further research in the field showed that is wasn't impossible to condition escape and avoidance responding, but that it was made difficult by the use of key-pecking. Once the difficulties were identified researchers tried alternative responses (Foree & LoLordo, 1970; Hoffman & Fleshler, 1959; MacPhail, 1968; Smith & Keller, 1970) or methods of shock delivery (Hineline & Rachlin, 1969) to shape avoidance of electric shock in pigeons. Smith and Keller devised an operant arrangement that employed a treadle-press in place of the key peck. An operant involving the treadle press requires the pigeon to depress a lever-like plate, located close to the floor, with its foot in order to receive reinforcers. This relatively arbitrary response allowed for the rapid acquisition of avoidance responding. Indeed, three of the four reported subjects were avoiding 98% of shocks by the 9th session, which compares favorably to the more than 3000 training trials that were necessary to shape a head raising response that would break a photo beam (Hoffman & Fleshler, 1959). The treadle press has proven to be a useful alternative to the key-peck and was therefore used in the current experiment. The treadle-response topography should create an experimental arrangement that was more similar to previous studies of contingent tolerance with rats and monkeys.

The overall aim of Experiment 2 was to make the pigeon experimental procedure similar to the rat procedure with respect to the arbitrary response topography. The use of the treadle, however, brings with it new methodological issues. When compared to the key-peck, a treadle-press requires more force to register a response and each response is more time consuming. Procedural accommodations related to the treadle press will be further discussed in the methods section.

Method

Subjects

The subjects were eight adult male, White Carneau pigeons (*Columba livia*). Six subjects had participated in a University of Florida Laboratory Methods class, and two, 820 and 958, were experimentally naïve. All eight subjects were naïve to cocaine and operant conditioning of the treadle-press response. Subjects were roughly 6 months to 1 year of age at the beginning of the experiment. Subjects 30, 549, 660, 802, 829, and 996 began training 102 days prior to subjects 820 and 958. The initial six subjects were involved in exploratory analyses designed to assess basic characteristics of the treadle-press response, and relevant aspects of the analyses are further discussed under the Training sub-heading in this section. Subjects had vitamin (Agrilabs™ Vitamins and Electolyte "Plus"®, St. Joseph, MO) enriched water available at all times in the home cage and were maintained at 85% of their *ad libitum* weight. The experimental weight was maintained by post-session feeding of Purina Pro-11 Grains for Pigeons™ and Purina™ Pigeon Chow® Checkers® in a 50:50 mixture. Subjects were housed individually in a windowless colony room that was maintained between 19° to 22°C, with ambient levels of humidity. Colony room lights were illuminated daily at 7:00 a.m. and the animals were subject to a 16/8 hr light/dark cycle.

Apparatus

Experimental sessions occurred in a custom built operant-conditioning chamber. The experimental space measured 36 x 36 x 36 cm. Four of the six chamber walls were translucent acrylic glass and one of the side walls was an aluminum plate that served as the intelligence panel. The intelligence panel included a centrally located 4.5- x 7-cm hole approximately 7.5 cm from the floor for access to hopper grain. The intelligence panel also included three non-operative horizontally aligned keys located 8 cm from the ceiling, 10 cm from each other, and

with the two outermost keys 8 cm from the chamber walls adjacent to the intelligence panel. Finally, the intelligence panel included a 2 cm-wide opening for the treadle that began at the chamber floor and ended 7 cm above the floor. The treadle design was based on the description provided in Smith and Keller (1970). The aluminum treadle plate was 7.7 x 6.6 cm, positioned at a 35° from horizontal angle. The bottom edge was 3 cm from the floor in the front and the top edge (closest to the wall) was 7 cm from the floor. Treadle responses were recorded if a force of 0.75 N was applied and a depression 2.5 cm from the resting position occurred. The force of 0.75 N was sufficient to make treadle-directed pecking ineffective. Each response produced a 30-ms, 2900- Hz tone from a Mallory ® Sonalert. Two miniature lamps were located 2 cm from the ceiling and 7 cm from each other on the wall opposite the intelligence panel. These 28-V miniature lamps provided light during the experimental session. The ceiling included tape strips demarking nine equal-area rectangles that were remnants from a previous study and are not assumed to have affected the current findings. Photographs of the custom-built operant-conditioning chamber are shown in Figures 3-1 and 3-2.

The chamber was housed in a Med Associates, Inc. (St. Albans, VT) ENV-016M Extra-Wide Sound-Attenuating Cubicle with internal dimensions of 55.9 cm x 38.1 cm x 35.6 cm. Extraneous sounds were masked by an internal fan located in the rear of the cubicle, as well as a constant 95-db white noise, emanating from a Coulbourn Instruments Tone/Noise Generator (Model A69-20), located in the room surrounding the cubicle. Programming and recording of experimental events was performed by a custom-built computer with 1-msec resolution (Palya & Walter, 1993). The computer was located in a room adjacent to the room housing the experimental chamber.

Procedure

Training. Six pigeons had previous experience in laboratory experiments and did not require magazine training. Magazine training of subjects 820 and 958 included repeatedly raising the grain hopper and illuminating the hopper light until they reliable ate from the hopper. Treadle-press responding was shaped through a method of differential reinforcement of successive approximations to the terminal response. Prior to the baseline conditions of the present experiment, subjects 30,549, 660, 802, 829, and 996 were exposed to a range of FR values. These exploratory analyses were used to determine the inter-reinforcement interval (IRI) that would most closely approximate a previous contingent-tolerance study that involved pigeons key-pecking under an FR 20 schedule of reinforcement (Marusich, 2008). The exploration included a range of FR values from FR 1 to FR 10. The ratio requirement increased by one the session after the previous session's average inter-response time was less than four seconds. The group average IRI associated with the FR 8 most closely approximated the group average from Marusich (2008). The exploratory analyses lasted for 66 sessions. Training for subjects 820 and 958 differed in that they were not subject to FR values greater then FR 8 and the training regimen lasted roughly seven days, across which the FR was increased from one to eight over consecutive sessions.

Baseline. The final schedule was an FR 8. Experimental sessions occurred once daily at roughly the same time, seven days a week. Sessions lasted until 40 reinforcers were delivered or 20 minutes had passed, whichever occurred first. Sessions began following a five-minute black-out period. During the black-out period no responses were recorded and no programmed stimuli were in operation. Baseline conditions were in effect until 50 sessions had occurred and a stability criterion was satisfied. The criterion required dividing 12 consecutive sessions into three blocks of four sessions, and the response rates of the sessions within the blocks were then

averaged. Criterion was reached when there no monotonically increasing or decreasing trends observed in aggregated response rates of the three blocks. Stability was reached by 60 or fewer sessions for all subjects. Baseline conditions were then extended 46 more days for subjects 30,549, 660, 802, 829, and 996 to characterize more fully the stability of treadle press responding. The extended baseline condition for the six subjects revealed that stability was maintained following the satisfaction of the stability criterion. That is, once established the daily baseline rates of responding did not show monotonic increasing or decreasing trends over 46 sessions.

Drug Regimen. Following baseline, the acute effects of cocaine on responding were determined by probe-drug administrations that occurred every five days. The initial range of doses included 0 (the vehicle), 10.0, 5.6, 3.0, and 1.0 mg/kg of cocaine. The initial range was administered twice and in a fixed, descending order. The fixed order of doses was used to detect systematic effects following repeated drug administrations (Sidman, 1960). No trends or systematic effects were observed. Following this initial-range assessment some doses were repeated, and doses of 4.2, 7.4, 13.0 and 17.0 mg/kg were administered as needed, to characterize more completely the individual dose-response functions. Assessments revealed that the amount of exposure and the potencies of doses differed for all subjects. The examination of the range of doses, rather than one dose allowed identification of functionally equivalent doses between subjects.

Following the acute determination of cocaine's effects, subjects were paired and the individuals in each pair were assigned randomly to one of two groups. The pairs were selected on the basis of similar dose-response functions and response-rate ranges. Furthermore, individual histories were equated across groups. That is, subjects 820 and 958, which had no

lab-class history, were in different groups and the remaining six were evenly distributed between the groups. Once assigned, the groups differed in the relationship between drug administration and exposure to the experimental session. One group, the Before group, received a daily dose of cocaine immediately prior to the experimental session and an injection of vehicle one hour after the session. The After group received a daily cocaine dose one hour after the session and an injection of vehicle immediately before the experimental session. All post-session injections occurred in the colony room where the subject home cages were located. The daily dose was one that decreased the individual's responding by more than sixty percent, but did not completely suppress responding. Subjects 549, 660, 820, 958, and 996 received a daily, chronic dose of 5.6 mg/kg, while subjects 802 and 829 received 7.4mg/kg, and subject 30 received 4.2 mg/kg of cocaine.

The effects of cocaine were reexamined following the 30th consecutive day of administration of the specified chronic dose. The reassessment, or chronic assessment, was conducted in the same manner as the acute assessment, except that the chronic dose was administered on the four days between probe doses. Specifically, on probe-injection days a dose of cocaine (or, vehicle) was administered before the session and the vehicle was administered after the session for subjects in both groups. This tactic allowed for the re-assessment of cocaine's effects on responding during the experimental session. Following the chronic assessment, the effects of cocaine after 30 days of abstinence were examined. During the abstinence phase no injections were administered either before or after that session. The re-assessment of cocaine's effects following abstinence was a direct replication of the acute assessment. Experiment 2 concluded following the Abstinence assessment.

Drug Procedure. Cocaine Hydrochloride (obtained from the National Institute on Drug Abuse) was dissolved in 0.9% saline. Daily doses were determined by the weight of cocaine salt, and injection volume was 1 ml/kg. Doses were administered by an intra-muscular (i.m.) injection in the pigeon's breast. During chronic administration the site of injection was alternated between the two sides of the breast.

Data Analysis. The main dependent variable was the session average rate of treadle pressing. Details pertaining to the calculation and presentation of data can be found in the Data Analysis section of Experiment 1 (Chapter 2).

