EFFECTS OF CHRONIC HALOPERIDOL AND ACUTE COCAINE ON VIGILANCE PERFORMANCE OF RATS

BECKY J. BROCKEL

Effects of Chronic Haloperidol and Acute Cocaine on Vigilance Performance of Rats

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An Abstract

Presented to the

Graduate and Research Council of

Austin Peay State University

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

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by

Becky J. Brockel

April 24, 1992

ABSTRACT

A vigilance task is a sensitive measure of arousal that has been used to measure the effects of centrally acting drugs. Cocaine, a behavioral stimulant, has been found to increase locomotor activity and increase detection rates of males in a vigilance paradigm. Haloperidol, an antipsychotic, has been shown to have various effects on locomotor activity depending on whether it is administered acutely or chronically. These different effects also depend on how many days the rat has been exposed to the drug. It is still unclear what the effects of chronic haloperidol will be on a vigilance task and how it will alter cocaine induced responding. In the present study haloperidol and placebo pretreated animals were tested with various dosages of cocaine on an auditory vigilance task.

Ten male and 10 female rats, approximately 245 days of age, served as subjects in one of two gender balanced pretreatment groups. After training on an auditory vigilance task, rats received 18 days of either 0.0 or 0.2 mg/kg haloperidol pretreatment. Immediately prior to each test session rats received one of three dosages of cocaine (0.0, 1.0, 2.0 mg/kg, ip.). A total of 3 replications were conducted. Following these testing procedures, a fourth replication was conducted, but instead of being tested on the vigilance task on cocaine days, rats were given access

to water for 5 minutes. The amount of water ingested was measured in cc's.

Since the rats responded in a manner that allowed them to obtain nearly all possible reinforcements, the enhancing effects of cocaine could not be observed. Haloperidol did not attenuate the effects of cocaine, but did attenuate overall responding in the first replication. Analysis of the false alarm data indicated that females responded more in the first portion of the session than males did at any time during the test session. Males ingested more water than females.

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To the Graduate and Research Council:

I am submitting herewith a Thesis written by Becky Jo Brockel entitled "Effects of Chronic Haloperidol and Acute Cocaine on Vigilance Performance of Rats." I have examined the final copy of this paper for form and content and I recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Arts with a major in general psychology.

Major Professor

We have read this thesis and recommend its acceptance:

Second Committee Member

Third Committee Member

Accepted for the Graduate and Research Council:

Dean of the Graduate School

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I appreciate the continual encouragement that my family has provided throughout my educational career. Finally, I would like to thank Leslee Wooton, Denise Squire, and Andrew Poklemba. Without their support this thesis would have not been possible.

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CHAPTER 1

Review of the Literature

Introduction

Haloperidol is an antipsychotic that is frequently prescribed in a clinical setting. Cocaine is a centrally acting stimulant that has become a drug of abuse. The effects of cocaine on an individual who is chronically treated with haloperidol are not well known. The effects of these drugs and their interactions on behavior have had somewhat limited attention in the research literature. The present study was designed to compare the effects of various levels of cocaine on haloperidol and placebo pretreated rats performing a vigilance task, a sensitive measure of arousal.

Arousal

An electroencephalogram recording with a desynchronized pattern, low amplitude, and high frequency is associated with cortical arousal. Electrical stimulation of the brainstem reticular formation produces desynchronization of cortical electrical activity (Starzl, Taylor, & Magoun, 1951a). Electrical stimulation of the reticular formation has been observed to increase a monkey's ability to discriminate (Fuster, 1958) and to decrease cats' reaction times (Isaac, 1960). Starzl, Taylor, and Magoun (1951b) found that somatic and auditory

stimuli also produce cortical arousal as measured by cortical electrical activity. Similarly, Isaac (1960) found that both electrical stimulation of the reticular formation and sensory stimulation produced reductions in cats' reaction times. Therefore, not only does sensory stimulation produce cortical arousal, but cortical arousal may be quantified by using behavioral measures.

Vigilance

A vigilance task requires a subject to detect a brief, low intensity stimulus that occurs at irregular intervals. Performance on a vigilance task has been used as a sensitive measure of arousal. For example, Chavez and Delay (1982) studied the effects of ambient illumination on human vigilance performance and found that illumination enhances performance. Similar results were obtained with squirrel monkeys (Delay & Isaac, 1980). Researchers also have used a vigilance task to measure arousal produced by centrally acting drugs (Delay & Isaac, 1980; Squire & Golden, 1988; Squire 1989; Grilly & Grogan, 1990).

