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Cocaine and Timing: Drug Effects Under a Mixed Fixed-Interval Extinction Schedule

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COCAINE AND TIMING: DRUG EFFECTS UNDER A MIXED FIXED-INTERVAL EXTINCTION SCHEDULE

by

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COCAINE AND TIMING: DRUG EFFECTS UNDER A MIXED FIXED-INTERVAL EXTINCTION SCHEDULE

Vincent O. Hodge, M.A.

Western Michigan University, 1991

The effects of cocaine hydrochloride (3.2-56.2 mg/kg) were determined in rats performing under a mixed fixed-interval 60-seconds extinction 120-seconds schedule of food delivery. Responses were recorded in successive 5-second bins. With the exception of the highest dose (56.2 mg/kg), cocaine did not significantly affect rate of responding under the fixed-interval component or extinction component, or the time of peak responding under the extinction component. The highest dose significantly reduced response rates and shifted the time of peak responding leftward to quicker and earlier moments. Results are discussed in terms of possible rate- and time-dependent effects of stimulant drugs.

ACKNOWLEDGEMENTS

As I write this acknowledgement, my thoughts turn to those who begat me, raised me, nurtured me, and now are tired. I would repay the bounty they have given me, but my debt to them is as the sky; it may never be approached.

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My deepest thanks and appreciation are extended to my mother, Helen Hooker; Ruth Spicketts; the Armstrong family; the Oosterbaan family; my aunt Laverne; Asa Dawson (in memoriam); and countless others for the love, support, sacrifice, and encouragement needed to accomplish this goal.

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Vincent O. Hodge

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INTRODUCTION

Background and Statement of the Problem

Background of the Problem

Cocaine abuse in the 1990s is proving to be a pervasive and menacing problem. "Crack" cocaine can be found in every neighborhood in any town. No one is insulated against the effects this drug is having on society. From the mixing pits of Peru to the very steps of Capital Hill, cocaine has now begun to infect the lives of millions of Americans. Even this nation's children, who are surrounded by and often involved in the illicit activities of the drug trade, are no longer insulated against the social, economic, and physical effects of this menacing substance.

As Musto (1989) indicates, in light of the empirical and anecdotal evidence of cocaine's debilitating effects, one must consider why the human species has failed to learn from its previous encounters with this deadly drug. Cocaine is such a powerful reinforcer that our cyclical and abusive history with it must be interrupted, if we are to save ourselves from the impending doom of social addiction. If anything is to be gained in the war against drug abuse, one has to investigate the behavioral phenomena that contribute to such a tragedy.

Pharmacology of Cocaine

Much of what is known about cocaine (i.e., local anesthetic properties, psychostimulant actions, subjective effects, cardiovascular effects) was described more than 100 years ago. Nahas (1989) indicates that Albrecht Erlenmeyer and Ludwig Lewin reported cocaine's subjective effects of euphoria, relief from fatigue, and other forms of stimulation as early as 1884. They also indicted cocaine for its addictive qualities (Erlenmeyer recorded the cases of 21 cocaine addicts in his clinics in 1885). Some of the pharmacological characteristics of cocaine were also described by Erlenmeyer and Lewin. Others, however, remain poorly understood even today.

According to Jones (1984), "it is generally assumed that methylphenidate, amphetamine, and related stimulants have actions and many mechanisms (of action) similar to cocaine" (p. 35). Cocaine alters the metabolism of the neurotransmitter substances norepinephrine, dopamine, serotonin, and acetylcholine. It possesses potent convulsive properties. Early studies of cocaine with humans indicated that it interfered with the inactivation of dopamine, epinephrine, and norepinephrine (Central nervous System [CNS] neurotransmitters) by blocking their reuptake (Jones, 1984). Cocaine alters serotonergic function in the CNS by blocking synaptic uptake of tryptophan (Knapp & Mandell, 1972).