Results and Discussion

The variances accounted for by the local and global models derived from Equation 2-6, using the same approach as in Experiment 1 are presented in Tables 3-1, 3-2, and 3-3. The total amount of variance is reported for each local model with regards to each treatment phase, and the global models are reported with regards to the each treatment phase, as well as the complete family of all the data. Under the global heading in the Acute and Chronic columns the amount of variance for by the global fit is presented for the individual treatment phases. The ED_{50} values were also derived from the local logistical fits. Specifically, the ED_{50} values for the acute and chronic phases were derived from models related to the r^2 values reported in Table 3-1 and the abstinence ED_{50} values were derived from those whose r^2 values are in table 3-2. Recall that the r^2 values derived from the computer program were based on all of the data points, not simply the mean. Overall the r^2 were high and showed that an adequate amount of variance was accounted for by the models.

The acute effects of cocaine on responding for individual subjects are illustrated as black circles on figures 3-4 and 3-5, group aggregates are presented in Figures 3-3 and 3-6. Measures of response rate means, minimums, maximums, standard deviations, and number of injections for

all subjects, phases, and doses can be seen in Tables 3-4 and 3-5. Response rate means are given next to the subject number in tables 3-4 and 3-5. The dose-response functions reveal a dose-dependent decrease in response rates for all subjects. There was variability in the sensitivity to cocaine between individuals. Drug-response rates were completely suppressed or near-zero (below 5% of saline responding) for subjects 30, 660, 820, and 958 following administrations of 10.0 mg/kg of cocaine. Subjects 549, 829, and 996 were similarly affected by doses of 13.0 mg/kg. Only subject 802 received a dose of 17.0, which completely suppressed responding. The effect of the smallest dose, 1.0 mg/kg of cocaine, on average, did not have a very large impact on responding. Response rate for subject 802, however, increased 24% above average saline control rates, whereas for subjects 660 and 30 the average deceased by 22% and 25%, respectively.

Visual comparisons of Before and After group acute dose-response functions did not reveal systematic differences. The form of the dose-response functions and general range of response rates were relatively consistent across individuals and groups (Figures 3-4 & 3-5). Likewise, a comparison of group aggregates did not show between group variations (Figure 3-6). An AIC_C model comparison between the aggregate dose-response functions of Before and After group revealed that the global model was 4.86 times more likely to be correct than the local model (Figure 3-3). This supports the notion that there were inconsequential between-group differences in cocaine's effects on responding during the acute assessment and that the groups were unlikely to have been biased by initial sensitivities to cocaine.

Following the Chronic administration regimen there is evidence of tolerance for all subjects, regardless of group designation (Compare circles and open squares in Figures 3-4, 3-5, and 3-6). The evidence of tolerance is revealed by the fact that chronic assessment dose-

response functions, for all subjects, fall to the right of the acute assessment dose-response functions, indicating that larger doses were required to decrease responding after exposure to daily administration. The majority of the functions retained the dose-dependent decreases seen in the acute assessment. The chronic dose-dependent decreases, however, began at greater doses than the acute assessment. Likewise, the ED_{50} estimates derived from fits of the logistic functions to the chronic dose-response data were greater than the acute counterparts for all subjects (Table 3-10).

As with the acute assessment, the individual dose-response functions reveal between-subject differences in the magnitude of tolerance following the chronic-dosing regimen. The dose-response function for subject 802 did not show the dose-dependent decreases mentioned above. That is, the dose-response function following the chronic assessment for subject 802 was relatively flat and illustrated insensitivity to the rate decreasing effects of cocaine. No dose of cocaine decreased 802's response rates by 50%, therefore the response rate was set to zero at 23.0, a point 1/8 log units greater than the largest administered dose of 17.0 mg/kg. A point that was 1/8 log units greater was chosen because this is the logarithmic distance between 10 and 13. This estimate of the dose that eliminated treadle pressing was chosen because it provided a conservative estimate of a dose that would eliminate responding. Thus, tolerance that is apparent upon visual examination of the administered doses is likely underestimated by the estimated-zero dose, given the observed dose-response function. The estimated-zero dose was only used in calculations and is not presented on any figures. The estimated-zero dose was designed to avoid possible harm (via drug overdose) to the subject, to comply with veterinarian approved Institutional Animal Care and Use Committee (IACUC) protocol, and provide a means to calculate the ED_{50} value for the chronic dose-response function if it did not turn down at any of

the does actually administered. Subject 802, of the Before group, also had the greatest estimated ED_{50} value, 18.31, after chronic administration. The lowest ED_{50} estimate, of 4.16 was derived from data provided by subject 30, a member of the After group (Figure 3-10).

Individual differences notwithstanding, the visual impression of both individual and group aggregate dose-response functions was consistently that of tolerance (Figures 3-4, 3-5, & 3-6). An AIC_C comparison of group aggregated dose-response functions found that the local model was preferred for both groups with the ratio of probabilities equaling 34.15 for the After group and the 603.85 for the Before group (Figure 3-6). This aggregate outcome was consistent with individual-subject AIC_C comparisons of dose-response functions, which showed that the local alternative was more likely to be correct for seven of the eight subjects (Table 3-11). Only subject 996, of the Before Group, had an AIC_C that resulted in the global model being more likely to correctly account for the data, however the probability ratio of 1.67 was comparatively low (Table 3-11). A visual analysis of data from 996 (Figure 3-5) showed that three doses proved to be behaviorally active during the acute assessment (5.6, 10.0, & 13.0 mg/kg). Following the chronic regimen responding following injections of 5.6 mg/kg dose recovered to near baseline control rates, responding following 10.0 mg/kg doubled, and responding in the presence of 13.0 mg/kg went from complete suppression to an average of response rate of 13.62 responses per minute, a rate that nearly doubles that of the acute 10.0 mg/kg response rates. In the cases of the behaviorally active doses that prolonged drug exposure attenuated the initial rate decreases in responding. It is therefore reasonable to argue that subject 996 did show tolerance, however, the magnitude of tolerance was less robust when compared to the other seven subjects.

Based on the outcome of Experiment 1 it was hypothesized that the use of an arbitrary response topography may allow contingent tolerance to be observed in the pigeon. The tolerance

observed in the Before group is consistent with the contingent tolerance literature. The overall pattern of tolerance for the After group, however, was not predicted by the contingent tolerance hypothesis, but was predicted by previous pigeon studies (Pinkston & Branch, 2004; Marusich, 2008). It appears that the role of response-topography is minimal in the development of tolerance in the pigeon, a finding that is inconsistent with Experiment 1. Further discussion related to this topic will occur in Chapter 4: General Discussion.

When the Before- and After-group outcomes are compared it is evident that they are qualitatively similar. Both groups developed tolerance to cocaine's rate-decreasing effects. There is, however, evidence of quantitative differences between the two groups. Specifically, it appears that the Before-group subjects showed a more robust recovery of responding, that is, more tolerance as a result of the chronic regimen. A comparison of graphs presenting individual and group-aggregated dose-response functions reveals the shift away from the acute dose-response function appears greater in the Before group dose-response function (Figures 3-4, 3-5, & 3-6). A between group comparison of dose-responses functions engendered by the same phases supports the notion that the Before groups illustrated greater relative tolerance (Figure 3-3). Furthermore, these visual analyses are supported by an AIC_C model comparison that directly evaluated the Before- and After-Group's chronic dose-response functions. The comparison found that a local model was 1.76 times more likely to account for the data correctly. The probability ratio reported is not very large but it does support the visual analysis and provides cause for further inquiry with additional subjects. Along with dose-response function comparisons, the range of ED_{50} estimates within groups also differed, the Before Group's estimated values ranged from 19.07 to 8.17, however, the After group range was from 10.95 to 4.16. These changes in range represent approximately an average ED_{50} increase of 220% for the

Before group and 158% for the After group. The visual effect of the individual and group (Figures 3-3, 3-4, 3-5, & 3-6), along with the supplemental AIC_c outcomes support the view that there is a slight, quantitative difference between the groups. This difference warrants further inquiry which will be discussed in Chapter 4: General Discussion.

Following the Chronic assessment of drug effects there was an attempt to see if an abstinence phase would reveal any further differences between the groups, and to see if the changes that had occurred during daily drugging would be maintained. After 30 sessions without drug, all subjects again showed dose-dependent decreases in responding. There did not, however, appear to be major between group differences seen in the abstinence-assessment phase (Figures 3-3, 3-4, 3-5, & 3-6). This was likely due to the fact that no consistent relationship between the abstinence phase and the previous treatment phases was observed. For instance, the dose-response functions generated during the abstinence phase were sometimes consistent with a subject's acute phase (subjects 829, 802, and 820), indicating that tolerance that had developed in the chronic phase had been lost. For other subjects, (subject 549, 30, 958, 660, 802, and 996), tolerance remained evident. The persistence of tolerance in only some subjects may have occurred because the length of the abstinence phase was too brief. The loss of tolerance observed in the behavior of subjects 829, 802, and 820, indicates the variables such as age, number of total sessions, and total number of injections was unlikely to account for the changes observed during the chronic assessment. Furthermore, and AIC_C model comparison of the After- and Before-group abstinence dose-response functions found that the global model was 3.173 times more likely to be correct. It appears that daily cocaine administration led to the development of tolerance.

Table 3-1. Total variance accounted (r^2) for by the local and global models fit to dose-response functions from the Acute and Chronic Drug Treatment Phases.

