To my grandfather, my parents, and the rest of my family.
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Abstract of Dissertation Presented to the Graduate School
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EFFECTS OF COCAINE ON FEEDING BY PIGEONS

By

Jin Ho Yoon

May 2006

Chair: Marc N. Branch
Major Department: Psychology

Traditionally, experiments that have investigated the effects of psychomotor stimulants on feeding have used rats almost exclusively as subjects, and no pigeons. Additionally, little is known about the effects of cocaine on feeding in pigeons, despite a growing body of work that has investigated the effects of cocaine on behavior that has been maintained by food reinforcement. Therefore, the main purpose of our study was to examine the effects of cocaine on feeding by pigeons when food is presented intermittently, for brief durations, as done typically in operant experiments using pigeons.

Sixteen food-deprived White Carneau pigeons served as subjects. Experiment 1 exposed 6 pigeons to a variable-time 1-min schedule of food delivery. Experiment 2 exposed 2 groups of 5 pigeons to a multiple fixed-time schedule (i.e., 10 s, 30 s, and 120 s) of food delivery. Both experiments assessed dose-effect curves when presession cocaine was administered acutely, daily, and then replaced by daily administrations of saline.

Subjects in Experiment 2 also experienced a condition in which cocaine was administered daily after sessions. Combined results showed that administration of presession cocaine
resulted in dose-related decreases in feeding. Daily administration of presession cocaine resulted in tolerance to the initially disruptive effects of cocaine on feeding. When cocaine administrations were replaced by daily saline, dose-effect curves were shifted to the left, showing a loss of tolerance. In Experiment 2, tolerance as a result of postsession administration of cocaine as well as maintenance of tolerance when cocaine was moved from before to after sessions suggested that tolerance was mostly pharmacological. Our results extend the generality of previous research conducted with cocaine and pigeons and psychomotor stimulants and rats to a novel combination of subjects and behavior, that of pigeons and feeding in the context of brief intermittent food deliveries.
CHAPTER 1
INTRODUCTION

Beginning with Dews’ seminal 1955 paper, operant procedures have been shown to be useful in examining the behavioral effects of drugs. Operant schedules engender reliable, orderly patterns of behavior (Ferster & Skinner, 1957) that can serve as useful baselines for examining various drug effects. One category of drugs that has been examined under operant conditions is psychomotor stimulants such as cocaine and amphetamine. Numerous studies have examined both the initial effects of psychomotor stimulants on behavior that is maintained under some schedule of reinforcement, usually food reinforcement, and the development of tolerance following chronic administration of psychomotor stimulants (Corfield-Sumner & Stolerman, 1978; Demellweek & Goudie, 1983; Wolgin, 1989). Tolerance refers to an attenuation of the effect of a drug such that increased dose of drug is required to recapture the original effect (Corfield-Sumner & Stolerman, 1978; Wolgin, 1989; Hardman, Gilman, & Limbard, 1995). Most studies, however, generally have not provided data on reinforcer consumption, unless consumption was the behavior of interest. The implicit assumption appears to have been that the edible reinforcers are always consumed, and that disruptions in schedule-controlled performance are the direct effects of drug on that performance. Our study examined effects of a psychomotor stimulant, cocaine, on eating by pigeons. Specifically, we examined the effects of cocaine on eating in a context essentially identical to that in which food-reinforced operant behavior usually is studied. Thus, our experiment was aimed at determining whether changes in operant performance under
cocaine administration might be related to effects of the drug on direct commerce with the usual reinforcer, food.

Pigeons have proven useful as subjects in general behavioral research for a variety of reasons, and similar reasons also make pigeons attractive for use in behavioral pharmacology research (McMillan 1990). A steady stream of studies (many from our lab) have examined the effects of chronically administered cocaine on pigeon behavior under a variety of circumstances (Table 1-1). Table 1-1 shows that pigeons have been used as subjects to examine tolerance to the effects of cocaine under a wide variety of experimental settings in which food is generally used as a reinforcer.

Of the studies listed in Table 1-1, however, only two provided any measure of feeding (Miller et al., 2001; Yoon & Branch, 2004). In those two studies, head-in-hopper times were measured via photobeam (Ziegler & Robert, 1971). Feeding by pigeons in general has been previously investigated (Zeigler, Green, & Lehrer, 1971; Zeigler, Levitt, & Levine, 1980; Klein, Deich, & Zeigler, 1985). To our knowledge, however, no studies have investigated the effects of psychomotor stimulants on feeding by pigeons, let alone the effects of cocaine when food is presented for brief durations as typically done in the previously mentioned experiments involving pigeons and cocaine.

The paucity of such research on pigeons contrasts sharply with that on rats. Several studies show dose-related decreases in food consumption by rats with acute administration of presession cocaine (Balopole, Hansult, & Dorph, 1979; Bedford et al., 1981; Blavet, DeFeudis, & Clostre, 1982). Tolerance to the disruptive effects of cocaine on feeding was also reported chronic administration of presession cocaine (Wilson & Brenkant, 1978; Woolverton, Kandel, & Schuster, 1978; Bowen, Fowler, & Kallman,
Most research, however, investigated the effects of amphetamine on feeding by rats (Wolgin, 1989; Wolgin, 2000), the results of which are generally consistent with those observed for cocaine. Thus, a large body of research examined the effects of chronically administering psychomotor stimulants on feeding, generally showing tolerance. That literature, however, used rats almost exclusively as subjects. Additionally, unlike experiments typically using operant schedules with pigeons, food was generally available continuously for relatively extended periods of time (anywhere from 1 h to 1 day), whereas in experiments on operant performance with pigeons, food typically is presented for brief periods (i.e., a few seconds). Therefore, a major purpose of our study was to examine the effects of cocaine on feeding by pigeons, under conditions of access similar to those that occur in operant-conditioning procedures.

Specifically, we examined tolerance development to the effects of cocaine on feeding. In the previously described literature involving rats and psychomotor stimulants, tolerance to the initially disruptive effects of drug on feeding was observed after chronic administration of drug. Additionally, the results of those experiments provide strong evidence that tolerance under those conditions was the product of behavioral mechanisms. Tolerance has been attributed to either behavioral or pharmacological mechanisms. In the case of behavioral tolerance, tolerance has been suggested to be mediated through some form of behavioral compensation (Demellweek & Goudie, 1983; Wolgin, 1989). The basic hypothesis is that administration of drug induces novel patterns of behavior that interfere with baseline reinforcement rates, for example, increased locomotor activity in rats, and repeated administration of drug results in some form of hypothesized behavioral compensation to the drug-induced behavior that
interferes with obtaining reinforcement (Wolgin, 1989). Although most of the evidence for this interpretation comes from data using rats, the results of Pinkston and Branch (2003) provide a line of comparison. In the Pinkston and Branch study, pigeons did not develop increased locomotor activity if a food reinforced operant response was available. In the absence of that operant, increased locomotor activity developed.

The compensatory behavior described above is presumably motivated by a loss of reinforcement (Schuster, Dockens, & Woods, 1966). Loss of reinforcement alone, however, has been shown to be insufficient for predicting the development of tolerance. Smith (1986), for example, examined the effects of amphetamine on rats pressing a lever under a multiple differential-reinforcement-of-low-rate (DRL) random-ratio (RR) schedule of reinforcement. Tolerance in the DRL component was only observed when the RR component was removed. Subsequent reintroduction of the RR component resulted in a loss of tolerance in the DRL component. Smith concluded that the relatively higher rate of reinforcement in the RR component was responsible for the lack of tolerance development in the DRL component when both components were available in the context of a multiple schedule. Other research, however, shows that tolerance can develop in the absence of reinforcement loss. In pigeons, tolerance to the behavioral effects of cocaine was observed even when the initial effect of cocaine was to increase reinforcement (Branch et al., 1999; Miller et al., 2001).

Regardless of the role of reinforcement loss in the development of tolerance, Chen (1968) introduced a useful procedure, sometimes referred to as the Before-After procedure, for assessing the potential role of behavioral factors in the development of tolerance. In the context of a circular-maze-running task, Chen studied two groups of
rats, both of which received repeated administrations of alcohol. The Before Group received drug prior to each exposure to the maze, whereas the After Group received administrations of alcohol following sessions. Once tolerance was observed in the Before Group, administrations of alcohol were moved prior to session for the After Group, which experienced alcohol in the context of the session for the first time. In Chen’s experiment, tolerance was observed only in the Before Group. Differences in tolerance development between the two groups were attributed to differences in behavioral experiences, since both groups received the same number of drug administrations; only the time of administration in relation to the session was different. In other words, the development of tolerance in the Chen experiment was contingent on experiencing drug in the test condition. Such tolerance is commonly referred to as “contingent tolerance” (Carlton & Wolgin, 1971).

The Before-After procedure has been used in several studies to examine the behavioral effects of a variety of psychoactive drugs, and those studies generally have replicated Chen’s findings (Wolgin, 1989). Contingent tolerance has also been observed to the disruptive effects of cocaine on eating in rats using variations of the Chen procedure (Wilson & Brenkert, 1978; Woolverton et al., 1978; Bowen et al., 1993). Only one previous experiment used the Before-After procedure with pigeons and cocaine. Pinkston and Branch (2004) examined the effects of pre- and post-session chronic administrations of cocaine on keypecking during a multiple fixed-ratio (FR) schedule of food reinforcement. Unlike the majority of previous research, tolerance was observed after post-session administrations of cocaine.
To summarize, the primary objective of our study was to investigate the effects of cocaine on feeding by pigeons, under conditions similar to those presented in typical experiments on food-reinforced operant behavior. Experiment 1 investigated the effects of chronic administration of pre-session cocaine on eating under a variable-time (VT) schedule of food delivery. Experiment 2 was an attempt to systematically replicate Experiment 1, this time using a three-component fixed-time (FT) schedule of food delivery. Additionally, Experiment 2 made use of the Before-After procedure by examining the effects of chronic pre- and post-session administration of cocaine.
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CHAPTER 2
EXPERIMENT 1

Methods

Subjects

Subjects consisted of 6 adult, male White Carneau pigeons maintained at 80% of their free-feeding weights. Subjects were experimentally and drug naïve prior to the start of Experiment 1. Outside of experimental sessions, the pigeons were individually housed in a temperature-controlled colony room with a 16:8 hr light/dark cycle. Pigeons had continuous access to vitamin-enriched water and health grit while in the home cage. Care and treatment of all subjects was approved by the local Institutional Animal Care and Use Committee.