Recognizing that the brain is the locus for most operant and respondent behavior, one must accept the fact that homeostatic levels of neurotransmitters afford effective and efficient interaction of an organism with its environment. If the brain's homeostasis is disturbed, as when cocaine is present, the result can only be an alteration in an organism's interactions with the environment. Given that cocaine affects noradrenergic and serotonergic neurotransmission, it is no surprise that the drug has a range of behavioral and physiological effects.

Several authors (e.g., Byrd, 1979; Julien, 1985; Ray & Ksir, 1987; Thompson & Pickens, 1971) have summarized the behavioral and physiological effects of cocaine. In brief, cocaine causes increases in respiratory rate and body temperature, and increases psychomotor behavior. The drug has discriminable properties, including the induction of euphoria, and can be readily established as a discriminative stimulus. Cocaine serves as a positive reinforcer in many species, including humans.

With respect to schedule-controlled operant behavior, cocaine generally increases responding under fixed-interval schedules, while decreasing response rates under fixed-ratio schedules (Byrd, 1979). This phenomenon, which was first observed in 1955 by Peter Dews (Poling, 1986), is commonly described as a rate-dependent effect.

Rate-Dependent Drug Effects

Rate dependency occurs when a drug's behavioral effects are influenced by the rate of ongoing behavior in the absence of that drug (Poling, 1986). Dews (1955) provided the first demonstration of such an effect. Specifically, he compared the effects of pentobarbital on the key-pecking of pigeons under fixed-interval 15-minute (FI 15-min) and fixed-ratio 50 (FR 50) schedules of food delivery . Results indicated that pecking of the birds under the FI 15-min schedule was markedly reduced by doses of pentobarbital that had no effect on, or increased, rates of responding under the FR 50 (Dews, 1955).

Rate-dependent effects have been reported with many drug classes (e.g., Poling, 1986; Sagvolden, Jenssen, & Brorson, 1983; Sanger & Blackman, 1976). Such effects are readily observed with cocaine and similar stimulants, which increase low-rate operant behaviors at doses that decrease high rate operants (Poling, 1986).

Dews and Wenger (1977) state that theories of rate-dependency entail four propositions:

> 1) The first and weakest proposition is that, with all the variables unchanging, a change in rate may change the behavioral effect of a drug.
> ...
> 2) The differences in rates of responding may lead to differences in the drug's behavioral effect, and these differences will determine differences in the effect of the drug. Also, there is a systematic relationship between response rate and drug effect.
> ...
> 3) The third proposition adds a quantitative constraint on the second: The control rate of responding relates to the effect of a drug so that the log of the effect is a linear function of the log of the control.
> ...
> 4) The fourth, and strongest proposition states that the response rate determines the drug dose effect, and the other variables influence drug dose effect indirectly via response rates. (pp. 169-174)

Dews and Wenger (1977) stated that the first time control rate was discussed as a general determinant of drug effect was in relation to psychoactive stimulants, and that the "limited information available at the time was compatible with the simple proposition that control rate was the sole determinant of the effects of [stimulants] on rate of responding" (p.172). This relationship applies over an extremely wide range of circumstances and can be readily determined.

Sanger and Blackman (1976), in a major review of rate-dependent drug effects, noted that a bin analysis of responding under FI schedules provides a ready demonstration of rate-dependency. Because different average response rates are associated with successive bins within the FI (e.g., ten successive 1-min bins in an FI 10-min schedule), a bin analysis of response rates during drug and control conditions allows drug effects to be assessed in terms of the rate dependency hypothesis. In the absence of drug, response rates under long FI schedules characteristically increase across bins from the beginning to the end of each interval. Although the exact pattern of increase varies, with both gradual and abrupt increases occurring (Weiss & Laties,

1967), low rates characteristically occur early in the interval in the absence of drug. When stimulant drugs are administered, these low rates increase. Although this effect is commonly considered as evidence for rate-dependency, an alternative account is that the drug disrupts "timing."