		Local		Global		
Group	Subject	Acute	Chronic	Acute	Chronic	All
Before	820	0.8223	0.6975	0.6336	0.5592	0.6082
	996	0.943	0.4337	0.8878	0.3875	0.6129
	802	0.8993	0.6746	0.3783	0.3655	0.4236
	660	0.7921	0.3992	0.4602	0.2059	0.4234
	Mean	0.815	0.5624	0.6887	0.3647	0.6067
After	829	0.8591	0.7422	0.8084	0.5365	0.7569
	958	0.8435	0.6963	0.8011	0.1408	0.6269
	30	0.8121	0.7332	0.7271	0.6152	0.7135
	549	0.8689	0.8428	0.8113	0.7748	0.8037
	Mean	0.7548	0.8022	0.6895	0.7051	0.7101

Table 3-2. Total variance accounted (r^2) for by the local and global models fit to dose-response functions from the Acute and Abstinence Drug Treatment Phases.

		Local		Global		
Group	Subject	Acute	Abstinence	Acute	Abstinence	All
Before	820	0.7998	0.9764	0.7943	0.9631	0.8827
	996	0.9653	0.8441	0.8899	0.7912	0.8429
	802	0.8802	0.1545	0.8105	0.3963	0.6456
	660	0.7309	0.7636	0.6911	0.709	0.7112
	Mean	0.815	0.7982	0.7875	0.7272	0.7852
After	829	0.9283	0.7474	0.8839	0.6274	0.789
	958	0.8194	0.8166	0.7277	0.3934	0.6518
	30	0.7663	0.9709	0.5625	0.3189	0.5685
	549	0.8017	0.9525	0.7728	0.8422	0.8146
	Mean	0.7548	0.8599	0.6986	0.7512	0.7425

Table 3-3. Total variance accounted (r^2) for by the local and global models fit to dose-response functions from the Chronic and Abstinence Drug Treatment Phases.

		Local		Global		
Group	Subject	Chronic	Abstinence	Chronic	Abstinence	All
Before	820	0.7599	0.9757	0.6803	0.8028	0.7877
	996	0.507	0.8342	0.4531	0.7406	0.5794
	802	0.5989	0.6708	0.2768	0.4336	0.3829
	660	0.5287	0.7822	0.4968	0.735	0.6799
	Mean	0.5624	0.7982	0.5168	0.7407	0.6169
After	829	0.7253	0.7092	0.5546	0.5676	0.5664
	958	0.7227	0.8213	0.2702	0.7298	0.5396
	30	0.6987	0.9412	0.6301	0.8037	0.7106
	549	0.8794	0.8527	0.8778	0.8482	0.8711
	Mean	0.8022	0.8599	0.7856	0.8409	0.8154

Table 3-4. Acute phase mean rate of responding (response / minute), minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the After group.

Dose of Cocaine									
Subject	Saline	1.0	3.0	4.2	5.6	7.4	10.0	13.0	17.0
829	43.58	45.19	35.99	-	31.37	25.03	1.26	0.00	
Min	35.25	44.70	32.18	-	27.73	22.85	0.10	0.00	
Max	60.93	45.68	39.80	-	33.20	26.98	3.00	0.00	
StDev	11.37	0.69	5.39	-	3.15	2.07	1.54	0.00	
No.	5	2	2	-	4	3	3	1	
958	49.08	53.79	50.23	51.94	15.31	-	0.00	-	
Min	41.93	53.63	49.65	50.6	0.00	-	0.00	-	
Max	56.13	53.95	50.80	53.28	31.23	-	0.00	-	
StDev	6.08	0.23	0.81	1.89	17.68	-	0.00	-	
No.	5	2	2	2	4	-	2	-	
30	57.44	48.78	26.66	7.07	2.80		0.00	-	
Min	38.45	44.63	0.00	1.00	0.00		0.00	-	
Max	77.4	52.93	43.63	13.14	6.45		0.00	-	
StDev	16.40	5.87	16.28	8.58	3.31		0.00	-	
No.	5	2	5	2	4		2	-	
549	53.78	55.13	44.90	-	18.31	-	4.81	2.67	
Min	49.28	53.60	35.70	-	0.13	-	0.00	2.67	
Max	58.20	56.65	54.10	-	38.70	-	11.33	2.67	
StDev	3.94	2.16	13.01	-	16.69	-	4.75	-	
No.	5	2	2	-	4	-	4	1	

Table 3-5. Acute phase mean rate of responding (response / minute), minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the Before group.

	Dose of Cocaine								
Subject	Saline	1.0	3.0	4.2	5.6	7.4	10.0	13.0	17.0
820	59.13	63.50	49.38	42.64	16.91		0.00		
Min	40.85	56.23	5.34	37.45	0.00		0.00		
Max	68.30	70.78	45.60	47.83	34.63		0.00		
StDev	9.62	10.29	53.15	7.34	19.54		0.00		
No.	6	2	2	2	4		2		
996	40.68	40.63	37.38		21.84		7.61	0.00	
Min	34.73	38.85	33.70		20.68		2.38	0.00	
Max	44.03	42.40	41.05		23.00		12.05	0.00	
StDev	3.86	2.51	5.20		1.64		4.54	0.00	
No.	5	2	2		2		6	1	
802	38.42	47.83	33.16		31.39	12.32	5.74	3.25	0.00
Min	31.33	45.45	31.65		26.93	7.73	0.18	3.25	0.00
Max	49.58	50.20	34.68		35.85	16.91	11.49	3.25	0.00
StDev	6.98	3.36	2.14		6.31	6.50	5.27		0.00
No.	6	2	2		2	2	4	1	1
660	37.68	29.38	26.11		10.25		0.00		
Min	28.50	24.93	23.53		0.30		0.00		
Max	46.55	33.83	28.70		24.40		0.00		
StDev	8.51	6.29	3.66		9.52		0.00		
No.	5	2	2		6		2		

Table 3-6. Chronic phase mean rate of responding (response / minute), minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the After group.

	Dose of Cocaine								
Subject	Saline	1.0	3.0	4.2	5.6	7.4	10.0	13.0	17.0
829	42.59	41.79	36.15	-	32.95	32.13	25.83	8.08	
Min	50.43	41.65	34.20	-	30.73	27.50	14.86	8.08	
Max	37.475	41.93	38.10	-	35.18	36.75	36.80	8.08	
StDev	3.64	0.19	2.76	-	3.15	6.54	15.52	8.08	
No.	10	2	2	-	2	2	2	1	
958	50.94	50.59	50.50	-	43.16	-	19.97	-	
Min	39.55	50.48	50.38	-	34.95	-	0.00	-	
Max	57.1	50.70	50.63	-	51.38	-	33.18	-	
StDev	5.58	0.16	0.18	-	11.61	-	17.59	-	
No.	9	2	2	-	2	-	3	-	
30	64.05	66.54	46.54	39.39	23.91	-	0.00	-	
Min	59.825	65.25	42.93	9.67	0.00	-	0.00	-	
Max	74.55	67.83	50.15	65.13	47.83	-	0.00	-	
StDev	4.25	1.82	5.11	24.65	33.82	-	0.00	-	
No.	12	2	2	4	2	-	2	-	
549	48.29	52.61	43.34	-	42.16	-	9.84	6.64	
Min	37.90	45.65	28.48	-	37.05	-	0.00	5.73	
Max	61.625	59.58	53.70	-	47.28	-	14.32	7.55	
StDev	7.12	9.85	13.20	-	7.23	-	6.69	1.29	
No.	11	2	3	-	2	-	4	2	

Table 3-7. Chronic phase mean rate of responding (response / minute), minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the Before group.

	Dose of Cocaine								
Subject	Saline	1.0	3.0	4.2	5.6	7.4	10.0	13.0	17.0
820	60.73	55.94	54.14	-	47.12	-	16.00	-	-
Min	59.80	52.95	47.28	-	38.58	-	0.00	-	-
Max	61.65	58.93	61.00	-	57.28	-	46.73	-	-
StDev	1.31	4.23	9.71	-	6.46	-	21.00	-	-
No.	2	2	2	-	10	-	4	-	-
996	39.75	37.18	32.45	-	32.15	-	16.63	13.62	0.00
Min	36.38	21.93	20.85	-	19.67	-	0.00	0.00	0.00
Max	43.125	52.43	44.05	-	45.75	-	33.25	27.23	0.00
StDev	4.77	21.56	16.41	-	9.51	-	23.51	19.26	0.00
No.	2	2	2	-	11	-	2	2	1
802	25.78	35.90	39.10	-	41.34	33.33	30.58	-	27.65
Min	24.80	32.11	38.30	-	36.08	20.20	29.25	-	27.65
Max	26.75	39.70	39.90	-	46.60	42.03	31.90	-	27.65
StDev	1.38	5.37	1.13	-	7.44	5.91	1.87	-	-
No.	2	2	2	-	2	11	2	-	1
660	36.88	37.11	36.30	-	31.10	-	9.45	-	-
Min	15.57	26.48	30.30	-	16.52	-	2.00	-	-
Max	49.925	47.75	42.30	-	43.93	-	16.90	-	-
StDev	12.72	15.04	8.49	-	8.86	-	10.54	-	-
No.	5	2	2	-	11	-	2		-

Table 3-8. Abstinence phase mean rate of responding (response / minute), minimum and maximum session response rates, standard deviations, and number of injections per dose per dose for subjects in the After group.

	Dose of Cocaine								
Subject	Saline	1.0	3.0	4.2	5.6	7.4	10.0	13.0	17.0
829	46.81	46.18	37.12	-	22.97	-	9.08	-	-
Min	42.48	44.98	33.80	-	0.00	-	7.17	-	-
Max	52.43	47.38	41.40	-	39.38	-	11.00	-	-
StDev	4.20	1.70	3.89	-	20.49	-	2.71	-	-
No.	4	2	3	-	3	-	3	-	-
958	43.53	47.24	48.23	-	44.16	-	10.19	-	-
Min	42.73	4.51	47.28	-	35.60	-	0.00	-	-
Max	44.68	44.05	49.80	-	51.08	-	20.38	-	-
StDev	1.02	50.43	1.37	-	7.87	-	14.41	-	-
No.	3	2	3	-	3	-	3	-	-
30	57.08	63.71	55.18	-	45.68	-	0.00	-	-
Min	55.275	61.15	48.38	-	39.40	-	0.00	-	-
Max	60.2	66.28	62.63	-	53.90	-	0.00	-	-
StDev	2.71	3.62	7.15	-	7.44	-	0.00	-	-
No.	3	2	3	-	3	-	3	-	-
549	51.75	52.39	44.98	-	42.05	-	6.99	-	-
Min	49.48	51.68	39.78	-	31.33	-	5.38	-	-
Max	54.65	53.10	52.05	-	56.25	-	8.60	-	-
StDev	2.64	1.01	6.35	-	12.82	-	2.28	-	-
No.	3	2	3	-	3.00	-	3	-	-

Table 3-9. Abstinence phase mean rate of responding (response / minute), minimum and maximum session response rates, standard deviations, and number of injections per dose for subjects in the Before group.