Apparatus

Sessions were conducted in an operant-conditioning chamber for pigeons. The inside of the chamber was 30 cm wide, 36 cm tall, and 35.5 cm deep. The front work panel was brushed aluminum, a steel mesh covered the chamber floor, and the rest of the chamber was painted white. A half-silvered glass, 21 cm by 24 cm, in the door of the chamber allowed observation of the pigeon. A 1.1-W, 28-VDC lamp (houiselight) on the work panel provided chamber illumination. The houselight was horizontally centered and located 2 cm from the ceiling, and light was deflected towards the ceiling by an aluminum shield. The work panel also had an aperture that was 6 cm wide and 5 cm tall through which food could be made available. Like the houselight, the aperture was horizontally centered and located 11 cm from the chamber floor. When mixed grain was
presented in the aperture the houselight was turned off, and the food aperture was
illuminated by a 1.1-W, 28 VDC lamp. Head-in-hopper time was measured with a
MED® Associates Single Channel I/R Source, Detector, and Control, which generated an
infrared beam across the opening of the food aperture. Entries and exits into and out of
the food aperture were detected by breaks in the photobeam. During sessions, a
ventilation fan, located on the back wall of the operant chamber, operated while white
noise of approximately 95 dB was also continuously present in the room that housed the
experimental chamber. Events were controlled and data collected by a dedicated
computer system (Palya, Walter, & Chu, 1995).

Dependent Measures

The main dependent measure was average head-in-hopper time as measured via the
photobeam. Although not a direct measure of eating, Zeigler and Robert (1971)
demonstrated that responses toward a food hopper as measured via photobeam and daily
food intake were highly correlated. Also, head-in-hopper time as an appropriate measure
of eating gains credence given that pigeons were almost 24 hrs food deprived prior to
each session and maintained at 80 % of their free-feeding weights. In other words, one
can confidently assume that pigeons were sufficiently motivated to eat if their heads were
in the hopper aperture. Average head-in-hopper time was calculated by summing the
individual head-in-hopper times during which the hopper was available and dividing that
total by the number of food presentations within a session. One potential limitation of the
head-in-hopper measure is that intermediate average head-in-hopper values may
represent two different patterns of eating. For example, a 50% reduction in head-in-
hopper time can be obtained if a pigeon enters the aperture every time the hopper
becomes available, but eats for only half the available time once they enter the aperture.
The same average head-in-hopper time can also be obtained if the pigeon enters the aperture on half of the hopper presentations but stays in the aperture for the whole time that the hopper is available. Therefore, we also recorded proportion of hopper entries, which was calculated by dividing the number of initial aperture entries when food was available by the total number of food presentations. Additionally, the average latency to those initial hopper entries was also calculated. Note that in calculating the latency measure, individual food presentations in which the pigeon did not approach the food aperture before the 20-s limited hold had expired were assigned a latency value of 20 s.

**Data Analysis**

A quantitative measure based on dose-effect curves is the effective dose at which a dependent measure is decreased to 50% of its control levels (ED50). The ED50 values were calculated by using the regression function in SigmaPlot 8.0. For both average head-in-hopper time and proportion of hopper entries, the average values at each dose were converted to a proportion of those observed during control sessions. An XY comparison was conducted in which X represented the doses in the dose-effect curve and Y represented the average value observed at each dose. In cases in which the dose-effect curve did not reach 0, the dose that was set at 1/8 of a log unit higher than the highest dose on the dose-effect curve was added and given a value of 0. Under the user-defined option, a two-parameter logistic function, \( f=(1+(X/ED50)^b) \), was used. The number of iterations and stepsize were set to 100 and tolerance was set to 0.0001. For the initial parameters, the slope (i.e., \( b \)) was set to –2 and the ED50 was marked within an 1/8 of a log unit of the predicted ED50 value. The ED50 values for average latency to hopper approaches were calculated similarly but with a few changes. Values were initially
converted to a proportion of the highest latency possible, 20 s. If the curve never reach 20 s, the next highest dose that was an 1/8 of log unit higher than the highest dose on the dose-effect curve was added and given a value of 20 s. Additionally, the initial parameter for the slope was set to 2. All other details are the same as above.

**Hopper Training**

Pigeons were initially trained to eat from the food hopper. The duration of food hopper presentation was gradually decreased within a session from approximately 30 s to approximately 3 s. Concurrently, the inter-food presentation time was increased from less than a second to varying times that averaged approximately 30 s. During hopper training as well as throughout the entire experiment, whenever the hopper was presented, all chamber lights were extinguished and the hopper light was illuminated. Lowering of the hopper resulted in extinguishing the hopper light and turning on of the appropriate chamber lights.

**Baseline**

After hopper training, all subjects were introduced to the final procedure. Sessions were conducted 7 days a week at approximately the same time each day. All sessions were preceded by a 5-min blackout period. During this time, no behavioral measures were recorded and all chamber lights were turned off. Sessions began with illumination of the houselight. The food hopper was presented on a VT 65-s schedule. The individual VT values ranged from 5 s to 125 s and were described by the function \((5 + 4n)\) s where \(n\) ranged from 0 to 29. Each VT value was presented randomly without repetition for a total of 30 food presentations. Following food presentation, if the pigeon did not enter the food aperture within 20 s, as detected by the photobeam, the hopper was then lowered, and the next VT value was initiated. If a photobeam break was detected before
the 20-s limited hold had elapsed, the pigeon received 2.1 s access to grain, timed from the onset of aperture entry. Baseline continued until average head-in-hopper time and daily net weight were observed to be stable as judged by visual inspection (101 to 108 days).

**Drugs and Drug-Administration Procedure**

Cocaine hydrochloride was dissolved in 0.9% sodium chloride (saline) solution. Drug doses were computed as the salt, and injection volumes were 1 ml/kg. Cocaine was administered via intramuscular injections into the pectoral muscle. Pre-session administrations of cocaine were conducted immediately prior to placement in the chamber. All drug-test and vehicle-test injections that occurred either during acute or various chronic-administration conditions were spaced apart by at least 5 days. When injections occurred daily, the injection site was alternated between the left and right pectoral muscles in order to minimize any potential trauma.

**Acute Administration**

All subjects initially received at least two administrations of the same doses of cocaine (1.0, 3.0, 5.6, and 10.0 mg/kg) in addition to vehicle-test (saline) administrations approximately once per week. Further administrations with some doses were conducted as necessary in order to assess the reliability of effects for individual doses. Additional doses (e.g., 4.2, 7.4, 13.0, & 17.0 mg/kg) were also sometimes administered in order to obtain a complete characterization of the dose-effect curve. For Pigeon 1867, a dose that eliminated head-in-hopper time was not administered as 17.0 mg/kg was the highest dose administered during the Acute Phase. Sessions conducted the day before drug-test or vehicle-test sessions provided control values. Initially, rightward shifts in dose-response functions were observed during assessment of acute dose-effect curves for some subjects.
Therefore, once stability was observed, we decided to use data from the last two probe administrations as representative of the final curve. Table 2-1 shows the number of administrations received during the Acute Phase, Chronic Phase, and Saline Phase for each subject in Experiment 1.

**Chronic Cocaine Administration**

Immediately following the Acute Phase, a chronic dose of cocaine was chosen for each subject that reduced head-in-hopper time without completely eliminating it. If a dose with such intermediate effects was not observed, the lowest dose that reduced head-in-hopper time to near zero was used. Italicized numbers in Table 2-1 indicate the chronic dose of cocaine used for each subject. Daily administrations of the chronic dose continued until stability in average head-in-hopper times was observed as judged by visual inspection of daily records (42 to 82 days). Next, dose-effect curves were assessed in the context of daily administrations of pre-session cocaine by administering probe doses in place of the chronic dose. As in the Acute Phase, each probe dose was administered at least twice. Further probe-dose administrations were sometimes carried out to assess the reliability of mean effects, and additional doses were given as needed to allow for a complete characterization of the dose-effect function. Sessions conducted the day prior to test-dose administrations served to provide representative effects of the chronic dose.

Immediately following the first Chronic Phase, Pigeon 1867 participated in a second Chronic Phase. Pigeon 1867’s chronic dose was lowered from 10.0 mg/kg to 5.6 mg/kg after tolerance to the disruptive effects of cocaine on feeding was not observed in the first Chronic Phase. The shift to a smaller chronic dose was made because previous studies have shown that daily administrations of a relatively large dose of chronic cocaine
may reduce or eliminate tolerance (Bowen et al., 1993; Stafford & Branch, 1996; Branch et al., 2000). The second Chronic Phase continued for 34 sessions after which dose-effect curves were reassessed in the context of the lower chronic dose of cocaine. All other procedural details are the same as those of the first Chronic Phase.

**Daily Saline Administration**

Following immediately after the Chronic Phase, subjects were administered daily injections of pre-session saline in place of cocaine. The Saline Phase continued until stability in average head-in-hopper times was observed as judged by visual inspection of daily measures (31 to 64 days). Dose-effect curves were then reassessed, now in the context of daily saline administrations, by substituting various test doses of cocaine in place of saline. Test-dose administrations were at least 5 days apart and sessions conducted the day prior to test-dose administrations served as representative sessions for saline.

**Results**

**Acute Phase**

Figures 2-1 through 2-4 show dose-response functions generated for average head-in-hopper time, proportion of hopper entries, average latency to hopper entries, and net weight during the Acute Phase, respectively. Overall, dose-related decreases in head-in-hopper time, hopper entries, and net weight were observed, whereas dose-related increases were observed with latency to hopper entries.