Time-dependent Drug Effects

If under an FI schedule a stimulant drug acted to initiate responding sooner after reinforcement than occurred in the absence of drug, the result might appear to be a rate-dependent drug effect. In actuality, however, this would be an indirect result of the earlier initiation of responding. Several authors (e.g., Killeen, 1970; Killeen & Fetterman, 1988; Maricq, Roberts, & Church, 1981) have used the term "timing" when discussing the point of response initiation under FI schedules, and drug effects that involve changes in the point of response initiation have been termed "time-dependent." When used in this simple descriptive sense, time-dependent drug effects are subject to empirical analysis. To date, however, relatively few studies have appeared in this area. This probably reflects the fact that relatively few procedures are capable of disentangling time- and rate-dependent effects.

One such procedure was devised by Eckerman, Segbafia, Manning, and Breese, (1987). Their procedure involved a mixed fixed-interval 60-seconds and extinction 120-second (FI 60-s EXT. 120-s) schedule of food delivery. In order to assess rate-dependent effects, they examined response rates in the presence and absence of drug under the FI 60-s schedule, whereas they assessed peak response times under the Ext 120-s schedule to examine time-dependent effects. When methylphenidate was administered under these conditions, rats began responding rapidly earlier in the EXT component, which indicates a time-dependent drug effect. But low baseline (i.e., non-

drug) rates of responding were increased by methylphenidate regardless of when they occurred under the FI component. This finding is indicative of true rate-dependency. Thus it appears that the drug produces both time-dependent and rate-dependent effects.

Whether other stimulants act similarly is unknown. The purpose of the present study was to examine the effects of acute administrations of cocaine under a procedure similar to that employed by Eckerman et al. (1987) with methylphenidate.

CHAPTER II

EXPERIMENT

Method

Subjects

Eight experimentally-naive adult male Sprague-Dawley rats, maintained at 80% of free-feeding weights, served as subjects. They were individually housed with unlimited access to water in a colony area with controlled temperature (23^{0} C) and lighting (12-hr light/dark cycle). The procedures employed were approved by the Institutional Animal Care and Use Committee prior to study onset (see Appendix A).

Apparatus

Four plastic and aluminum operant chambers (Lehigh Valley), each 20 cm long, 12.5 cm wide and 15 cm high, were used. Each chamber was equipped with two response levers, which were located 5 cm from the ceiling and 3.25 cm apart on the 12.5 x 15 cm front wall. Above each lever, and 0.75 cm from the ceiling, was a 1.25-cm diameter screen which concealed a white light. A feeder, located 5.25 cm below the right lever, delivered 45 mg Noyes food pellets (P.J. Noyes Co., Lancaster, NH) when required. The left lever remained inoperable throughout the study. Ambient illumination was supplied during the experimental sessions by a 7-W white houselight, which was located to the left of the front wall. Masking sound was provided by a white noise generator, through a speaker which was located 1.9 cm above the houselight. The floor consisted of six 1.9-cm diameter aluminum grids. Programming

of experimental events and recording of data were controlled by a PDP-8/a computer (Digital Equipment Co., Inc., Maynard, MA) equipped with interfacing supplied by State Systems Inc. (Kalamazoo, MI).

Behavioral Procedure

The procedure in this study was similar to that used by Eckerman et al. (1987). Following lever press shaping, rats were initially trained (with tone present) to respond under an FI 2-s schedule of food delivery, with a 28-s blackout between FI's. This schedule, which lasted for 20 minutes, provided a total of 40 FI presentations. All sessions were conducted five days a week, at about the same time each day. The FI length was gradually increased across sessions until an FI 60-s schedule was reached. When all subjects responded reliably a mixed FI 60-s EXT 120-s schedule was introduced. Each 50-minute session was arranged as a computer-scrambled sequence of 12 FI and 18 EXT components. A 10-s inter-trial interval (ITI) separated all components. The houselight remained on during the ITI, but the tone was off. The tone was on at all other times. Lever presses had no scheduled effect during the ITI, or during the extinction components.