	Dose of Cocaine								
Subject	Saline	1.0	3.0	4.2	5.6	7.4	10.0	13.0	17.0
820	55.18	53.67	42.68	-	23.85	-	3.29	-	-
Min	49.33	50.93	42.33	-	8.50	-	0.00	-	-
Max	60.95	56.33	43.03	-	50.45	-	7.25	-	-
StDev	5.81	2.70	0.50	-	23.13	-	3.63	-	-
No.	3	3	2	-	3	-	7	-	-
996	38.35	37.12	41.55	-	43.89	-	21.64	-	-
Min	35.28	34.83	35.05	-	36.36	-	0.00	-	-
Max	39.70	41.28	48.05	-	55.05	-	65.18	-	-
StDev	2.09	3.61	9.19	-	9.86	-	30.21	-	-
No.	4	3	2	-	3	-	4	-	-
802	29.83	37.15	39.68	-	32.88	-	7.80	-	-
Min	25.93	33.18	29.85	-	15.63	-	1.00	-	-
Max	34.70	38.68	39.95	-	38.93	-	31.23	-	-
StDev	1.81	1.64	3.32	-	6.98	-	5.99	-	-
No.	4	3	3	-	3	-	6	-	-
660	49.30	51.96	40.41	-	27.56	-	9.64	-	-
Min	44.23	42.40	36.48	-	8.58	-	0.00	-	-
Max	55.85	60.38	43.83	-	44.23	-	25.81	-	-
StDev	5.53	9.04	3.70	-	17.93	-	9.33	-	-
No.	4	3	3	-	3	-	6	-	-

Table 3-10. The estimated Effective Dose 50 (mg/kg) values for the group means and individual animals for all phases. The asterisk denotes an estimate involving a hypothetical-zero dose that was necessary calculation, for further discussion please see the Data Analysis paragraph of the Procedures subheading in the Methods section .

Group	Subject	Acute	Chronic	Abstinence
Before	820	4.67	8.38	4.14
	996	5.46	10.22	9.84
	802	5.58	18.31*	8.09
	660	4.94	8.17	4.81
	Mean	5.16	11.46	6.72
After	829	7.67	10.95	2.63
	958	5.43	8.96	8.36
	30	3.04	4.16	6.25
	549	4.02	7.84	6.62
	Mean	5.04	7.98	5.96

Table 3-11. Model Comparisions using Akaike's Corrected Information Criteria. The numbers in parenthesis represent the probabilities ratio discussed in the Data Analysis subheading in the Methods section.

Group	Subject	Acute and Chronic	Acute and Abstinence	Chronic and Abstinence
Before	820	Local(749.03)	Global (7.30)	Local(>9999)*
	996	Global (1.67)	Local(9.45)	Local(1.17)
	802	Local(>9999)*	Global (274.76)	Local(>9999)*
	660	Local(2104.76)	Global (2.44)	Global(1.17)
	Mean	Local(603.85)	Local(2.88)	Global(1.06)
After	829	Local(611.3)	Local(4.09)	Local(16.59)
	958	Local(45.87)	Local(25.79)	Global(19.00)
	30	Local(23.43)	Local(>9999)*	Global(1.41)
	549	Local(21.86)	Global(1.06)	Global(1.06)
	Mean	Local(34.15)	Local(29.30)	Global(2.26)

Figure 3-1. A photograph of the custom-built operant-conditioning chamber used in Experiment 2. Details pertaining to the exact dimensions are located in the Methods section under the Apparatus sub-heading.

Figure 3-2. A close-up photograph of the treadle plate and hopper opening for the custom-built operant-conditioning chamber. Details pertaining to the exact dimensions are located in the Methods section under the Apparatus sub-heading.

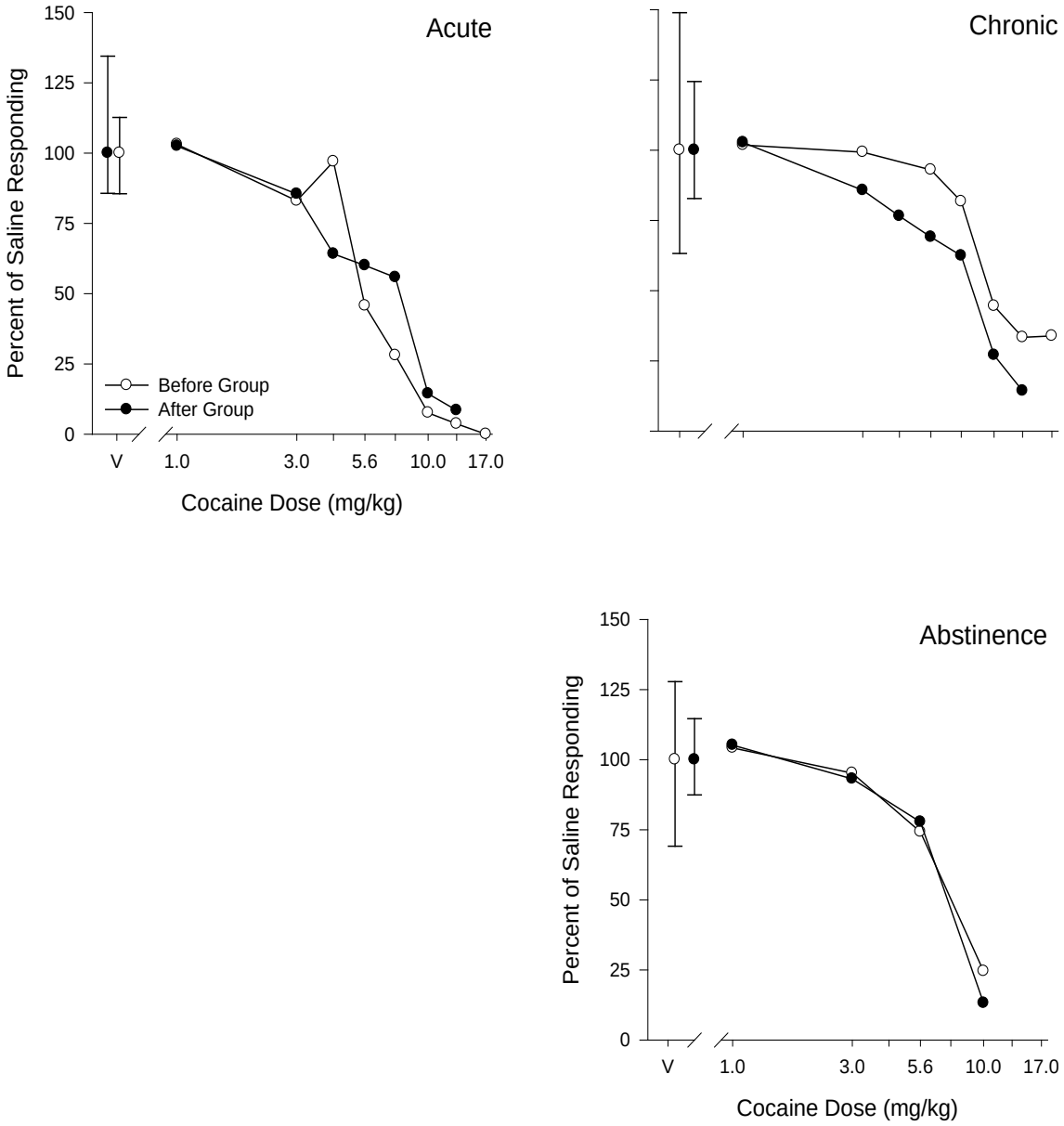

Figure 3-3. Before and After group mean response rates as a function of cocaine dose. Response rates are presented as percent of vehicle control. Panels compare mean dose-response functions for the Before and After groups for each drug treatment phase. The drug treatment phase is identified in the top-right corner of each panel. Points above "V" represent the vehicle mean for the group and the bars represent the range of individual subject averages.