All subjects generally stayed in the aperture for the entire time when the hopper was available under control conditions and when small doses were given (Figure 2-1). The lowest dose that almost completely eliminated head-in-hopper time was 5.6 mg/kg for one subject (1837), 10.0 mg/kg for 2 subjects (1977 & 1872), and 13 mg/kg for 2
subjects (1984 & 1951). Average head-in-hopper time was only reduced by half at 17.0 mg/kg for Pigeon 1867. Overall, dose-effect curves for proportion of hopper entries in Figure 2-2 mapped closely on to those for average head-in-hopper time in Figure 2-1. Some deviations, however, were observed. Data for Subjects 1984, 1872, and 1867, particularly at the high end of the dose-effect curves, show that head-in-hopper times were decreased to a greater relative extent than hopper entries at certain doses. Take for example, data for Pigeon 1867. The hopper entry measure was little affected by 17.0 mg/kg of cocaine (Figure 2-2). Head-in-hopper time, on the other hand, was decreased by half (Figure 2-1). Dose-effect curves for net weight (Figure 2-4) did not map on to head-in-hopper time as closely as hopper entries did. The patterns, however, were qualitatively similar. Subjects generally showed positive net weights at the lower end of the dose-response function, whereas all net weights were negative at the highest two doses for each subject. The highest net weight observed was 12 g whereas the lowest net weight seen was –7 g.

Comparisons between Figures 2-1 and 2-2 suggest that decreases in head-in-hopper time can be the result of two patterns of eating. At one end, subjects may enter the aperture every time that food is available, but may not stay in the aperture for the entire time available. At the other end, subjects may keep their head in the hopper for the entire available time, but simply not enter the hopper every time that food became available. Therefore, conditional head-in-hopper time, head-in-hopper time given that an initial hopper entry occurred, was also analyzed (Figure 2-5). The combined results of Figures 2-1, 2-2, and 2-5 show that reductions in head-in-hopper time were generally the result of not staying in the hopper aperture as long when food was available. Two minor
deviations from this rule were observed at 3.0 mg/kg for Pigeon 1837 and 5.6 mg/kg for Pigeon 1977. At these doses, decreases in head in hopper time were mainly the result of not initiating hopper entries.

In contrast to the other measures, increases in latency with higher doses of pre-session cocaine were observed (Figure 2-3). During control sessions as well as lower doses of cocaine, the average latency to entering the hopper aperture when the hopper became available was approximately 1 s. When compared to dose-effect curves for average head-in-hopper time, curves for average latency to hopper entry were generally mirrored. In other words, how long it took the pigeon to enter the hopper appeared to be negatively correlated with how long they spent within it. Some exceptions, however, were observed. For example, at 5.6 mg/kg only a minor decrease in average head-in-hopper time was observed for Pigeon 1951 (Figure 2-2), being comparable to those observed for the lower end of the dose-effect curve. Latencies, on the other hand, more closely approximated values observed at the high end of the dose-effect curve. Likewise, while decreases in average head-in-hopper time were observed at the highest three doses for 1867, latencies stayed the same. Thus, even though Pigeon 1867 ate less at the higher doses, the delay to initiate eating was unchanged. Note that at these doses, Pigeon 1867 almost always entered the hopper as well (Figure 2-2).

Chronic Phase

Figures 2-6 through 2-9 compare dose-response functions generated during the Acute Phase (black filled circles) with those obtained in the context of daily administrations of pre-session cocaine (gray filled squares). Except for 1867’s data, shifts to the right in dose-response functions for all dependent measures were observed, showing tolerance to the initially disruptive effects of pre-session cocaine on eating
following daily administration of pre-session cocaine. Overall, close correspondence across the dependent measures was observed, as observed during the Acute Phase. Even for the net weight measure, which shows the least amount of correspondence, pigeons whose data showed the greatest relative shifts in dose-effect curves for the other dependent measures (i.e., 1984 and 1837), also showed the greatest shifts in dose-effect curves for net weight. Likewise, pigeons whose data showed relatively the least amount of change in net weight also showed the smallest dose-effect curve shifts for the other dependent measures.

Only Pigeon 1867’s behavior failed to exhibit tolerance, instead showing sensitization as indicated by shifts to the left in the various dose-effect curves. Only after the chronic dose was lowered from 10.0 mg/kg to 5.6 mg/kg (white diamonds) was tolerance observed by a shift to the right in the dose-effect curve for average latency to hopper entry. Tolerance was not observed, on the other hand, for neither average head-in-hopper time nor proportion of hopper entries, although no opportunity to observe tolerance was in truth available in the hopper entry measure. Lowering the chronic dose, however, did attenuate the sensitization that was observed when the chronic dose of cocaine was higher.

Figure 2-10 shows ED50 values obtained from dose-effect curves for our three primary dependent measures during all phases of Experiment 1. The results of the ED50 analysis confirmed our initial, visual interpretations of tolerance. Except for Pigeon 1867’s data, a comparison of ED50 values from the Acute Phase and Chronic Phase shows increased ED50 values for all subjects across all three dependent measures. Two-fold increases in ED50 were often observed, and in some cases three fold increases were
seen. Comparison of ED50 values across dependent measures also revealed that although absolute values were occasionally different, the relative differences observed between the Acute Phase and Chronic Phase were generally similar across measures. For Pigeon 1867, decreased ED50 values during the first Chronic Phase showed sensitization. The ED50 values obtained from the second Chronic Phase showed attenuation of the initial sensitivity observed during the first Chronic Phase. Tolerance in the average latency measure, however, was minor according to the ED50 measure when compared to our initial, visual interpretations.

**Saline Phase**

Dose-effect curves assessed in the context of daily pre-session administrations of saline are shown in Figures 2-11 through 2-13. Two general patterns were observed for all dependent measures. First, shifts to the left in the dose-effect curves were observed when compared to those for subjects whose data showed tolerance during the Chronic Phase. In some cases, dose-effect curves assessed in the context of daily saline recaptured curves obtained during the Acute Phase. Second, data from individual sessions were relatively more variable than those observed during the Acute Phase and Chronic Phase, particularly at doses on the descending portion of the dose-effect curves. The range of variation generally covered the range of effects observed from Acute and Chronic Phases. In other words, the shift in dose-effect curves appear to be often due to increased variability from individual sessions. To see if trends in the variability existed, such as increases or decreases in tolerance, the data were examined by plotting successive administrations of the doses that showed variability. The analysis did not reveal any consistent trends between successive administrations of a given dose over time and are therefore not reported here. For Pigeon 1867, whose data largely failed to demonstrate
tolerance throughout Experiment 1, dose-effect curves were generally similar to those observed during the Acute Phase. Dose-effect curves for the average latency measure, in which tolerance was observed during the second Chronic Phase, showed a shift to the left.

The ED50 values in Figure 2-10 confirmed the visual analysis, showing increased ED50 values from the Chronic Phase compared to the Acute Phase for 5 out of 6 subjects in all three dependent measures. Additionally, the relative differences in ED50 values between the Chronic Phase and Saline Phase across the various dependent measures were generally minor. Pigeons 1977 and 1872 showed relatively less tolerance for average head-in-hopper time when compared to the other 2 measures and Pigeon 1867 showed relatively little sensitization in the latency measure compared to the other two measures. By and large, however, differences in ED50 values across conditions for each dependent measure were minimal across subjects. For Pigeon 1867, ED50 values showed a return to levels observed during the Acute Phase, showing an overall attenuation of the sensitization observed during the two Chronic Phases. The change in ED50 values for the average latency measure, in which tolerance was observed and to certain degree maintained, was not demonstrated with the ED50 analysis.

**Discussion**

The three primary dependent measures proved to be useful in characterizing eating. The measures were related to a certain degree, with maximum uniformity occurring when the proportion of approaches was zero, which has to be true. At all other values, however, such relational constraints were minimal. Except for a few exceptions, the three behavioral measures mapped on closely with each other, particularly when converted to ED50 measures. Overall, the range of variation between tests of a particular dose was
also relatively small throughout Experiment 1. The greatest variation was observed during the Saline Phase, and that variation appeared to be a mixture of patterns observed during the Acute and Chronic Phases. Even the dose-effect curves for net weight shown in Figures 2-4, 2-9, and 2-14, although they did not map on as closely as the primary dependent measures, net weight did follow the general patterns observed. Not only was reliability relatively high across measures, but within a measure as well.

The results of Experiment 1 extend the generality of behavioral pharmacology research investigating the effects of cocaine on pigeon behavior to a new topography, that of eating. Across a variety of different measures, tolerance to the initial disruptive effects of cocaine on feeding was clearly observed following daily administrations of pre-session cocaine in 5 out of 6 subjects across a wide variety of behavioral measures. For the remaining subject, 1867, tolerance was observed in the average latency measure after the chronic dose was lowered when compared to dose-effect curves observed during the Acute Phase, although this difference was less dramatic according to the ED50 measure.

Once daily administrations of cocaine were replaced with that of saline, attenuation of whatever cocaine’s effects were during the Chronic Phases was observed, resulting in dose-effect curves to that were somewhere between those observed during the Acute and Chronic Phases. Such results, from a behavioral perspective of tolerance, are puzzling. To the degree that tolerance reflects a presumably operant compensatory response that is under the stimulus control of the behavioral effects of drug, tolerance should then persist even if drug has not been administered for some time. For example, Stafford et al. (1994) showed persistence of tolerance to the disruptive effects of cocaine on keypecking in pigeons. In one case, tolerance was observed to persist for up to 100 sessions. Pinkston
and Branch (1994b), however, showed diminished tolerance in pigeons’ keypecking during a multiple fixed-interval schedule with a small tandem ratio requirement.

We therefore investigated, in Experiment 2, if the development of tolerance was contingent on the subjects experiencing cocaine during the experimental session, thus giving them the opportunity to learn to compensate. Additionally, Experiment 2 examined the relationship between tolerance and different inter-food presentation times using a multiple FT schedule of food delivery.
Table 2-1. Number of test-dose administrations for each subject for all phases of Experiment 1.