Pharmacological Procedure

Cocaine was administered when an individual rat's performance appeared to be stable across two consecutive control sessions. The control sessions entailed an intra-peritoneal (IP) injection of isotonic saline solution (1 ml/kg), given 20 min prior to behavioral testing. The effects of 5 doses of cocaine (3.2, 10.0, 17.0, 32.0, 56.2 mg/kg) were examined. Each rat received each dose of drug twice in random order. All drug doses were dissolved in isotonic saline solution, and administered at a 1 ml/kg

injection volume. *Doses* refer to the total salt. Injections were given IP 20 minutes prior to behavioral testing. Thus, with respect to injection parameters and behavioral testing, active drug injection and control sessions were identical.

CHAPTER III

RESULTS

The effects of cocaine on the rate of responding across time under the extinction component are of primary importance in the present investigation. By assessing whether the time at which the highest rate of responding occurred differed in control and drug sessions, the effects of cocaine on "timing" can be assessed. Figure 1 shows for the group of subjects the temporal point in the extinction component at which the highest rate of responding occurred under all experimental conditions. Individual data points in this figure represent group means (plus and minus one standard deviation) and were determined by ascertaining from bin data the time at which responding peaked for each rat in a given session, then calculating the average.

Visual analysis of the data depicted in Figure 1 indicates that (a) considerable variability was evident, and (b) a clear effect was evident only at the highest (56.2 mg/kg) cocaine dose. Statistical analysis confirms these conclusions. The data depicted in Figure 1 were analyzed via a one-factor repeated measures analysis of variance. This analysis revealed a statistically significant overall difference in the mean time of peak responding ($F = 9.07$, $df = 7, 35$, $p < .01$). Planned comparisons (Fisher's PLSD) revealed no significant difference in performance during vehicle and baseline (no injection) sessions. When data for drug sessions were compared to data for vehicle sessions, a significant difference ($p < .05$) was evident only at the 56.2 mg/kg cocaine dose. At that dose, the mean rate of responding for the group of rats