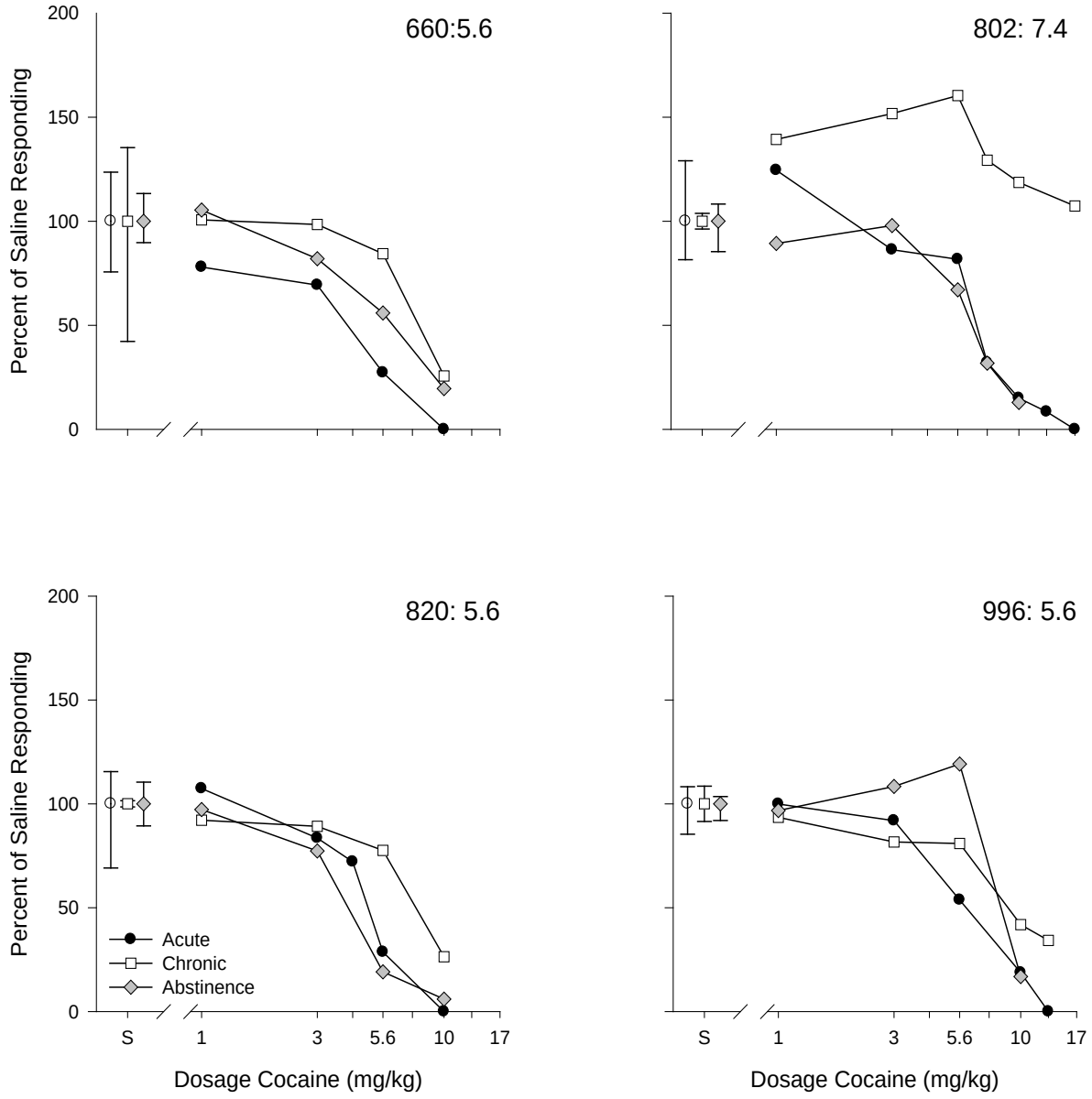

Figure 3-4. Session-average responses per minute for the acute, chronic and abstinence drug phases as a function of cocaine dose for individuals in the Before group. Response rates are presented as percent of vehicle control. Each graph presents data from an individual subject. The subject number and chronic dose are presented in the top-right corner of the panels. Black circles represent data collected during the acute-cocaine assessment, white squares represent data collected during the chronic assessment, and the gray diamonds represent data collected during the abstinence phase of the experiment. The three points and bars above "V" correspond to the average vehicle response rates and range of session rates, respectively. Unlabeled tick marks correspond to 4.2, 7.4, and 13.0 mg/kg cocaine, as read from left to right. For further information pertaining to dose means, ranges, standard deviations, and number of injections please refer to tables 2-1 through 2-6.

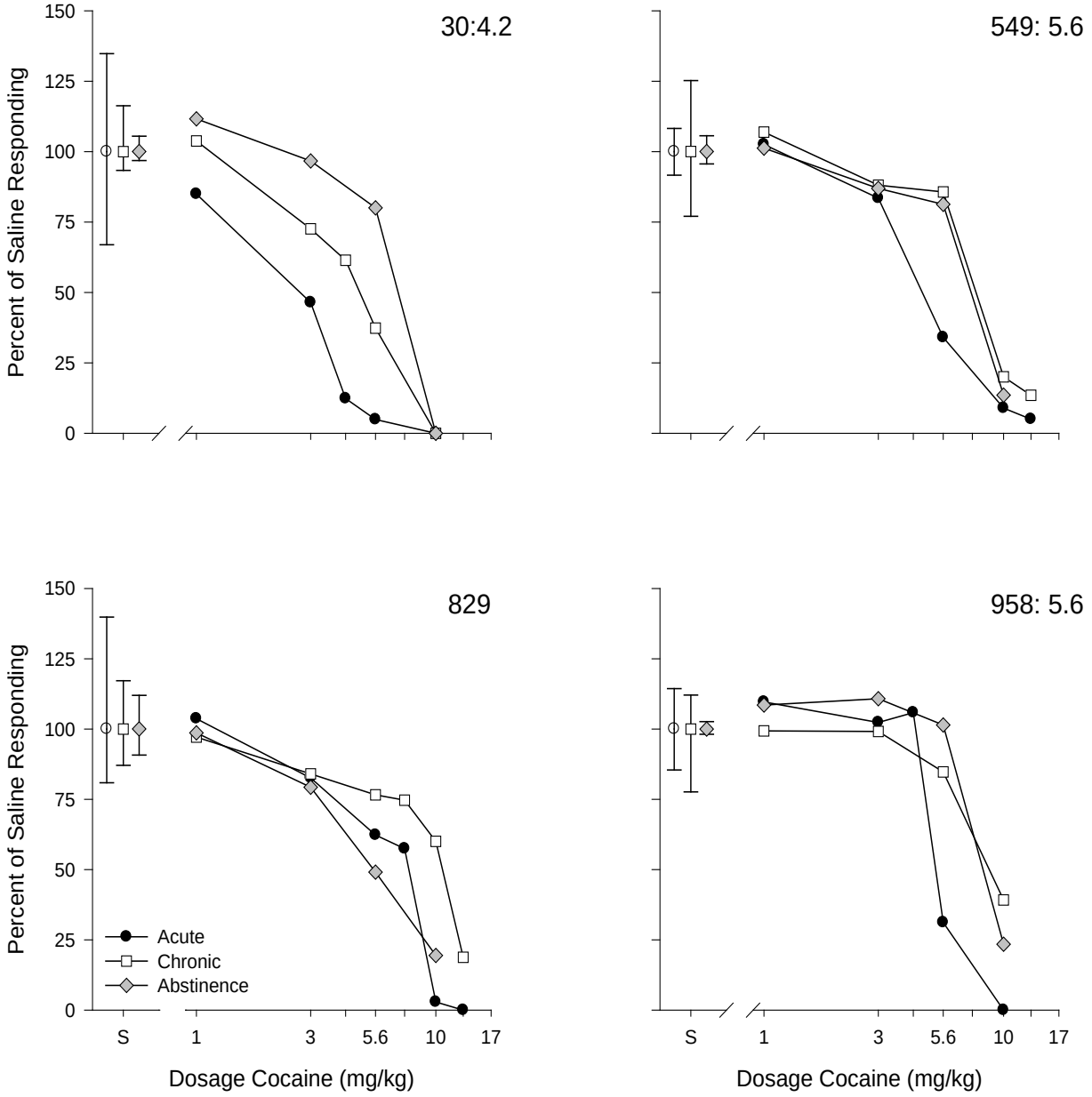

Figure 3-5. Session-average responses per minute for the acute, chronic and abstinence drug phases as a function of cocaine dose for individuals in the After group. Response rates are presented as percent of vehicle control. Each graph presents data from an individual subject. The subject number and chronic dose are presented in the top-right corner of the panels. Black circles represent data collected during the acute-cocaine assessment, white squares represent data collected during the chronic assessment, and the gray diamonds represent data collected during the abstinence phase of the experiment. The three points and bars above "V" correspond to the average vehicle response rates and range of session rates, respectively. Unlabeled tick marks correspond to 4.2, 7.4, and 13.0 mg/kg cocaine, as read from left to right. For further information pertaining to dose means, ranges, standard deviations, and number of injections please refer to tables 2-1 through 2-6.

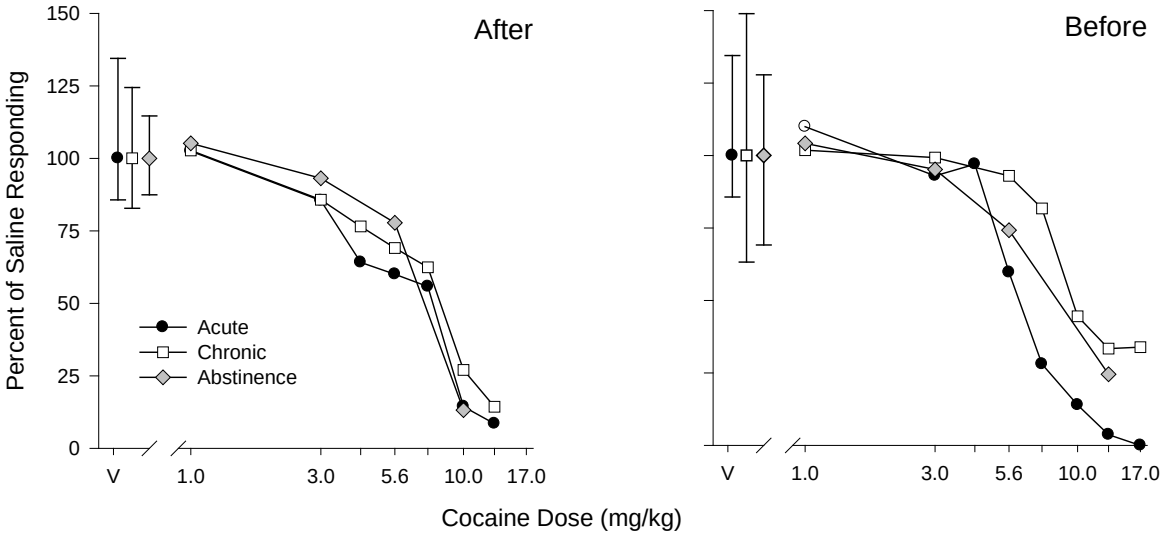

Figure 3-6. Group Aggregate Dose response functions are presented on individually labeled panels. Response rates are presented as percent of vehicle control. Black circles represent data collected during the acute-cocaine assessment, white squares represent data collected during the chronic assessment, and the gray diamonds represent data collected during the abstinence phase of the experiment. The three points and bars above "V" correspond to the average vehicle response rates and range of session rates, respectively. Unlabeled tick marks correspond to 4.2, 7.4, and 13.0 mg/kg cocaine, as read from left to right. For further information pertaining to dose means, ranges, standard deviations, and number of injections please refer to tables 2-1 through 2-6.