<table>
<thead>
<tr>
<th>Pigeon</th>
<th>Dose(mg/kg)</th>
<th></th>
<th></th>
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<td>4.2</td>
<td>5.6</td>
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<td>10.0</td>
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<td>-,-,-</td>
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<td>2,18,2</td>
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<td>13</td>
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Number triplets represent the number of administrations for each dose during the Acute Phase, Chronic Phase, and Saline Phase for each subject. Italicized numbers indicate the chronic dose during the Chronic Phase. The numbers at the bottom of the table represent the number of test-dose administrations during the second Chronic Phase for Pigeon 1867. Doses that were not administered during a phase are denoted by dashes. Doses with a relatively large number of administrations are from sessions conducted immediately prior to test-administration sessions.
Figure 2-1. Average head-in-hopper times as a function of dose of cocaine during the Acute Phase. White open circles represent data from individual sessions at a specific dose of cocaine, and black filled circles represent the mean of those individual points for that dose. When individual values are the same at a given dose, symbols appear to have a thick outline. Points above C show means from control sessions immediately preceding test-dose sessions. Points above S are means from sessions preceded by saline injections.
Figure 2-2. Proportion of hopper entries as a function of dose of cocaine during the Acute Phase. All other details are as in Fig. 2-1.
Figure 2-3. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 2-1.
Figure 2-4. Net session-weight change as a function of dose of cocaine during the Acute Phase. All other details are as in Fig. 2-1.
Figure 2-5. Conditional head-in-hopper time as a function of dose of cocaine during the Acute Phase. All other details are as in Fig. 2-1.
Figure 2-6. Dose-effect curves for average head-in-hopper time during the Acute and Chronic Phases. Black filled circles are the same as those from the Acute Phase. Open white squares and smaller open white diamonds represent data from individual sessions at specific doses of cocaine during the Chronic Phase. Grey filled squares and larger white diamonds represent the mean of those individual points for that dose during the appropriate Chronic Phase. All other details are as in Fig. 2-1.
Figure 2-7. Dose-effect curves for proportion of hopper entries as a function of dose of cocaine during the Acute and Chronic Phases. All other details are as in Fig. 2-6.
Figure 2-8. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase and Chronic Phases. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 2-6.
Figure 2-9. Net session-weight change as a function of dose of cocaine during the Acute Phase and Chronic Phases. All other details are as in Fig. 2-6.
Figure 2-10. The ED50 values calculated from dose-effect curves during the various phases of Experiment 1. Bars above A, C, and S show ED50 values from the Acute Phase, Chronic Phase, and Saline Phase, respectively. The second C point for 1867 represent ED50 values obtained from the second Chronic Phase. Starting from the left for each subject, dashed lines separate ED50 values obtained for average head-in-hopper time, proportion of hopper entries, and average latency to hopper entries.
Figure 2-11. Dose-effect curves for average head-in-hopper time during the Acute and Saline Phase. Larger triangles represent averages of individual sessions, as shown by the smaller triangles, from the Saline Phase. All other details are as in Fig. 2-1.
Figure 2-12. Dose-effect curves for proportion of hopper entries as a function of dose of cocaine during the Acute and Saline Phase. All other details are as in Fig. 2-11.
Figure 2-13. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase and Saline Phase. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 2-11.
Figure 2-14. Net session-weight change as a function of dose of cocaine during the Acute Phase and Saline Phase. All other details are as in Fig. 2-11.
CHAPTER 3
EXPERIMENT 2

Introduction

The primary purpose of Experiment 2 was to examine if the tolerance to the disruptive effects of cocaine on feeding was contingent on when subjects experienced cocaine in relation to the session utilizing a Before-After design (Chen, 1968). Additionally, we examined whether the degree of tolerance observed was dependent on the inter-food presentation time. Previous research with pigeons and cocaine has shown tolerance to be dependent on FR-parameter size (Hoffman et al., 1987) but independent of FI-parameter size (Schama & Branch, 1989). Therefore, we exposed subjects to three different FT values (10 s, 30 s, & 120 s) based on the baseline reinforcer rates observed in both the Hoffman et al. and Schama and Branch studies. Each FT value was paired with a distinct stimulus, making the final schedule a 3-component multiple FT schedule of food presentation.

Methods

Subjects

Initially, twelve adult, male White Carneau pigeons maintained at 80% of their free-feeding weights served as subjects. During the course of the experiment, 2 subjects died before completing the experiment, and their data are not presented. The pigeons were experimentally and drug naïve prior to the start of Experiment 2. Outside of experimental sessions, the pigeons were individually housed in a temperature-controlled colony room with a 16:8 hr light/dark cycle. Pigeons had continuous access to vitamin-
enriched water and health grit while in the home cage. Care and treatment protocols for all subjects were all approved by the local Institutional Animal Care and Use Committee.

**Apparatus**

Sessions were conducted in two similar operant-conditioning chambers for pigeons (one chamber was the same one used in Experiment 1) with a few modifications to the front panel. Beginning 9.5 cm from the right side of the front panel, 6 equally spaced houselights were installed across a 19 cm span. Each houselight was located 2 cm from the ceiling. The houselights alternated white, red, green, white, red, and green going from left to right. An 8 cm by 35.5 cm frosted, translucent panel was then connected to the front panel, 7 cm below the chamber ceiling. The board jutted away and upwards from the panel at a 45-degree angle, effectively covering the houselights from view of the subjects. The houselights and the translucent panel permitted the chamber to be illuminated with 1 of 3 diffuse, colored lights.

**Data Analysis**

The ED50 values were measured in the same manner as in Experiment 1. Note that ED50 values were not assessed for subjects that exhibited flat, no-response dose-effect curves.

**Hopper Training**

Hopper training in Experiment 2 was conducted similarly to that of Experiment 1 except for one detail. The chamber was sequentially illuminated white, red, green, and then the sequence was started over across successive inter-hopper-elevation intervals.

**Baseline**

After hopper training, subjects were introduced to the final schedule, a 3-component multiple FT schedule of food presentation. The session proper was preceded
by a 5-min blackout period during which all the chamber lights were extinguished and no behavioral measures were recorded. Session began with presentation of one of the FT components. The individual component values were 10 s, 30 s, and 120 s, which were associated with white, red, and green chamber lights, respectively. Components were presented randomly and without repetition within each block of 3 components, and each component consisted of 4 hopper presentations. If the pigeon did not approach the hopper aperture after food was made available, a 20-s limited hold was in place after which the hopper was lowered and the next FT value was presented. If the hopper aperture was entered, as detected via photobeam, the pigeon had 2-s access to food. Although 2.1 s of access were delivered in Experiment 1, the intended value was 2.0 s. The extra 0.1 s of access was due to features of the program code execution and data collection. After Experiment 1 was concluded, the code was analyzed and new, alternative programming methods of monitoring food delivery and data collection were used. Baseline continued until stability in average head-in-hopper times as well as daily net weight was observed as judged by visual inspection of daily records (61 to 77 days).

**Drugs and Drug-Administration Procedure**

Procedures were similar to those used in Experiment 1. During the various chronic conditions, the injection site for pre- and post-session administrations of cocaine was alternated during chronic administration, and post-session administrations occurred immediately after sessions. Additionally, we decided not to administer doses higher than 17.0 mg/kg. All other details were the same as that of Experiment 1.

**Acute Administration**

Acute dose-effect curves were assessed in the same manner as in Experiment 1. Table 3-1 shows the number of administrations received during each experimental
condition for all subjects in Experiment 2. Figure 3-1 shows a visual diagram of the various experimental conditions in Experiment 2.

**Chronic Administration**

Immediately after the Acute Phase, subjects were exposed to three different chronic conditions. In the COC-SAL condition, subjects received daily administrations of cocaine prior to session and saline following session. The order of injections was reversed in the SAL-COC condition. Subjects received saline both prior to and after sessions in the final condition, SAL-SAL. The chronic dose of cocaine was individually picked based on acute dose-response functions. Either a chronic dose that resulted in intermediate effects on average head-in-hopper times during acute assessments was chosen, or if a dose with an intermediate effect was not available, the lowest dose that eliminated head-in-hopper time was used.

Each of the three chronic conditions continued for at least an initial 28 days and until stability in average head-in-hopper times was observed as judged by visual inspection of daily records. Dose-effect curves were then assessed while chronic administrations continued. During the COC-SAL condition, various test doses of cocaine were substituted for the chronic dose. During the SAL-COC condition, various test doses were presented prior to session during test-dose administration sessions, and saline was presented after the session. During the SAL-SAL condition, various doses of cocaine were administered prior to session in place of the regular saline injection. For all chronic conditions, each dose was administered at least twice when determining dose effects (except when all doses resulted in no eating. See Results), and further administrations were conducted as necessary to assess the reliability of the mean effect. Sessions conducted immediately prior to test administrations served as representative of the
chronic dose during the COC-SAL condition and saline sessions during both the SAL-COC and SAL-SAL conditions.

Half the pigeons were exposed to the COC-SAL condition first. The rest were exposed to the SAL-COC condition first. Specifically, subjects were initially paired together based on their acute dose-response functions. Each member of a pair was then randomly assigned to one of two groups using a coin-flip. For the first chronic condition, the Before-First Group was introduced to the COC-SAL condition and the After-First Group experienced the SAL-COC condition. During the second chronic administration condition, which immediately followed the first condition, the order of injections was reversed for each group. The final condition for both groups was SAL-SAL. To summarize, the order of conditions for the Before First Group was COC-SAL, SAL-COC, and SAL-SAL; the order for the After First Group was SAL-COC, COC-SAL, and SAL-SAL.

Three subjects were exposed to minor variations in the procedure during the chronic conditions. During the COC-SAL condition, average head-in-hopper time for Pigeon 1117 was consistently at zero levels, even during pre-session saline-test administrations. Pigeon 1117 therefore received 9 weekly administrations of pre-session saline until head-in-hopper time recovered when saline was administered prior to session. This procedure was implemented, because Miller and Branch (2004) demonstrated that occasional administrations of saline could evoke key pecking in pigeons whose responding had been completely suppressed by chronic pre-sessions administrations of relatively large doses of cocaine. Pigeon 22 also received weekly administrations of saline 6 times prior to receiving any other test-doses during the COC-SAL condition.
Data from these saline-administration sessions for Pigeons 22 and 1117 were not included in the dose-response functions. Based on the unique dose-effect curve observed during the SAL-COC condition (see Results) for Pigeon 1136, a short chronic condition was conducted prior to the SAL-SAL condition in which 1.0 mg/kg was administered prior to session and 10.0 mg/kg was administered after session. The condition was conducted for 33 sessions and then a single 10.0 mg/kg pre-session test-dose was administered. After 6 more sessions in which 1.0 mg/kg was administered before session and 10.0 mg/kg was administered after session, the SAL-SAL condition was introduced.