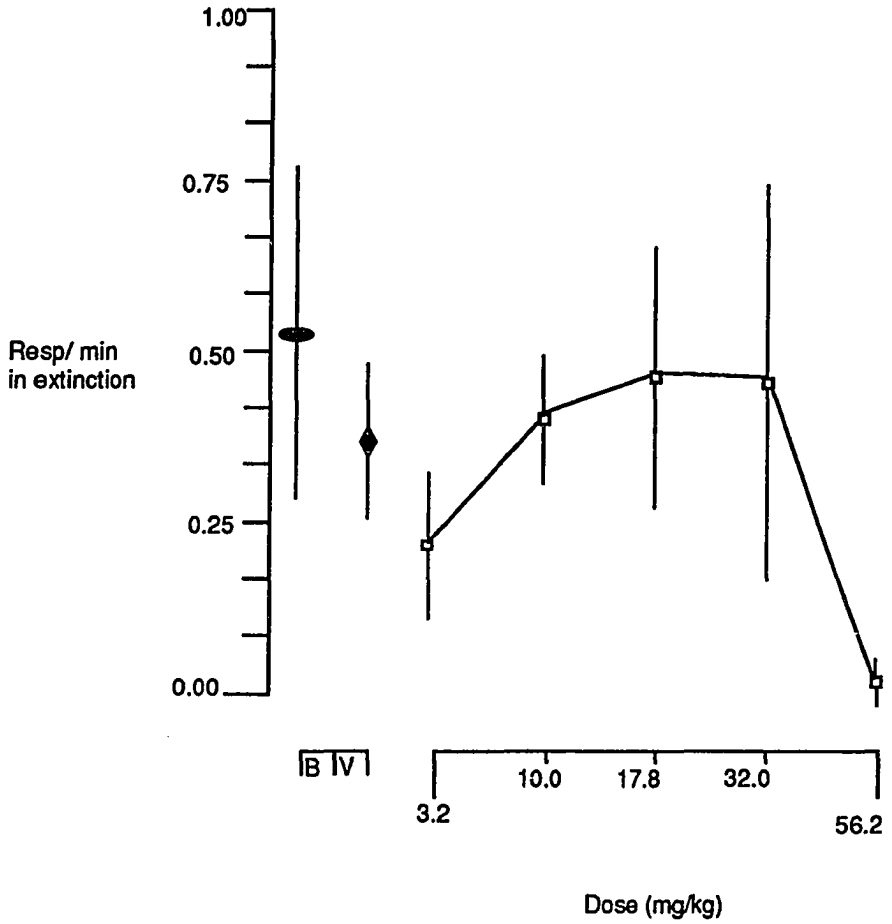

Figure 1. Effects of Cocaine on Overall Response Rates in the Extinction Component.

peaked 5.27 seconds into the extinction interval. During vehicle sessions, the time of peak responding was 61.4 seconds into the extinction interval.

Although the 56.2 mg/kg dose of cocaine affected the time of peak responding under the extinction component, that dose dramatically decreased the overall rate of responding in extinction. This effect is evident in Figure 2, which shows the mean maximum rate of responding (plus and minus one standard deviation) in each bin during extinction under all experimental conditions. The data depicted in Figure 1 were analyzed via a one-factor repeated measures analysis of variance. This analysis

revealed a statistically significant overall difference in the mean maximum rate of responding across conditions ($F = 6.27$, $df = 7, 35$, $p < .01$). Planned comparisons (Fisher's PLSD) revealed no significant difference in performance during vehicle and baseline (no injection) sessions. When data for drug sessions were compared to data for vehicle sessions, a significant difference ($p < .05$) was evident only at the 56.2 mg/kg cocaine dose. At that dose, the mean peak rate of responding for the group of rats was much lower than the vehicle control rate.

The effects of cocaine on response rates under the FI component are shown in Figure 3. This figure depicts the mean rate of responding (plus and minus one standard deviation) for the group of rats under all experimental conditions. The data depicted in Figure 3 were analyzed via a one factor analysis of variance. This analysis revealed a statistically significant overall difference in response rates across all FI conditions ($F = 2.909$, $df = 6,42$, $p < .05$). Planned comparisons (Fisher's PLSD) revealed no statistically significant difference in the rate of responding in the FI component during vehicle and baseline sessions. Planned comparisons indicated that there was no significant difference in the response rate obtained under vehicle and any drug condition.