CHAPTER 4
GENERAL DISCUSSION

The goal of these experiments was to determine if differences in outcomes between studies designed to assess contingent tolerance in pigeons versus rats could be the result of differences in types of response topographies. Studies with rats have often used responses that are more arbitrarily related to the reinforcing consequence than have studies with pigeons. Procedures with pigeons have used a response (i.e., pecking), which is a response involved in eating, under operant procedures in which the response was required to earn access to food. These experiments have resulted in tolerance that was not dependent on the drug being active during test sessions, and therefore cannot be described as contingent tolerance (Marusich, 2008; Pinkston & Branch, 2004). By contrast, studies with non-pigeons (i.e., rats and monkeys) that have been consistent with a contingent-tolerance interpretation have employed reinforcement (via food presentation) of a response (e.g., lever-pressing) that is not similar in form to behavior involved in eating (Branch & Sizemore, 1988; Campbell & Seiden, 1973; Chen, 1968; Smith, 1990). The current experiments were based on the possibility that it is necessary to use responses that are arbitrarily related to the behavior involved in consuming the reinforcer for contingent tolerance to develop to drug effects on operant behavior. Thus, the work focused on the response topography maintained by operant-conditioning procedures.

In Experiment 1, rats performed a licking response to obtain a liquid reinforcer, thus making the required operant response similar in form to the behavior involved in consuming the reinforcer. In Experiment 2, pigeons pressed a treadle to earn food, thus making the required operant response substantially different in form from the behavior needed for consumption. The results of Experiments 1 and 2 revealed that experience with the experimental contingencies while under the effects of drug were not necessary for the development of tolerance. That is,

contingent tolerance was not observed in either study. It therefore, appears that the different response topographies did not play a significant role in determining whether performance while drugged played a role in tolerance development.

Experiment 1 used rats and a reinforcer-related response class, which approximated the conditions of previous pigeon experiments. The procedures of Experiment 1 resulted in tolerance for both the Before and After groups. This finding was consistent with outcomes of previous experiments with pigeons but not with those of previous experiments with rats. This outcome supported the notion that reinforcement of responses similar to those involved in ingestion would not lead to contingent tolerance. The outcome is also consistent with the view that failure to observe contingent tolerance in pigeons has been dependent on the use of species-typical response topographies, that is, topographies wherein the reinforced behavior is similar in form to behavior involved in consumption of the reinforcer. The second experiment employed pigeons and a species-arbitrary response, treadle pressing, and was presumed to approximate more closely previous experiments with rats that had resulted in contingent tolerance. This experiment, however, resulted in tolerance for both the Before and After groups, indicating that for pigeons, at least, the presumably more arbitrary response, treadle pressing, was not one that revealed contingent tolerance. The outcome of Experiment 2 makes it difficult to conclude that the type of response employed in the test of tolerance was the cause for the species difference in tolerance.

With regards to species differences, therefore, the outcomes of the current experiments are interestingly mixed. Results of Experiment 1, involving rats, are contrary to the results of the majority of previously published experiments involving that species. That is, tolerance did not appear to be dependent upon receiving the drug before test sessions in the current experiment,

whereas in the majority of prior research it did depend on such a relationship (Bowen, et al., 1993; Campbell & Sieden, 1973; Carlton & Wolgin, 1971; Chen, 1968; Smith, 1990; Wenger, et al., 1981; Woolverton, et al., 1978). Experiment 1 represents the first study to show not-contingent tolerance to the effects of psychomotor stimulants with rats. It is also, to my knowledge, the second example of not-contingent tolerance in rats, with the first example occurring to the effects of physostigmine under a Multiple FR 10 Extinction 60 s (EXT 60s) schedule (Genovese, Elsmore, & Witkin, 1988; A more in-depth description is included below). The results of Experiment 2 are consistent with previous literature on pigeons. The response topography differed from previous experiments (Marusich, 2008; Pinkston & Branch, 2004), but the results were similar in that tolerance developed for both Before and After Groups, thus extending the generality of the finding in pigeons to a new response topography and species

The outcome of Experiment 2 is of further interest because the tolerance observed in the Before and After groups was qualitatively similar, however, there is a suggestion of quantitative differences in the amount of tolerance observed between the two groups. Figure 2-3, which directly compares the group aggregates shows that the tolerance may be slightly more robust for the Before group. In support of this possibility, an AIC_C comparison between chronic dose-response assessments determined that two separate models fit to data corresponding to each group characterized the data 1.76 times better than a single fit to all the data. This is, admittedly a relatively small evidence ratio, so no firm conclusion can be drawn. If this apparent quantitative difference is in fact reliable, it is in the direction predicted by contingent tolerance. That is, the attenuation of cocaine's effects was more robust in the Before group than in the After group. If the modest difference between groups is reliable, it would represent a novel finding in studies with pigeons. The possible difference between groups makes further inquiry into the

procedures worthwhile. Follow-up studies including more subjects, or examining different operants could lead to more or less robust differences between the groups. An increase in the number of individuals observed would help to increase the confidence of how reliable the difference between groups. Therefore, inclusion of a greater number of subjects in the group comparison will help to clarify the quantitative difference.

One possible reason that Experiment 2 did not reveal contingent tolerance is that the procedure did not produce an arbitrary response The pigeons included in Experiment 2 were required to fulfill a simple schedule of eight treadle presses to attain reinforcement, but it is not apparent that the treadle was the source of control for responding. Anecdotally, visual observations of the behavior maintained by this arrangement did not lead to the conclusion that pigeons were "deliberately" pressing the treadle. In other words the response may not have been entirely operant in nature, in that the presentation of food may have been evoked or elicited responding and treadling was involved in the evoked act. That is, it appeared that the some pigeons were pressing their breast into the corner in which the intelligence panel met the wall opposite the door, and that others were raising their heads into the top of the same corner. In either case, it appeared that the treadle was pressed inadvertently during this performance. This point is anecdotal, but the arrangement of greater schedule control in the environment may have engendered responding that appeared to be directed toward the treadle.

The current two experiments did not result in the predicted pattern of results, but as argued above there may be questions about the application of treadle-pressing as means to engender species-arbitrary responding in pigeons. It is possible, however, that the use of an FR 8 schedule, and not the response topography was what engendered corner directed walking, and therefore may have contributed to the failure to see contingent tolerance in the pigeons.

Consequently, it may be useful to replicate Experiment 2 using a different schedule types that might engender less corner-directed behavior and more treadle-directed behavior.

One possible strategy to minimize the possibility of elicited behavior like that just described would be to use more complex schedules (e.g., Multiple, Mixed, Chained, or Tandem) or studying different schedule types. For example, simple schedules like an IRT > *t* would require schedule-appropriate responding rather than one repetitive movement that may inadvertently be followed by reinforcement. For instance, compare behavior engendered by an IRT > *t* schedule to the simple FR 8 schedule used in Experiment 2. The IRT>*t* would require the pigeon to make a treadle response then wait a specified amount of time before the second response was made. This contingency could eliminate the tactic of corner directed movement previously described. If it corner directed movement was not eliminated by the IRT>*t* schedule then non-operant sources of control, like those described in previous experiments with pigeons (e.g., autoshaping) could be a factor in the behavior engendered by treadles.

The nature of the corner-directed behavior warrants further discussion because it appears to be similar to the behavior described by Timberlake and Lucas (1985). The authors observed behavior of pigeons under various arrangements of response-independent food presentation via the type of feeder used in the present experiments. Food was presented every 15 seconds and they found that pigeons directed their behavior to the wall through which they obtained food. Specifically, they noted "wall walking," which consisted of side-to-side pacing with the breast pushed against the wall. The corner-directed behavior of Experiment 1 shared some similarity to the behavior observed by Timberlake and Lucas. Additionally, the FR 8 schedule of Experiment 1 was chosen because the baseline rate of reinforcement was approximately one food presentation every 15 seconds. A major conclusion by Timberlake and Lucas was that the

behavior generated by response-independent food presentation was a pre-organized ("innate") behavior pattern associated with food begging. That is, they systematically observed behavior evoked by the presentation of food. In Experiment 2 we did not systematically make visual observations of the behavior of the pigeons; however, informal observation revealed apparent similarities between behavior engendered in the current experiment and that of Timberlake and Lucas. The apparent similarities between the corner-directed behavior of Experiment 2 and "wall-walking" raise the possibility that the behavior observed in the current experiment may have been species-typical, food-related behavior, and not arbitrary as originally thought. It is possible that the current procedures inadvertently arranged conditions sufficient to evoke "innate" food-related activity and that temporal pattern of food presentation was controlling behavior, including inadvertent treadle pressing. A study dedicated to determining if the behavior engendered by the procedures of Experiment 2 was controlled by operant treadle-pressing, Timberlake-and-Lucas-like food presentation, or some other variable(s) would help to flesh out the role of responding in the development of tolerance.

Countering an interpretation of the results of Experiment 2 based on the non-arbitrary nature of the treadle pressing that was generated are reports of previous studies of treadle pressing. These experiments appear to have engendered treadle pressing that functioned more like an arbitrary response, not a food-evoked one. For example, in IRT > *t* schedules pigeons have been able to attain a greater number of reinforcers when treadle-pressing instead of key-pecking is the maintained response (e.g., Hemmes, 1975: Richardson & Clark, 1976). Likewise, shaping and maintaining shock-avoidance using key-peck responses has been reported to be difficult and time consuming; however, treadle pressing is easily shaped and maintained (Foree & Lolordo, 1970; Hineline & Rachlin, 1969; Hoffman & Fleshler, 1959; Smith & Keller, 1970).