**Results**

**Acute Phase**

Figures 3-2 through 3-7 show dose-effect curves for average head-in-hopper time, proportion of initial hopper entries, and latency to initial hopper entries, respectively. Overall, dose-related decreases were observed in average head-in-hopper time and proportion of hopper entries, whereas dose-related increases were observed in the average latency measure. Head-in-hopper time was almost completely eliminated at 10.0 mg/kg for 1 subject (98), 13.0 mg/kg for 2 subjects (76 & 1117), and 17.0 mg/kg for 5 subjects (96,95,76, 22, & 97). For the remaining 4 subjects, 17.0 mg/kg was the highest dose administered. With few exceptions, dose-effect curves for each of the dependent measures mapped closely on to one another. For Pigeon 23 and 1136, however, proportion of hopper entries (Figure 3-2) was affected relatively less at specific doses of cocaine relative to average head-in-hopper time (Figure 3-3). For Pigeon 1117, latency measures (Figure 3-7) were relatively more sensitive to the effects of cocaine at lower doses when compared to effects of the same doses on the other two dependent measures (Figures 3-5 and 3-6).
Comparison of dose-effect curves across components showed no systematic differences based on FT value for average head-in-hopper times and proportion of hopper entries. A small but consistent relationship was observed in the latency measure under control and saline conditions in which average latencies were positively correlated with FT value.

The COC-SAL Condition

Figures 3-8 to 3-10 and 3-11 to 3-13 show results of the COC-SAL condition for the Before-First and After-First Groups, respectively. The results for average head-in-hopper times are shown in Figures 3-8 and 3-11. Except for the notable exception of Pigeon 1117, tolerance, as evidenced by shifts to the right in dose-effect curves, to the disruptive effects of cocaine on average head-in-hopper time was observed for all subjects. In some cases, evidence of tolerance was either limited to a particular dose (i.e., Pigeon 23 and 19) or to the right end of the dose-effect curve (i.e., Pigeon 76 and 1136). Overall, the degree of tolerance was similar for the Before-First and After-First Groups, and the degree of tolerance observed was similar across components for all subjects.

Figures 3-9 and 3-12 show data for proportion of initial hopper entries for the Before-First and After-First Groups, respectively, during the COC-SAL condition. Subjects that exhibited tolerance for the average head-in-hopper measure generally showed tolerance for the proportion of initial hopper entries measure as well. Only Pigeon 23’s data failed to show tolerance across all three components, but only the large FT component had any room for tolerance to be exhibited, and tolerance was observed in that component. As seen for the average head-in-hopper time measure, the degree of tolerance observed was generally similar across components except for the previously mentioned exception of Pigeon 23. Unlike the patterns of tolerance shown for average
head-in-hopper time, almost complete recovery was observed at all doses for most subjects for the proportion measure, comparable to values observed at control levels. Only Pigeons 96 and 98 showed patterns of tolerance that were similar for both measures.

Figures 3-10 and 3-13 show data for average latency to initial hopper entries. Overall, patterns of tolerance were similar to those observed for average head-in-hopper time, with subjects who exhibited more tolerance for the head-in-hopper measure generally showing more tolerance for the latency measure. The degree of tolerance was generally similar across components as well, except for Pigeon 23’s data, which matched the pattern of tolerance observed for the proportion of hopper entry measure mentioned above.

Figures 3-14 through 3-16 show average ED50 values for all subjects across the various conditions of Experiment 2 for the three primary dependent measures. Observed differences in ED50 values between components were relatively minor, therefore ED50 values were averaged across components for each subject. Note that bars showing ED50 values of 0 mg/kg represent flat, or no-response, dose-effect curves for which ED50 analyses were not conducted. Comparison of ED50 values from the Acute (leftmost set of black bars in each plot) and the COC-SAL condition (bars diagonal lines) shows tolerance, as shown by greater ED50 values in the COC-SAL condition compared to the Acute Phase, was observed for all subjects across all dependent measures except for Pigeon 1117. Overall, the results of the ED50 analysis confirm the visual interpretations made of the data.

The SAL-COC Condition

Results from the SAL-COC condition, when cocaine was administered immediately after session, for the three primary dependent measures are shown in Figures
3-17 to 3-19 and Figures 3-20 to 3-22 for the Before-First Group and After-First Group, respectively. The most striking finding was that feeding was suppressed in 1 subject in the Before-First Group and in 4 out 5 subjects in the After-First Group. Only Pigeon 97’s feeding was not suppressed and actually exhibited tolerance as shown by shifts to the right in dose-effect curves for all three measures and across all three components.

In contrast, in the Before-First Group, only Pigeon 96’s feeding was completely suppressed, although Pigeon 1136’s behavior was suppressed at the lower end of the dose-response function, particularly when saline was administered prior to session. For the remaining subjects, dose-effect curves generated during the SAL-COC condition were largely unchanged with those observed during the COC-SAL condition and the SAL-COC condition. Increased variability was observed during saline administrations for Pigeons 95 and 76. Pigeon 1136’s behavior was unique in that responding was suppressed during daily sessions in which saline was administered prior to session but levels of feeding were similar to those observed during the COC-SAL at higher doses (i.e., 5.6 mg/kg, 10.0 mg/kg, & 17.0 mg/kg of cocaine). Initially responding was also relatively lower at 1.0 mg/kg and 3.0 mg/kg of cocaine. Subsequent administrations of those doses showed increased responding back to control levels, even though responding continued to be suppressed during sessions when presession saline was administered.

Examination of ED50 values in Figures 3-14 to 3-16 provided quantitative confirmation of the conclusions based on our visual observations. Any tolerance observed during the COC-SAL condition in the Before-First Group was maintained during the SAL-COC condition. For the After-First Group, the only subject that showed tolerance during the SAL-COC condition, Pigeon 97, did not show additional tolerance
when cocaine administrations were moved to the beginning of sessions. Figure 3-23 compares ED50 values across the three different primary dependent measures during the various conditions in Experiment 2. Results from the SAL-COC condition are not shown as they were either similar to those observed during the COC-SAL condition or not calculated when no-response, flat dose-effect curves were observed. Overall, relative and absolute ED50 levels were similar across all three dependent measures for a given subject. For Pigeon 23, absolute ED50 values were lowest for the head-in-hopper measure for both the Acute Phase and the COC-SAL condition compared to the other dependent measures, although the relative difference between the two conditions were similar across the three measures. For Pigeon 1136, ED50 values were higher during the Acute Phase for proportion of approaches, although the absolute levels for ED50 values during the COC-SAL condition were similar across all three measures.

**Pairing 1.0 mg/kg Presession with 10.0 mg/kg Postsession**

Figure 3-24 shows average head-in-hopper times from daily sessions for Pigeon 1136 when 1.0 mg/kg of cocaine was administered prior to sessions and 10.0 mg/kg of cocaine was administered immediately after sessions. Note that this condition was initiated after feeding recovered to those levels observed during control sessions when 1.0 mg/kg of cocaine was administered prior to session during the SAL-COC condition (Figure 3-17). Decreases in average head-in-hopper time were observed at approximately the 20th session and continued to decrease over the course of the next 7 sessions. The results show that 1136’s average head-in-hopper time was suppressed when the presession dose was paired with a relatively large postsession dose, 10.0 mg/kg, as was observed when saline was administered prior to session and 10.0 mg/kg was administered after session. Taken together, the results suggest that Pigeon 1136’s behavior was
sensitive to doses administered prior to session, when those doses reliably predicted postsession administrations of 10.0 mg/kg. Note that administration of 10.0 mg/kg of cocaine prior to session resulted in average head-in-hopper times that were comparable to those observed during both the SAL-COC and the COC-SAL conditions, where tolerance had been observed.

**The SAL-SAL Condition**

Figures 3-25 to 3-27 and Figures 3-28 to 3-30 show dose-effect curves for the Before-First and After-First Groups, respectively. By and large, for both groups, dose-effect curves for all three dependent measures were shifted to the left, and in some cases they closely mirrored those observed during the Acute Phase. Pigeon 1177’s behavior was noteworthy in that very little loss of tolerance was observed. Also, Pigeon 1136’s behavior showed relatively greater loss of tolerance in average head-in-hopper measure in comparison to the other two dependent measures. Our visual observations were generally confirmed according to the ED50 values (Figures 3-14 to 3-16 and Figure 3-23).

**Within-Session Analysis**

Figures 3-31 to 3-39 show dose-effect curves for average head-in-hopper times broken down by component in addition to consecutive blocks within a session. Within-session data are shown for all subjects except for Pigeon 1117, who did no show tolerance within any condition. Only data from the Acute Phase and the COC-SAL condition are shown since dose-effect curves from the SAL-COC condition were either similar to those observed in the COC-SAL condition or flat, as in the case of the majority of the After-First Group. The within-session analysis focused on average head-in-hopper time since the pattern of effects were similar for the average latency to hopper measure.
and little variation was observed in the proportion of hopper entry measure. Comparison of the figures shows two general trends. Dose-effect curves from either condition tended to be shifted to the right the further the session progressed. In other words, average head-in-hopper time generally recovered as the session progressed. Additionally, as observed in our overall analyses, little difference was observed in dose-effect curves between components for a given subject, even when analyzed within a block.

Figure 3-40 shows ED50 values for dose-effect curves shown in Figures 3-31 to 3-39, with the addition of ED50 values for Pigeon 1117 from the Acute Phase. Since dose-effect curves were generally similar across components, ED50 values were averaged across components, within a block. In concordance with our visual analysis, ED50 values were consistently greater in the 3rd block compared to the 1st block for all subjects in both the Acute Phase and COC-SAL condition, although differences were not always large. Figure 3-41 shows the net difference in average ED50 values between the Acute Phase and the COC-SAL condition for each block. The results show that patterns of tolerance within session were not systematic across subjects or groups.

**Discussion**

The results of Experiment 2 systematically replicated our findings in Experiment 1 and extended those findings to a multiple FT schedule of food delivery. Tolerance to the dose-related initial decreases in feeding was observed in 9 out of 10 subjects after daily administration of presession cocaine during the COC-SAL condition, across all three dependent measures. Additionally, as seen in Experiment 1, shifts back to the left in dose-effect curves were observed when daily administrations of saline during the SAL-SAL condition replaced daily cocaine administration.
When cocaine was administered prior to session during the COC-SAL condition, the degree of tolerance observed was not predicted by the FT value. In other words, tolerance was independent of FT-parameter size. Tolerance to the initially disruptive effects of presession cocaine has been shown to be sensitive to parameter size under a multiple FR schedule of food reinforcement in pigeons (Hoffman et al., 1987; Nickel et al., 1993; van Haaren & Anderson, 1994; Pinkston & Branch, 2004a; Yoon & Branch, 2004) as well as squirrel monkeys (Hughes & Branch, 1991). The FT values in Experiment 2 were chosen to approximate the baseline reinforcer rates observed in the Hoffman et al. study. Under experiments with similar reinforcer rates as those observed in the Hoffman et al. study, parameter-independent tolerance has been observed in pigeons to the initially disruptive effects of cocaine under fixed-interval (FI) schedules (Schama & Branch, 1989), tandem FI-FR schedules (Pinkston & Branch, 2004b), and conjunctive FI-FR schedules of food reinforcement (Yoon & Branch, in prep.). The current results are therefore similar to those observed under various compound schedules in which both time and response requirements must be met in order to obtain reinforcement. In Experiment 2, if the behavior associated with obtaining food (i.e., orienting to and approaching the feeder) is considered as a response, the current procedure similarly requires both time and response requirements as those experiments in which parameter-independent tolerance has been observed.