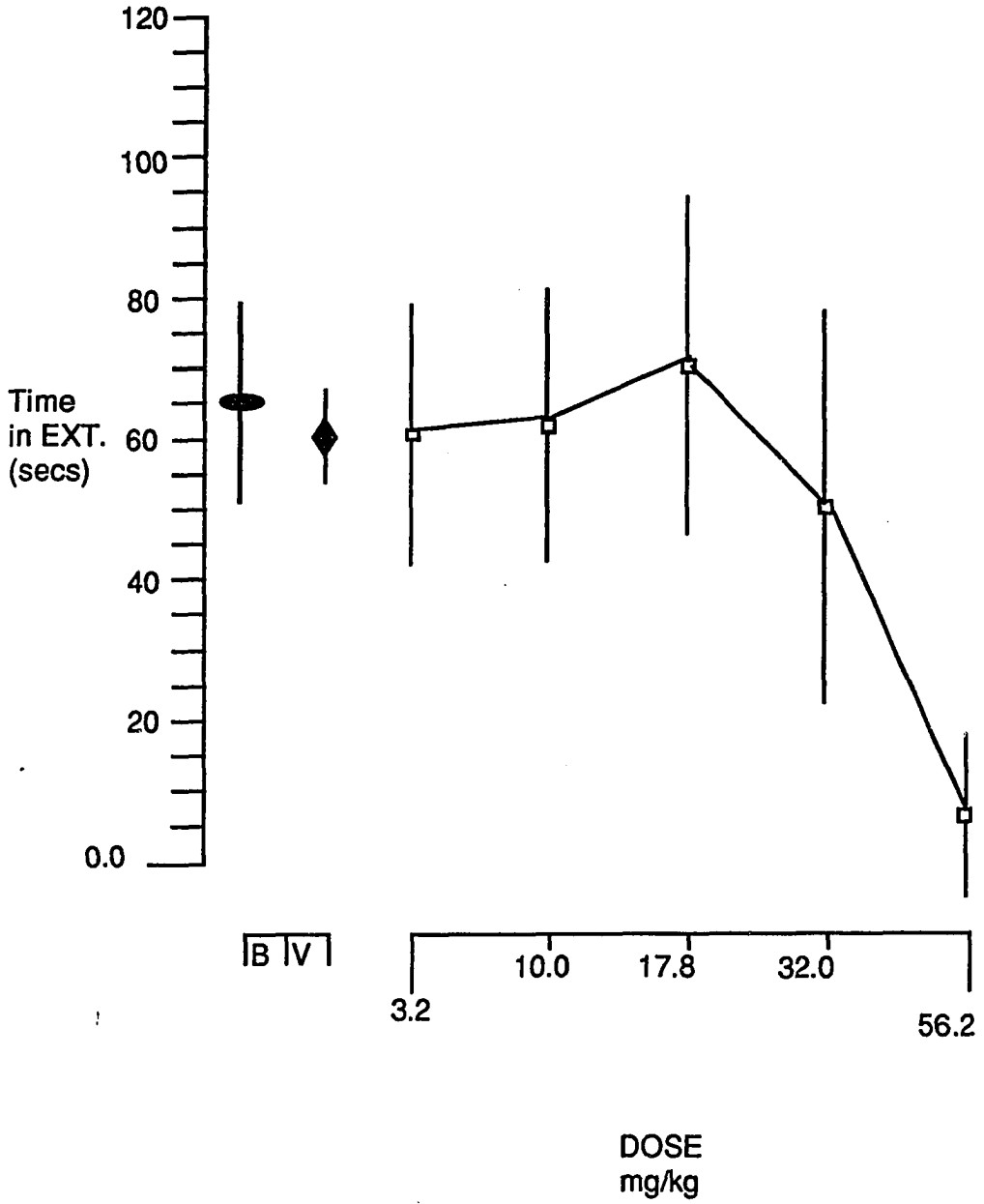

Figure 2. Effects of Cocaine on Peak Time of Responding in the Extinction Component.