The study of Behavioral Contrast is another area of research that has shown differential outcomes based on the response topography used with pigeons. Typically, positive contrast is found when key-pecking is maintained, whereas treadle-pressing has not revealed positive contrast (Hemmes, 1973; McSweeney, 1982). All of the evidence just presented supports the interpretation that treadle pressing is controlled to some extent by different variables than is key-pecking. An illustrative direct comparison of the treadle-pressing and key-pecking was conducted by Green and Holt (2003). In this study pigeons were exposed to two-component multiple schedules, in one component the first response following an average of two minutes would arrange the presentation of food, while the other component arranged the same contingency, except that response-independent food was presented on the average of 15 seconds. That is, the pigeons were subject to a Multiple Variable-Interval (VI) 2 min, Conjoint VI 2 min Variable-Time (VT) 15-s schedule of reinforcement. In two separate conditions either treadle-pressing or key-pecking was maintained. Green and Holt reported the inclusion of response-independent food decreased treadle-responding in the conjoint-schedule component, but increased key-peck responding. It was therefore concluded that key-pecking was susceptible to biologically relevant variables and treadle-pressing was controlled by what Green and Holt called economically relevant variables. This experiment and prior research conducted with treadle pressing supports the notion that treadle pressing is a species-arbitrary response controlled by operant conditioning. Therefore, if the treadle pressing in the present study was food-evoked rather than arbitrarily related to the reinforcer, it would indicate that there are particular conditions that can make it so. Further research will be needed to determine if there are circumstances that render treadle pressing less arbitrary.

Another important factor in the development of not-contingent tolerance observed in both experiments may be the schedule of reinforcement. That is, with a few exceptions, not-contingent tolerance has been shown in simple FR schedules with relatively low response requirements. Specifically, pigeons subjected to an FR 20 in Marusich (2008) and Pinkston and Branch (2004) and FR 8 in Experiment 2 of the current examination. Likewise, an experiment conducted by Genovese, Elsmore, and Witkin (1988) with rats in a multiple FR10 EXT 60s schedule showed that post-session administration of physostigmine led to tolerance in the FR 10 component. A notable study reporting contingent tolerance that employed a low FR schedule, however, was conducted by Chen (1968). Chen tested tolerance to alcohol with rats in a circular maze running procedure that required two passes around the circular portion for spaghetti reinforcers to be delivered. That is, the rats were subjected to an FR2 schedule of maze running. Although the schedule is nominally low, presumably the running of the maze requires more effort and more coordination of behavior to complete than a lever-press, key-peck, sipper-tube lick, or treadle press requires. It therefore appears that the nature of the task used by Chen may have led to a situation in which tolerance would develop with a low FR requirement; however, this should be empirically tested. In more traditional operant arrangements (e.g., key pecking), the use of relatively low FR requirements may have created favorable conditions for the tolerance to develop, so it developed regardless of the relationship between drug administration and test session. It may therefore be useful to examine the effects of FR schedules with greater response requirements. The results of Pinkston and Branch (2004) may lead one to believe that the relatively high FR requirement they used (i.e., FR100) would not lead to tolerance; however, this parameter value was only examined in a multiple schedule, so it is possible that a simple, large FR schedule would lead to tolerance. Other schedule types should also be examined,

particularly those schedules that have proven to engender contingent tolerance in rats. A replication of the IRT > *t* used by Campbell and Seiden (1973), as well as the FI 5-minute and FR 40 schedules examined in Smith (1990) would provide a comparison between schedules that have previously led to contingent tolerance. Furthermore, chained schedules like those used in Branch and Sizemore (1988) could be helpful in further testing the influence of schedule type, and would also help to differentiate the experimental environment from the home-cage environment. That is, the use of chained schedule could help to differentiate the experimental environment from the home cage because responding would result in conditioned reinforcers in the experimental setting, an outcome that presumably would not occur in the home cage.

The outcome of Experiment 1 is notable because it represents a study using rats that did not support contingent tolerance. This outcome was consistent with the prediction that the use of species-typical response topographies would lead to tolerance regardless of the relationship between time of drug administration and exposure to experimental contingencies. Experiment 1, nevertheless, also included characteristics that may allow for at least two alternative explanations for the outcome. First, the total amount of repeated drug exposure in Experiment 1 exceeded that of the previous studies that have illustrated contingent tolerance, a characteristic that was also true for Experiment 2. Second, extra-experimental tolerance may have developed in the home cage and generalized to the experimental setting. These two possibilities are elaborated below, with the "generalization" account discussed first.

Tolerance may have developed through extra-experimental conditioning and subsequent generalization to the experimental environment. The apparent development of tolerance in the After group in the experimental chamber may have been caused by daily-water rations that were administered while the animals were under the influence of drug in the home cage. Drinking

under the influence of cocaine occurred in the home cage because the animals were water deprived and could only earn up to 80-seconds of water reinforcement during the session. The amount of water obtained during this time period is below the recommended daily-water intake (Baker, Lindsay, & Weisbroth, 1980; Hughes, Amyx, Howard, Nanry, & Pollard, 1994; Louisiana Veterinary Medical Association, 2007). It is possible that the initial effects of cocaine in the home cage disrupted the subjects' ability drink (although this was not measured), thus creating a situation which tolerance is known to occur (i.e., the Reinforcement-Loss Hypothesis; Schuster, et al., 1966). To put it another way, the After-group arrangement of home-cage water in Experiment 1 paralleled that of the Before groups of experiments that did not explicitly employ operant conditioning of a response (Bowman, et. al., 1993; Carlton & Wolgin, 1971; Woolverton, et al., 1978). Specifically, untrained-operant Before groups were given liquid access for a period of time while under the influence of drugs. Initially, the administration of the drug disrupted the animals' ability to ingest. Tolerance to this initial disruption typically occurred and this allowed the animals to regain usual levels of fluid intake. It is therefore possible that tolerance in Experiment 1 of the present dissertation was a result of extra-experimental tolerance developed in the home-cage through the mechanism(s) described by the Reinforcement-Loss hypothesis, and that this tolerance generalized to the test-chamber environment.

Two experiments with pigeons conducted in Marusich (2008), however, may limit the credibility of the "generalization" interpretation of the not-contingent tolerance observed in Experiment 1. The initial experiment by Marusich (2008) showed that a simple FR 20 schedule did not result in contingent tolerance. That is, pigeons in either a Before group or an After group showed tolerance to effects of cocaine on key-pecking maintained by food reinforcement. Like

Experiment 1 here, generalized tolerance from home-cage eating to experimental setting key-pecking was a viable explanation for the tolerance observed in the After group. Marusich's second experiment focused on characteristics of post-session drug regimens and the development of tolerance. In Experiment 1 by Marusich, (2008), as well as Pinkston and Branch (2004) all of the After group subjects were exposed to drug in the in the home-cage, which typically coincided by a supplement of grain that was required to maintain a healthy experimental weight. This practice is noteworthy because of the response topography of key pecking was similar to grain-directed pecking that occurred during eating in the home cage. It was possible that post-session grain-directed pecking (i.e., eating) was initially disrupted by post-session injections of cocaine and that attenuation the disruptive effects, that is, tolerance, occurred. This tolerance, gained in the home-cage, then could have generalized to the experimental-testing chamber. As with her Experiment 1, the test of tolerance in Marusich's Experiment 2 depended on the pigeons pecking a transilluminated key 20 times to gain access to grain for three seconds. Her Experiment 2 also included two groups of six pigeons. One group received the drug injection immediately after the session and home cage food immediately after the injection. Thus, the conditions for this drug-immediate group, resembled the regimen used in the previous pigeon experiments (Experiment 1 Marusich, 2008; Pinkston & Branch, 2004), Experiment 1 of the current examination, as well as the Before groups in the "untrained-operant" experiments described in the introduction to this dissertation (Bowman, et al., 1993; Carlton & Wolgin, 1971; Wenger, et al., 1981; Woolverton, et al., 1978). The second group was given food immediately after the session, but the drug was delayed by one hour. This drug-delayed arrangement was designed to eliminate, or at least decrease, the association between post-session grain directed pecking and the effects of drug administration. The outcome of Experiment 2 was that tolerance developed in both groups. It is

therefore less likely that any tolerance obtained in the home-cage eating while under the influence of drug generalized to the experimental-test environment.

There is, however, an important difference in the feeding regimen of the current dissertation's experiment that included rats and the Marusich dissertation studies with pigeons. Specifically, the rats of Experiment 1 of the current dissertation were only allowed a limited amount of time with the post-session water. The pigeons of the Marusich dissertation were given an allotment of food, which remained until the animal completed eating it. The effects of this difference in post-session feeding remain to be tested in a systematic fashion.

Marusich's results cast doubt on the idea that learned tolerance from eating in the home-cage generalized to experimental environment in the current experiment with rats (Experiment 1). Firm conclusions, however, await the results of further research into how tolerance developed in Experiment 1. A good starting point would be a systematic replication of Experiment 2 of Marusich (2008) involving rats and the sipper-licking arrangement. That would help to clarify the role of learning, generalization, and physiology in the expression of tolerance in the experimental environment. That is, a simple change in the post-session drugging regimen should decrease the association between drug and licking for water and allow for a test of the "generalization" interpretation of Experiment 1's outcome. Such an experiment would also help determine if there is a species difference in tolerance development under circumstances of post-operant-test drug administration.