When cocaine was administered immediately after sessions (as in the SAL-COC condition), various degrees of within-session suppression of feeding were generally observed. That is, with post-session dosing the pigeons often did not eat at all during sessions. Complete suppression of feeding in the form of flat, no-response dose-effect
curves was observed in 4 out of 5 subjects in the After-First Group and one subject (96) in the Before-First Group. In the Before-First Group, Pigeon 1136’s behavior showed suppression at the lower end of the dose-effect curve, and Pigeons 76 and 95’s data showed increased variability during saline sessions due to occasional decreased feeding. Therefore, overall 8 out of 10 subjects showed some variation of reduced feeding during daily session in which saline was administered prior to session and cocaine afterwards.

Previous research in which relatively large doses of postsession psychomotor stimulants have been used has shown similar results in pigeons. Pinkston and Branch (2004b) showed suppression of keypecks in the context of a multiple FR schedule of reinforcement, even when postsession administration of relatively large doses of cocaine was delayed by at least 20 minutes. Glowa and Barrett (1983) also showed suppression of keypecking during both an FI schedule and FR schedule of reinforcement, when amphetamine was administered following sessions. Although evidence of suppression was observed in the Before-First Group once cocaine was moved from immediately prior to immediately after sessions in the SAL-COC condition, it is important to note that a flat, no-response dose-response curves was observed only in 1 out of 5 subjects, compared to the After-First Group in which 4 out 5 subjects exhibited flat, no-response dose-effect curves.

One potential explanation of the disparate results between the two groups is that once tolerance developed in the Before-First Group during the COC-SAL condition, the chronic dose for a given subject was functionally not as high of dose as that during the Acute condition. Presumably, administering a higher postsession dose for these subjects would potentially result in similar levels of suppression as observed in the After-First
Group during the SAL-COC condition. Pinkston and Branch (2004b) found that smaller post-session doses were less likely to result in suppression of responding in sessions than were larger doses.

From a behavioral perspective of tolerance, the development of tolerance in Pigeon 97’s feeding following daily administration of postsession cocaine (SAL-COC) was singular. No aspects of Pigeon 97’s acute dose-effect curves or the chronic dose stand out as remarkably different from that of the other subjects. The vast majority of previous research investigating the effects of psychomotor stimulants has shown contingent-tolerance, such that tolerance was only observed when drug was administered prior to session (Wolgin, 1989). That body of literature, however, has almost exclusively used rats as subjects and occasionally nonhuman primates. Recent research, on the other hand, in which pigeons have been used as subjects, has demonstrated tolerance after daily administration of postsession cocaine. For example, Pinkston and Branch (2004b) were the first to report tolerance to the rate-decreasing effects of cocaine on responding after daily administration of postsession cocaine. In their study, functionally small doses, doses that had little effect on keypecking during acute administrations, were administered. As noted earlier, when they studied larger post-session doses, responding during sessions was decreased, usually to zero.

In the Pinkston and Branch (2004b) study, additional tolerance was observed in the smaller of two FR components when daily cocaine administrations were moved to before sessions. It was therefore concluded that tolerance was the product of both behavioral and pharmacological influences. Tolerance has also been observed in the majority of 17 pigeons that were given a behaviorally active dose, a dose that initially reduced
responding more than 50% of baseline, chronically postsession under a simple FR schedule of reinforcement (Marusich & Branch, personal communication). In the majority of cases, tolerance was still observed when postsession cocaine was administered an hour after session and temporally disassociated with postsession feeding. Additionally, increased tolerance was not observed when cocaine was moved to before session, as was the case for Pigeon 97 in the current experiment. Taken together, the results of the three investigations involving pigeons and daily postsession administrations of cocaine appear to suggest that lower doses of cocaine generally result in tolerance whereas higher doses were more likely to produce within session suppression of responding in pigeons.

As seen in Experiment 1, dose-effect curves were shifted back to the left once administration of cocaine, whether before or after session, was replaced by daily administrations of saline in the SAL-SAL condition. Replacing presession cocaine administrations with daily saline administrations alone per se, however, did not result in leftward shifts in dose-effect curves, as seen in the results of the Before-First Group when shifted to the SAL-COC condition. Tolerance that developed during the COC-SAL condition in the Before-First Group was maintained during the SAL-COC condition, even though drug was no longer experienced during sessions except for during test-dose administrations.

Additionally, the degree of tolerance lost was relatively similar for both the Before- and After-First Groups, even though the Before-First Group experienced two consecutive conditions (SAL-COC & SAL-SAL) in which saline was administered prior to daily sessions, whereas the After-First Group had just completed the COC-SAL condition. In
contrast with the current findings, previous research has shown a loss of tolerance to the
disruptive effects of psychomotor stimulants on feeding when drugs were no longer
administered prior to sessions. Both Wolgin and Hughes (1997) and Hughes, Popi, and
Wolgin (1999) observed leftward shifts in dose-effect curves when presession drug
administrations were moved to after sessions or replaced by daily administrations of
presession saline. These studies, however, differed from our study in that rats were used
as subjects, sweetened condensed milk was continuously available as the feeding task,
and amphetamine was the drug.

Despite these differences, our results conflict with the previous authors explanation
of tolerance loss. It has been suggested, that tolerance reflects a learned compensatory
response, and that loss of tolerance results when subjects experience sessions in the
absence of drug. Subjects presumably learn to no longer engage in the compensatory
response during sessions when drug is no longer experienced during sessions. This
viewpoint is supported by results in which tolerance has been maintained in subjects
when drug administrations and sessions were suspended together (Wolgin et al., 1991;
Wolgin & Hughes, 2001). Implicit in this interpretation of tolerance loss is that the
compensatory response is under the control of the session-related stimuli (e.g., features of
the experimental chamber), as opposed to the drugs behavioral effects. Such an
interpretation, however, cannot explain the maintenance of tolerance in the Before-First
Group during the SAL-COC condition. Additionally, the individual results for Pigeon
1136 suggest that for some subjects, it may be possible that behavior during a session can
come under stimulus control of the presession dose. Unfortunately, the only other study
to investigate postsession cocaine dosing in pigeons (Pinkston & Branch, 2004b) cannot
be directly compared to the current results as a tolerance producing pressession dose was never then immediately administered chronically, following sessions in that study. Therefore, it is unknown as to whether or not tolerance would have been maintained when a tolerance-producing dose of cocaine was moved to after session. To the best of our current knowledge, only one other experiment is currently investigating the effects of postsession dosing on pigeons in similar manner to the current Experiment. The preliminary results of the Marusich and Branch study shows subjects generally developed tolerance when administered cocaine prior to sessions. Additionally, subsequently moving drug administrations to after sessions generally resulted in maintenance of tolerance, thereby replicating the findings of Experiment 2.

To summarize the major findings of Experiment 2: 1) tolerance to the initially disruptive effects of cocaine on feeding was observed when cocaine was administered prior to sessions and that tolerance was independent of FT-parameter size 2) Administration of cocaine immediately after sessions resulted in suppression of feeding within each session to varying degrees across most subjects, although the degree of suppression depended on the order in which the conditions were experienced 3) Dose-effect curves were generally shifted back to the left following replacement of cocaine with that of daily saline administrations both before and after sessions, in some cases replicating dose-effect curves observed during the Acute Phase.
Table 3-1. Number of test-dose administrations for each subject for all phases of Experiment 2.

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Number quadruplets represent the numbers of administrations for each dose during the various conditions. Numbers for the subjects are from the Before-First Group and show number of administrations for the Acute Phase, COC-SAL, SAL-COC, and SAL-SAL conditions, respectively. Numbers of administrations during the Acute Phase, SAL-COC, COC-SAL, and SAL-SAL conditions for the After-First Group are represented on the bottom half of the table. Doses with a relatively large number of administrations are from sessions conducted immediately prior to test-administration sessions. Dashes show doses that were not administered during a condition for a particular subject.
Before-First Group