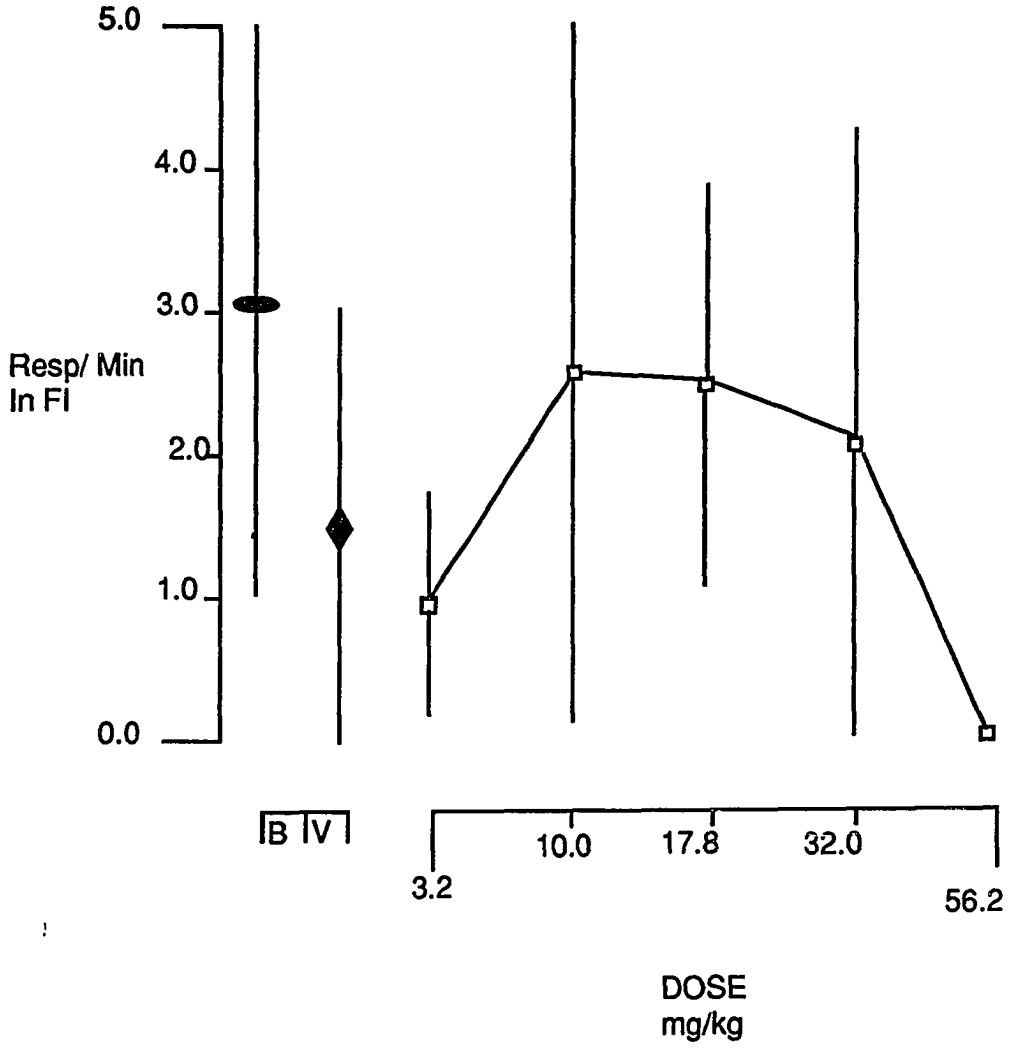

Figure 3. Effects of Cocaine on Overall Response Rates in the Fixed Interval Component.

CHAPTER IV

DISCUSSION

The purpose of this study was to investigate the effects of the stimulant cocaine on what Eckerman et al. (1987) referred to as "timing" in rats. The rationale for this study was two-fold: (1) Analysis of drug effects in terms of the disruption of timing has recently become popular (e.g., Eckerman et al., 1987), but cocaine has not been evaluated under timing procedures; and (2) Cocaine abuse in the United States has reached epidemic proportions among humans, yet much of what is known about the drug's behavioral effects is anecdotal. There is an obvious need for further empirical study of cocaine among humans.

As Eckerman et al. (1987) used the term, "timing" under interval schedules is operationally defined according to (a) the point relative to some reference (e.g., the most recent reinforcer) at which responding begins, and (b) the point relative to that reference at which the rate of responding is maximal. Timing in this sense is relevant to the effects of cocaine because, if under an FI schedule the drug acted to initiate responding sooner after reinforcement than occurred in the absence of drug, the result might appear to be a rate-dependent drug effect. In actuality, however, this would be an indirect result of the earlier initiation of responding. As Eckerman et al. indicated, stimulant drugs might actually reduce high-rate operants and increase low-rate operants, in a manner consistent with rate-dependency (Dews & Wenger, 1977). But, when FI schedules are considered, "a potentially separate effect of these drugs is to shift

temporal discriminations so that earlier times affect behavior as though they were later (i.e., speeded timing)" (Eckerman et al., 1987, p. 1).