The work of Smith (1990), may also call into question the "generalization" interpretation for outcome of Experiment 1 because in his experiment contingent tolerance was shown to be specific to experimental situations. In his experiment, rats were exposed to three situations involving different experimental chambers, response topographies, and schedules of

reinforcement, with all three environments experienced on a daily basis. Specifically, a nose-poking response into a recessed enclosure was maintained in blackened (via black construction paper fixed to the chamber walls) Model C Gerbrands Rat Cage under a shock-avoidance schedule where shocks occurred every 5 s (5-s shock-shock interval) if no nose poke occurred, and each nose poke postponed shock for 30 s (a 30-s response-shock interval); nose-poking of a transilluminated key was maintained under FI 5-minute schedule of food presentation in another unblackened Model C Gerbrands Rat Cage; and lever pressing was maintained in a relatively small (25-cm long x 15-cm wide x 15-cm high) clear lucite operant-conditioning chamber under an FR 40 schedule of food reinforcement. The three environments were encountered in the same order each day. Over the course of the experiment the time of drug administration was moved from just after the third daily session, to before the third, to before the second, and finally to before the first. Smith reported that tolerance only occurred in one of the sessions if the drug was repeatedly injected just before that session, and that tolerance did not generalize from one situation to another. Thus, even though tolerance was evident in the session that the drug preceded, performance in the other sessions was unaffected. This outcome supports the view that tolerance was unlikely to generalize in the Experiment 1. Experiment 1, however, was much simpler than that of Smith (1990), in that only two situations were used, and they were similar in response topography and schedule of reinforcement. That is, Experiment 1 can be viewed as involving one setting, for the After group, of the home-cage with licking for water reinforced under an FR1 schedule (i.e., every lick results in water), and a second setting, for the Before group, of the experimental setting with an FR20 schedule of licking maintained by water reinforcers. The relative similarities between response and schedule in the two settings may have created conditions that would allow for the generalization of tolerance across environments.

In contrast, the relative specific associations created between environments, response topographies, and reinforcement schedules employed in Smith (1990) could have decreased the likelihood of tolerance generalization in his study. A systematic examination of the number of environments, response topographies, and reinforcement schedules could further elucidate the conditions under which generalization can or will occur across situations.

The procedure of Experiment1, as well as Experiment 2 also diverged from previous experiments reporting contingent tolerance in the amount of repeated drug exposure that occurred during the chronic drugging regimen. Prior experiments included repeated-drug exposure of between 12 to 45 days (Bowen et al., 1993; Branch & Sizemore, 1988; Campbell & Seiden, 1973; Carlton & Wolgin, 1971; Chen, 1968; Smith, 1990; Woolverton et al., 1978; Wenger et al., 1981). Experiments that have not found the contingent- tolerance outcome have included between 30 and 60 sessions of daily repeated administration, prior to the subsequent assessment of dose effects of cocaine (Marusich, 2008; Pinkston & Branch, 2004). It may be the case that the extended exposure to cocaine precluded the observation of contingent tolerance in the current arrangement. In other words, tolerance may take longer to develop when drugs are administered following the session. A study designed to vary systematically the amount of repeated post-session exposure could help to clarify the role that the length of post-session drugging regimen plays in the development of tolerance.

Overall, the two experiments described here resulted in tolerance that did not appear to be contingent on the subject's experience with the experimental contingencies while drug effects were active. The results of Experiments 1 and 2 are thus contrary to much of the literature on contingent tolerance, except for studies involving pigeons. The majority of prior B-A Tests of Tolerance involving cocaine have resulted in contingent tolerance when rats (Bowen et al., 1993;

Smith, 1990 and Woolverton et al., 1978) and monkeys (Branch & Sizemore, 1988) have been studied. Moreover, tests involving other drugs (Chen, 1968; Carlton & Wolgin, 1971; Campbell & Seiden, 1973; Tang & Falk, 1978; Wenger, et al., 1981; Woolverton et al., 1978), "trained-operants" (Branch & Sizemore, 1998; Chen, 1968; Campbell & Seiden, 1973; Smith, 1990) and "untrained operants" (Bowen et al., 1993; Carlton & Wolgin, 1971; Wenger, et al., 1981; Woolverton et al., 1978) have resulted in contingent tolerance. Conversely, the results of Experiments 1 and 2 are consistent with the much smaller literature about pigeons. Research with pigeons conducted by Branch and colleagues (Marusich, 2008; Pinkston & Branch, 2004) has consistently shown tolerance in both the Before and After groups. This pigeon-typical outcome was replicated by the current examination with rats and pigeons in Experiments 1 and 2, respectively. In both experiments "trained-operant" arrangements were established, and both of these experiments resulted in not-contingent tolerance. Importantly, there have been no attempts to perform an "untrained-operant" (i.e., simple ingestion) test of tolerance with pigeons, while many examples of the employment of that approach are included in the contingent tolerance literature with animals other than pigeons. Perhaps a simple "untrained-operant" arrangement may help to illustrate the prominence of learning processes in the development of tolerance in pigeons.

The current results are also inconsistent with the Reinforcement-Loss hypothesis (Schuster, et al., 1966). Traditional B-A Tests of Tolerance are thought to support the Reinforcement-Loss hypothesis because only the Before group exhibits tolerance, or has more robust tolerance when compared to the After group. The Reinforcement-Loss hypothesis can account for this finding because the Before group is the only group in which drug effects cause the density of reinforcers to decrease, or be completely lost. Therefore, the animals have the

opportunity to learn methods to compensate for the effects of drugs as a means to regain reinforcement. The Reinforcement-Loss hypothesis supposes that tolerance is mediated through the learned compensation just described. In both of the current experiments, After groups did not lose reinforcers during the experimental condition, yet both displayed tolerance following extended-repeated exposure to cocaine following the session. It therefore appears that the Reinforcement-Loss hypothesis may describe conditions sufficient to cause tolerance, while the current outcomes and previous experiments on pigeons (Marusich, 2008; Pinkston & Branch, 2004) illustrate that reinforcement loss is not necessary for the development of tolerance.

In conclusion, the results of the current experiments do not appear to support the notion that the use of species-typical versus species-arbitrary response classes in procedures that arrange consequences according to an intermittent schedule will lead to differential patterns of tolerance. With regards to species differences in the results of B-A Tests of Tolerance, the source of control is still unidentified, and it appears likely mechanisms not involving learning may play a greater role in the development of tolerance with pigeons. It remains to be determined, however if, the tolerance observed in Experiment 1 might have been the result of generalization and if the procedures in Experiment 2 actually engendered species-arbitrary responding, as intended. At this point, the generality of contingent tolerance seems to be limited to mammals; however, more research is required for an unequivocal conclusion.

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BIOGRAPHICAL SKETCH

My career goal is to be a research professor at an academic institution that values research and education. This setting will allow me to study environmental and behavioral interactions with various drugs. It will also allow me to teach and to hopefully inspire students to pursue a career in the behavioral sciences. I have been working to attain the goal of academic researcher since my time as an undergraduate student at Allegheny College, in Meadville, PA. As an undergraduate I was interested in the human condition and naturally gravitated to psychology. Allegheny is where I was introduced to formal study of the Experimental Analysis of Behavior. Along with class work, there were several formal and informal opportunities at Allegheny that led me from a general interest in psychology to a budding Behavior Analyst. The first formal event was an internship program that allowed me to counsel and interact with troubled youths that the state of Pennsylvania had placed at the Bethesda Youth Services Home, in Meadville, PA. During this experience I came to the realization that the adolescents I counseled did not possess unobservable intrinsic qualities (often negative) that drove them to behave in the manner that had earned them a place at the home. That is, the teens did not live up to the labels given to them by courts or clinical psychologists. Rather, they were very impressionable, and for the most part, intelligent, but under-motivated young people that had not been given the proper opportunity or guidance to become stable individuals in our society. I witnessed first hand the dynamic between immediate environment and the behavior of the individual when time, and time again, the "bad seed" transformed into the productive student and promising young person. The most important philosophical lesson from that experience was that I began to identify and understand the role that the environment, both historical and immediate, played in determining behavior.

Another formal training opportunity provided by Allegheny College that helped to shape my future was a Senior Thesis that I performed in the area of Behavioral Pharmacology. Specifically, it addressed the phenomenon of withdrawal in Oxycodone-dependent rats. This thesis was my first attempt to empirically observe and describe a phenomenon. Furthermore, it involved non-human animals to model a drug effect that was (is) a problem in American society. This aspect of the study was significant to me because this is when, or shortly after, I began to view laws of behavior in the same manner as laws of physics. That is, that they are orderly, generic, and are always at play, regardless of species, ethnicity, or mental capabilities. This was also my introduction to Behavioral Pharmacology and I found it to be very interesting and to have great potential to help society at large.

Following graduation I was involved in the Human Behavioral Pharmacology Laboratory at the University of Kentucky. There, as a Senior Research Assistant, I helped to implement drug discrimination studies with cocaine-abusing and other human populations. At this time I was able to focus solely on the practice of scientific research and found the process rewarding. During that time I also applied to various graduate programs and accepted an offer to attend the University of Florida.

My time at the University of Florida has been spent as a student, researcher, and teacher. These various positions have allowed me to gain skills in areas that are important to studying and teaching the Experimental Analysis of Behavior and Behavioral Pharmacology. Some areas of study include philosophy, ethics, research design and methods, statistical and graphical analysis of data, manuscript preparation, the NIH grant application processes, and many other topics. Furthermore, my research has been particularly geared towards Behavioral Pharmacology and has included studies aimed at basic topics such as, the phenomenon of tolerance, cocaine

research, schedules of reinforcement, pigeon-drug modeling, rat-drug modeling, and various response topographies (e.g., key-pecking, locomotion, and treadle pressing).

My formal education culminated in a dissertation that focused on the possible impact that various response topographies could have on the expression of cocaine tolerance with both rats and pigeons. The dissertation process and my prior training at the University of Florida have reinforced my aspiration of becoming an academic researcher and teacher. I feel that by studying and teaching of Behavioral Pharmacology, and more broadly the Experimental Analysis of Behavior, will help to inform our society about the multifaceted nature of drugs, human behavior, and the interaction between the two.