After-First Group

Acute Phase

COC-SAL

SAL-COC

SAL-COC

COC-SAL

SAL-SAL

Figure 3-1. Visual illustration of the order in which the various conditions were experienced by each of the two groups in Experiment 2.
Figure 3-2. Average head-in-hopper times as a function of dose of cocaine during the Acute Phase for the Before-First Group. Component data are organized by columns and subject data are organized by rows. All other details are as in Fig. 2-1.
Figure 3-3. Proportion of hopper entries as a function of dose of cocaine during the Acute Phase for the Before-First Group. All other details are as in Fig. 3-2.
Figure 3-4. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase for the Before-First Group. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 3-2.
Figure 3-5. Average head-in-hopper times as a function of dose of cocaine during the Acute Phase for the After-First Group. All other details are the same as in Fig. 3-2.
Figure 3-6. Dose-effect curves for proportion of hopper entries as a function of dose of cocaine during the Acute Phase for the After-First Group. All other details are as in Fig. 3-2.
Figure 3-7. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase for the After-First Group. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 3-2.
Figure 3-8. Average head-in-hopper time during the Acute and COC-SAL condition for the Before-First Group. Black filled circles are the same as those from the Acute Phase. Grey filled squares represent the mean of individual points at specific doses shown by open white squares. All other details are as in Fig. 3-2.
Figure 3-9. Proportion of initial hopper entries during the Acute and COC-SAL condition for the Before-First Group. All other details are as in Fig. 3-8.
Figure 3-10. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase and COC-SAL condition for the Before-First Group. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 3-8.
Figure 3-11. Average head-in-hopper time during the Acute and COC-SAL condition for the After-First Group. All other details are as in Fig. 3-8.
Figure 3-12. Proportion of initial hopper entries during the Acute and COC-SAL condition for the After-First Group. All other details are as in Fig. 3-8.
Figure 3-13. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase and COC-SAL condition for the Before-First Group. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 3-8.
Figure 3-14. The ED50 values for average head-in-hopper time for various conditions in Experiment 2. ED50 values for the Before-First Group and After-First Group are shown in the left and right columns, respectively. Individual bars represent ED50 values averaged across the 3 FT components. Error bars represent +1 standard deviations. Bars above A, CS, SC, and SS represent mean ED50 values for the Acute Phase, COC-SAL, SAL-COC, and SAL-SAL respectively.
Figure 3-15. The ED50 values for proportion of initial hopper entries for various conditions in Experiment 2. All other details are as in Fig. 3-15.
Figure 3-16. The ED50 values for average latency to initial hopper entries for various conditions in Experiment 2. All other details are as in Fig. 3-15.
Figure 3-17. Average head-in-hopper time during the Acute and SAL-COC condition for the Before-First Group. Larger triangles represent the mean of individual points at specific doses shown by the smaller triangles. All other details are as in Fig. 3-8.
Figure 3-18. Proportion of initial hopper entries during the Acute and SAL-COC condition for the Before-First Group. All other details are as in Fig. 3-17.
Figure 3-19. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase and SAL-COC condition for the Before-First Group. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 3-17.
Figure 3-20. Average head-in-hopper time during the Acute and SAL-COC condition for the After-First Group. All other details are as in Fig. 3-17.
Figure 3-21. Proportion of initial hopper entries during the Acute and SAL-COC condition for the After-First Group. All other details are as in Fig. 3-17.
Figure 3-22. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase and SAL-COC condition for the After-First Group. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 3-17.
Figure 3-23. The ED50 values for various conditions in Experiment 2
Figure 3-24. Data from sessions in which 1.0 mg/kg was administered prior to session and 10.0 mg/kg was administered following session for Pigeon 1136. The ordinate shows average head-in-hopper time from the three FT components and the abscissa shows consecutive sessions. The cluster of data points near the right side of graph marked by “10.0” represent data from a session in which 10.0 was administered prior to session and saline was administered following that session. The first break in the data is due to a session that was terminated due to program failure. Those data are not shown.
Figure 3-25. Average head-in-hopper time during the Acute and SAL-SAL condition for the Before-First Group. Black filled circles are the same as those from the Acute Phase. Larger diamonds represent the mean of individual points at specific doses shown by smaller diamonds. All other details are as in Fig. 3-2.
Figure 3-26. Proportion of initial hopper entries during the Acute and SAL-SAL condition for the Before-First Group. All other details are as in Fig. 3-25.
Figure 3-27. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase and SAL-SAL condition for the Before-First Group. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 3-25.
Figure 3-28. Average head-in-hopper time during the Acute and SAL-SAL condition for the After-First Group. All other details are as in Fig. 3-25.
Figure 3-29. Proportion of initial hopper entries during the Acute and SAL-SAL condition for the After-First Group. All other details are as in Fig. 3-25.
Figure 3-30. Average latency to hopper entries as a function of dose of cocaine during the Acute Phase and SAL-SAL condition for the After-First Group. Note that the ordinate is on a log scale with a maximum of 20 s. All other details are as in Fig. 3-25.
Figure 3-31. Average head-in-hopper times as a function of dose of cocaine by block and component during the Acute Phase and the COC-SAL condition for Pigeon 96. Components are shown horizontally and blocks vertically. Note that the abscissa begins at 1.0 mg/kg of cocaine. All other details are as in Fig. 3-9.
Figure 3-32. Average head-in-hopper times as a function of dose of cocaine by block and component during the Acute Phase and the COC-SAL condition for Pigeon 95. All other details are as in Fig. 3-31.
Figure 3-33. Average head-in-hopper times as a function of dose of cocaine by block and component during the Acute Phase and the COC-SAL condition for Pigeon 23. All other details are as in Fig. 3-31.
Figure 3-34. Average head-in-hopper times as a function of dose of cocaine by block and component during the Acute Phase and the COC-SAL condition for Pigeon 76. All other details are as in Fig. 3-31.
Figure 3-35. Average head-in-hopper times as a function of dose of cocaine by block and component during the Acute Phase and the COC-SAL condition for Pigeon 1136. All other details are as in Fig. 3-31.
Figure 3-36. Average head-in-hopper times as a function of dose of cocaine by block and component during the Acute Phase and the COC-SAL condition for Pigeon 22. All other details are as in Fig. 3-31.
Figure 3-37. Average head-in-hopper times as a function of dose of cocaine by block and component during the Acute Phase and the COC-SAL condition for Pigeon 1177. All other details are as in Fig. 3-31.
Figure 3-38. Average head-in-hopper times as a function of dose of cocaine by block and component during the Acute Phase and the COC-SAL condition for Pigeon 98. All other details are as in Fig. 3-31.
Figure 3-39. Average head-in-hopper times as a function of dose of cocaine by block and component during the Acute Phase and the COC-SAL condition for Pigeon 97. All other details are as in Fig. 3-31.
Figure 3-40. Block ED50 values for average head-in-hopper time. The left and right columns of show ED50 values for the Before-First Group and After-First Group, respectively. Within a given plot, ED50 values from the Acute Phase and the COC-SAL condition are shown in the left and right triplet of bars, respectively. Individual bars show ED50 values averaged across components within a given block, and error bars represent +1 standard deviation.
Figure 3-41. Net ED50 values for plots shown in Figure 3-40. Bars represent differences between ED50 values from the COC-SAL condition and the Acute Phase for each subject. Note that a positive net ED50 value indicates tolerance within a given block. All other details are as in Fig. 3-40.
CHAPTER 4  
GENERAL DISCUSSION

The major findings of both Experiment 1 and 2 are: 1) that presession administrations of cocaine resulted in dose-related decreases in feeding during the Acute Phase; 2) that tolerance to cocaine’s initially disruptive effects on feeding was generally observed following daily administration of presession cocaine; and 3) that shifts back to the left in dose-effect curves were observed once cocaine administrations were replaced by daily administrations of saline. Overall, these results replicate the general pattern of effects observed in previous experiments, which involved operantly conditioned behavior under similar contexts, with cocaine and pigeons and extend them to a new activity, feeding. Additionally, the results of the current experiments increase the generality of previous work done concerning psychomotor stimulants and feeding to a new context and species, that of pigeons when food is provided intermittently for brief durations.

Although the general patterns of findings between Experiment 1 and 2 were similar, one observed difference was that ED50 values both during the Acute Phase and when cocaine was administered prior to session were greater in Experiment 2 than Experiment 1 (Figures 2-10 and 3-23). One possible explanation for the observed differences is that Experiment 1 used a VT schedule, whereas Experiment 2 used a 3-component multiple FT schedule of food delivery. Wolgin (2004) argues that the anorexic effects of psychomotor stimulants in rats result from increased locomotor activity and stereotypy induced by drug, which interferes with eating. Furthermore, tolerance to these disruptive effects occurs after animals learn to suppress or inhibit
behavior that interferes with eating, which is the presumed compensatory response. Pinkston and Branch (2003) showed cocaine causes increased locomotor activity in the absence of an explicit operant requirement in pigeons, and Wolgin and Hertz (1995) showed that tolerance to cocaine’s disruptive effects on milk intake (in rats) were accompanied by reductions in cocaine-induced locomotor activity. To the degree that Wolgin’s perspective is true, the relatively more predictable food deliveries in the FT schedule may have made facilitated subjects’ ability to inhibit locomotor activity while food was being presented compared to a VT schedule of food delivery.

Despite the differences in ED50 values between Experiments 1 and 2, the ED50 values in our study were generally greater than those observed in other studies that have examined the effects of cocaine on operant behavior in pigeons. Two previous studies have explicitly reported ED50 values under an FR 20 schedule (Miller & Branch, 2002) and a 3-component multiple FR schedule in which hopper-access time was correlated with the FR requirement (Yoon & Branch, 2004). For comparison with the Yoon and Branch study, the average ED50 values from only the smallest component (i.e., FR 10) were examined. Values from that component tended to be the largest seen in the study. The group average Acute ED50 values from Experiments 1 and 2 of our study were 8.2 mg/kg and 9.48 mg/kg, respectively. In comparison, the selected previous studies reported Acute ED50 values 4.14 mg/kg (Miller & Branch, 2002) and 3.30 mg/kg (Yoon & Branch, 2004). A comparison of ED50 values obtained when cocaine was administered chronically pre session shows a similar pattern. The averaged ED50 values for Experiment 1 and 2, when cocaine was administered chronically pre session, were 11.6 mg/kg and 14.6 mg/kg, respectively. In comparison, Miller and Branch (2002)
observed average ED50 values of 7.74 mg/kg. The Yoon and Branch study had 4 different, consecutive conditions in which cocaine was chronically administered prior to sessions. The average ED50 values from those 4 conditions were 4.91 mg/kg, 6.18 mg/kg, 4.19 mg/kg, and 9.50 mg/kg, respectively. The first 3 conditions involved administration of different doses of cocaine prior to consecutive sessions, whereas the same dose of cocaine was administered prior to sessions in the 4th condition. That is, the 4th condition was most similar to the current study. All conditions, except the 2nd condition, which provided 4.5-s access to food, provided 1.5-s access to food once the FR-10 requirement was completed. Therefore, although the relative degree of tolerance developed for a given study appears to be similar, the dose-effect curves in our study appear to be shifted to the right in comparison with the selected studies according to ED50 values. This pattern, in which dose effect curves are shifted relatively to the right, appears to be generally representative of the rest of the literature that has investigated the effects of cocaine on food-reinforced behavior in pigeons under similar contexts.