Note that the evidence for a shift in temporal discriminations is indirect. Response allocations are surely altered, but the conclusion that this is the result of a disruption of temporal discriminations is an inference. Moreover, it is a small step from inferring a disruption of temporal discriminations to positing an explanatory fiction: The drug disrupts timing (a shorthand replacement for temporal discriminations), and it is this disruption that is responsible for the altered pattern of responding. Here, there is no evidence for disrupted timing apart from the change in behavior that it is supposed to explain. As is made clear in a special issue of Learning and Motivation devoted to "animal timing" (Maier, 1991), from the 1950s to the present the literature has been filled with references to "timing" (which is used as an explanatory fiction). As Michael (1990) explained, terms such as timing can be both valuable and harmful: "As a name for a relatively consistent environment-behavior relation for a particular person--they are useful; as an explanation for the environment-behavior relation (in general)--they are almost always explanatory fictions" (p. 32). Unfortunately, explanatory fictions such as timing appear plausible to laypeople because they are common terms which are presumed to have real and consistent meanings. This is especially true if the word suggests an inner cognitive process, or something that has to do with computers (e.g., an internal pacemaker, or the information processing model).

It is, of course, possible that response allocation under FI schedules can be related to observable behavioral processes. One possibility involves adjunctive, or schedule-induced, behaviors. According to this analysis, responding in a given interval begins with consummatory behavior (e.g., eating), which is followed by interim

activities (e.g., walking in circles) during the period when the probability of food delivery is low. When interim activities cease, operant behavior begins. In short, subjects engage in repetitive and stereotypic "behavioral chains" that are relatively consistent from interval to interval (Killeen & Fetterman, 1988; Staddon, 1977). The consistencies of these chains are responsible for the production of similar patterns of operant responding in each interval of a FI schedule.

If operant response distributions under FI schedules do depend on adjunctive behaviors, drug-induced disruptions of adjunctive behavior would also affect operant responding. Eckerman et al. (1987) proposed that this may occur with stimulant drugs, but did not directly test the possibility.

In the present investigation, cocaine at nontoxic doses did not significantly affect operant response rates or response distributions. These results differ somewhat from those reported by Eckerman et al. (1987), who reported that methylphenidate affected both rates and response distributions (i.e., timing). They did not, however, provide a statistical analysis to support this conclusion, although only group data were presented. Further investigation is required to ascertain the conditions under which stimulants disrupt timing, and how these disruptions relate to the well-established rate-dependent effects of these drugs.

Appendix A

Approved Institutional Animal Care and Use Application

November 17, 1987

TO: Faculty and Students

FROM: Leonard J. Beuving, Chair
Institutional Animal Care and Use Committee
and
Donald E. Thompson
Assistant Vice President for Academic Affairs and
Chief Research Officer

RE: Animal Use and Care at WMU

It is now WMU policy that *all* use of vertebrate animals will be reviewed and approved by our Institutional Animal Care and Use Committee (IACUC) before the project is started. This regulation applies to direct use of vertebrates in WMU facilities or at WMU sponsored functions for any research, teaching or organized recreational purpose.

The enclosed form provides information about this process and is the application you should use to obtain IACUC approval. Please submit the completed form to the Chairperson of IACUC (Leonard J. Beuving, Professor). Approval for proposed use of vertebrates in Category A, in most cases, will be given within ten days. When uses in Categories B and C are proposed, they will be considered at the next IACUC meeting.* These are held in the Research and Sponsored Program offices on a monthly basis. You are welcome to attend.

Please understand that our role is to support humane care and use of animals. These new oversight regulations will cause some inconvenience and delay but they will also improve planning and our accountability with the community that supports us.

**These categories of animal use are defined in the application form.*

INVESTIGATOR CERTIFICATION

If any of the above procedures are changed, I will submit a new protocol.

I understand that any failure to comply with the *Animal Welfare Act*, the provisions of the *DPHS Guide for the Care and Use of Laboratory Animals* and requirements set down by the IACUC may result in the suspension of my animal studies.

Signature: Principal Investigator	*Department*	*Date*
		10-17-90

REVIEW BY THE INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

_____Disapproved ✓ Approved _____ Approved with the provisions listed below

Provisions: _____

IACUC Chairperson	*Date*
Alan Poling	10/30/90

Researcher's Acceptance of Provisions:

Signature: Principal Investigator	*Date*
IACUC Chairperson Final Approval	*Date*

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