One procedural difference that may be responsible for the generally greater ED50 values in our study, as compared to ED50 values from experiments on operantly conditioned performance, may be the response requirement. Compared to other studies examining food-reinforced behavior, the response-requirement in the current experiment will always be less than in studies of conditioned operant behavior simply because in those studies some response, typically keypecking, must be completed in addition to the actions involved in feeding. Therefore, the response requirement in the current study is arguably the smallest among the studies that have involved pigeons and cocaine, with the possible exception of locomotor activity (Pinkston & Branch, 2003). For example, Yoon
and Branch (2004) showed that as the FR requirement increased (i.e., FR 10, FR 30, and FR 100) ED50 values decreased (i.e., 3.30 mg/kg, 3.28 mg/kg, and 2.06 mg/kg, respectively) during the Acute Phase. Although ED50 values were not explicitly reported, similar patterns were observed by Hoffman et al. (1987). We estimated ED50 values by measuring 50% of the control rate and drawing a line parallel to the x-axis until it intersected with the dose-effect curve. Estimated acute ED50 values for the FR-5 component were all 4.2 mg/kg, ranged from 2.3 mg/kg to 4.2 mg/kg for the FR-25 component, and ranged from 1.0 mg/kg to 2.3 mg/kg for the large-FR component, which was an FR 125 for 2 subjects and an FR 50 for the third subject. Therefore, both studies provide evidence that response requirements are correlated with drug effects, although relatively large differences in the FR requirement were needed to produce much change in the ED50 values. The overall influence of response requirement on ED50 values in our study is therefore likely minimal.

Another procedural difference between our study and earlier studies of operant performance is the limited-hold that was in effect following food presentations. In our study, once food was presented, a pigeon had 20 s to initiate feeding. By contrast, in most operant-conditioning studies, food is usually available for a fixed amount of time, typically 3 to 4 s of access. The results of both Experiment 1 and 2 show dose-related increases in average latency to hopper entries. At certain doses during both the Acute and chronic conditions in which cocaine was administered pre-session, latencies were high enough that food would not have been obtained had it been presented for only 3 s. Therefore, the limited-hold in the current study may have facilitated subjects obtaining the food at higher doses of cocaine, whereas had the limited-hold not been in effect,
pigeons might have learned not to approach the food hopper at higher doses as a result of a history of not approaching the hopper quickly enough to obtain food at those higher doses. A useful follow-up study, therefore, would be to examine conditioned operant performance under conditions in which the reinforcer is made available in a manner similar to that used in the present study, that is, with a limited hold.

The results of our study are pertinent the question as to whether the effects of cocaine on food-reinforced behavior are mediated by the effects of cocaine on feeding. In our study, we observed dose-related decreases in feeding under conditions of intermittent limited-time access. These results are similar to those observed with operants examined under parameters similar to the current study. The relative rightward shift in dose-effect curves observed in our study when compared to previously selected studies may initially suggest that rate decreases in food-reinforced operant behavior occur at doses lower than those required to decrease behavior related to feeding. Before it is assumed that there is no interaction between cocaine’s effects on feeding and schedule maintained behavior that is reinforced by food, however, two points should be considered. First, as mentioned above, the limited-hold present in the current set of experiments may have been at least partly responsible for the rightward shifts in dose-effect curves. Without the limited-hold, dose-effect curves for feeding may have been shifted more to the left, supporting more strongly the view that behavior related to feeding has an impact on operant behavior reinforced by food. Second, whether schedule-maintained responding is necessarily affected at lower doses than feeding, for a given subject, has not been formally examined. For a given subject, it is possible that
feeding may be more sensitive than schedule-maintained behavior, such as keypecking, to the effects of cocaine. Only subsequent research can answer these questions.

In regards to the second point that feeding may be more sensitive than schedule-maintained behavior, Yoon and Branch (2003) collected data on obtained unit price, a cost-to-benefit measure used in the field of behavioral economics (DeGrandpre, Bickel, Hughes, & Laying, 1993; Bickel, Green, & Vuchinich, 1995). In their study, unit price was measured as the ratio of the FR-response requirement to head-in-hopper time, that is, in units of responses per second of food access. The data in that study showed that obtained unit price increased at 5.6 mg/kg in the larger FR components, as the result of decreased head-in-hopper times, even though the FR requirement was being completed. Rates across components, regardless of differences in head-in-hopper times at 5.6 mg/kg, were similar across subjects. Therefore, at some doses in some components, feeding was observed to be more sensitive than FR-maintained responding despite no differences in rate of responding.

Another example of an interaction between schedule performance and reinforcer consumption was reported by Hughes and Branch (1991), who studied food-reinforced lever pressing in squirrel monkeys during a 3-component multiple FR schedule. In that study, different dose-effect curves, assessed during chronic administration, were observed for one subject. The shape of the curve depended on whether or not the monkey consumed earned reinforcers (food pellets). Additionally, FR-parameter related tolerance was only observed when pellets were being consumed. Interestingly enough, that subject still responded when programmed reinforcers were not being consumed. These two studies, therefore provide evidence that a) schedule-maintained performance may not
necessarily be more sensitive than feeding to the effects of cocaine and b) that the effects of cocaine on operant responding maintained by food may be mediated by the effects of cocaine on behavior related to feeding, at least for some subjects.

Some results of the present research that merit further investigation are the development of tolerance following chronic post-session administration of cocaine and the maintenance of tolerance in the Before-First Group once chronic cocaine administrations were moved to after sessions in Experiment 2. Previous research that supported a behavioral interpretation showed tolerance to psychomotor stimulants developed only if subjects experienced the effects of cocaine during session (Wolgin, 1989). Tolerance was lost if drug was not experienced during continued sessions, even though cocaine was administered after session (Wolgin & Hughes, 1997; Hughes, Popi, & Wolgin, 1999). A variety of differences, however, between the current investigation and previous work may potentially account for the disparate findings. First, pigeons were used as subjects in the current study, whereas generally rats and in some cases nonhuman primates were used in previous research. It may be, therefore, that traditional behavioral accounts of tolerance do not apply to pigeons. Second, in our study food was presented intermittently, for brief durations, whereas previous research generally had food available continuously and for longer durations. Third, in experiments with rats the eating task generally employed food (e.g., sweetened milk and sweetened mash) that was different from what the rats normally consumed (i.e., rat chow). In the current Experiment, the grain mixture used during session was different from that used for post-session supplemental feeding, but the differences were most likely relatively minor in comparison to that in experiments with rats.
At least two of our results, however, do suggest potential behavioral influences on tolerance. First, whether feeding was suppressed or not depended on the order in which the SAL-COC condition was experienced. When experienced after the COC-SAL condition, as did the Before-First Group, post-session cocaine was less effective in suppressing feeding. In other words, the chronic dose appeared to be functionally lower, after the COC-SAL condition had been experienced. Since the Before-First Group received cocaine for a longer period of time before experiencing the SAL-COC condition, however, the results are not inconsistent with a pharmacological interpretation. Second, stronger evidence comes from Pigeon 1136’s results showed that feeding could come under the stimulus control of dose administered prior to session when paired with post-session administrations of 10.0 mg/kg of cocaine. A purely pharmacological interpretation has difficulty explaining subsequent suppression of responding during session since responding during session when 1.0 mg/kg was administered presession had already recovered. Overall, our results, particularly those from Experiment 2, suggest that tolerance in our study is primarily a product of pharmacological influences. Combined with the results of Pinkston and Branch (2004a) and Marusich and Branch (personal communication), growing evidence suggests that tolerance in pigeons may have more pharmacological influences than previously assumed.

In summary, the results of the current extend the generality of previous findings regarding feeding and psychomotor stimulants to a new species and a context in which pigeons were presented with food intermittently for brief durations. Additionally, the current study brings to the forefront potential mediation of the effects of cocaine on
behavior maintained by a food-reinforced schedule by the effects of cocaine on consumption of the food-reinforcer.
LIST OF REFERENCES


BIOGRAPHICAL SKETCH

After graduating from Beverly Hills High School in 1992, I was enrolled in the University of Pennsylvania’s liberal arts program. As an undergraduate, I majored in psychology with a focus on premedical school course requirements. After graduating with a B.A., I became an intern at the BioBehavioral Unit at Children’s Seashore House in Philadelphia, PA. My main responsibilities consisted of conducting functional analyses and developing treatment programs for inpatient clients who were developmentally delayed and had severe problem behavior. My primary advisor was F. Charles Mace, but I also interacted with a variety of excellent mentors including the following professors: Tim Vollmer, Jo Lalli, Pat Progar, and Lee Kern. It was through their guidance and my rewarding experiences at Seashore House led me to pursue a career in behavior analysis. My initial interests in the medical field, coupled with my growing knowledge of behavior analysis seemed to make the subfield of behavioral pharmacology a perfect choice for me.

In pursuit of this goal, I applied to and was accepted into the University of Florida’s Experimental Analysis of Behavior (EAB) program under the guidance of Marc Branch. I also took courses with a variety of eminent behavioral professors including: Tim Hackenburg, Tim Vollmer, Hank Pennypacker, and Brian Iwata. Under their tutelage, my education in behavior analysis continued in good hands. My research interests, while at the University of Florida, were primarily concerned with behavioral tolerance (specifically, examining the effects of cocaine on responding in pigeons).
My initial research examined the interaction between various dosing regimens and different schedule parameters in the context of a multiple fixed-ratio schedule of reinforcement on the development of tolerance. The main results of that research showed that tolerance developed under both fixed- and variable-dosing regimens. Tolerance that was related to fixed-ratio-parameter size, however, was only observed when the chronic-dosing regimen was fixed. This study was later published in the journal, *Behavioral Processes*. My next study continued to explore the relation between different parameter values and the development of tolerance. I conducted a study investigating effects of cocaine on keypecking under different conjunctive schedules. In a conjunctive schedule, two or more schedule requirements must be completed for reinforcement to be delivered, but the order in which they are completed does not matter. Two studies examined different combinations of fixed-interval and fixed-ratio requirements. In one study, the fixed-ratio requirement was kept constant while the fixed-interval requirement was altered. In the other study, the fixed-interval was held constant whereas the fixed-ratio requirement was now varied. Results of both studies showed that development of tolerance was independent of schedule-parameter size. Additionally, both studies showed leftward shifts in dose-response functions when chronic administrations of cocaine were replaced by daily administrations of saline. The last area of research I explored while attending UF investigated the effects of cocaine on eating by pigeons. That research was funded by a predoctoral grant awarded by the National Institute of Health and is the focus of this dissertation.
I am currently continuing my career in behavior analysis and am currently situated at the University of Vermont. Here, I am investigating the role of voucher-reinforcement based therapy on helping drug users either quit or maintain abstinence.