Cocaine

Cocaine, a behavioral stimulant (White, 1991), is believed to alter the levels of the neurotransmitters norepinephrine, dopamine, and serotonin (Ho, Taylor, Estevez, Englert, & McKenna, 1977; Scheel-Kruger, Braestrup, Nielson, Golembiowska, & Mogilnicka, 1977;

Bhattacharyya, Aulakh, Pradhan, Ghosh, & Pradhan, 1979; Hurd, Weiss, Koob, & Ungerstedt, 1990). Norepinephrine has been associated with states of cortical arousal (Azzaro, & Rutledge, 1973; Carey, 1976; Ho, et al., 1977; Van Dyke & Byck, 1977). Dopamine, a precursor to norepinephrine, also is believed to play a major role in behavioral arousal and has been hypothesized to mediate cocaine induced schedule-controlled behavior (Ho, et al., 1977; Scheel-Kruger, et al., 1977; Spealman, 1990). Lower levels of serotonin are associated with activity and higher levels with reduced cortical arousal (Jouvet, 1967; Scheving, Harrison, Gordon, & Pauly, 1968).

According to Scheel-Kruger, et al. (1977), cocaine's main mechanism of action is the blocking of reuptake of dopamine and noradrenaline. These researchers reported that cocaine also affects the release mechanism of these neurotransmitters. Hurd, et al. (1990) reported that acute administration of cocaine increased dopamine overflow in the caudate-putamen. With repeated administrations of cocaine, dopamine overflow was attenuated and extracellular acetylcholine levels were decreased. Kalivas and Duffy (1990) found that acute administrations of cocaine increased extracellular dopamine concentrations in the nucleus accumbens, but this increase was not correlated with a motor stimulant response. Repeated administration of cocaine lowers serotonin concentrations in the brain

(Ho, et al., 1977). Scheel-Kruger, et al. (1977) described the response of rats to cocaine after being pretreated with nialamide, a monoamine oxidase inhibitor, as amphetamine-like.

Cocaine produces a desynchronized electroencephalogram recording and increases multiple unit activity of the reticular formation (Wallach & Gershon, 1971). Research has indicated that cocaine increases locomotor activity following acute administrations (Ho, et al., 1977; Scheel-Kruger, et al., 1977; Wood & Golden, 1987, and Kalivas & Duffy, 1990). It also has been demonstrated that cocaine increases detection rates of rats on a vigilance task without increasing false alarm responses (Squire, 1989). No increase in false alarms indicates that the increase in detection rates was not due to an overall increase in responding. In the same study by Squire (1989), amphetamine was found to increase false alarm responding without increasing detection rates. Grilly and Grogan (1990) found that cocaine enhanced vigilance performance of rats equally well for both low and high arousal conditions.

Haloperidol

Haloperidol, an antipsychotic drug, lowers dopamine levels in the brain by blocking post-synaptic dopamine receptors (Bhattacharyya, et al., 1979; Lappalainen, Hietala, Koulu, Seppälä, Sjöholm, & Syvälahti, 1990).

Lappalainen, et al. (1990) reported that haloperidol had no significant effects on serotonin. It has been suggested by Ramirez and Wang (1986) that acute administration of haloperidol increases norepinephrine neurotransmission, whereas chronic administration decreases norepinephrine neurotransmission. Researchers have found that haloperidol modifies the effects of cocaine (Scheel-Kruger, et al., 1977; Bhattacharyya, et al., 1979). In contrast, LeDuc (1989) found that 12 days of haloperidol pretreatment decreased activity levels but did not attenuate the effects of cocaine. After 18 days of pretreatment, rats exhibited an increase in locomotor activity. This increase in locomotor activity was enhanced by acute administrations of cocaine. Rastogi, Singhal, and Lapierre (1982) suggested that the increases in locomotor activity of rats after chronic treatment with haloperidol was due to supersensitivity of dopamine receptors.

Gender Differences

In any type of behavioral research gender differences must be addressed. Females exhibited more locomotor activity when treated with cocaine under alternating quiet and noise conditions than did males (Wood, 1986). Squire (1989) found that females had more correct detections on a vigilance task than did males. Females responded consistently across trial blocks, whereas males decreased detection rates across trial blocks. Haloperidol

attenuated the effects of illumination on locomotor activity with male rats but not females (Murphy & Golden, 1982). Male rats pretreated with haloperidol had fewer responses on an operant task than females (Van Hest, Van Haaren, & Van De Poll, 1988). Van Hest, et al. (1988) concluded that males are affected by the inhibitory effect of haloperidol more than are females. LeDuc (1989) found that after 6 days of haloperidol pretreatment males engaged in more cocaine induced locomotor activity than females. No gender differences were observed for the 12 day pretreatment group. Females in the 18 day pretreatment group were more active than were males.

Summary

Vigilance has been used in the past as a sensitive measure of cortical arousal. The literature suggests that dopamine plays an important role in the behavioral effect of cocaine. It is still unclear whether chronic haloperidol pretreatment reverses the effects of cocaine or whether it enhances the effects. Therefore, this study was designed to examine the effects of chronic haloperidol and acute cocaine on the vigilance performance of rats. It was hypothesized that females would receive more reinforcements than males. Cocaine was expected to facilitate correct detections in a dose dependent manner without increasing false alarm responses. Haloperidol pretreatment was expected to modify cocaine induced vigilance performance.

It was predicted that haloperidol pretreatment would cause the rats to increase false alarm responses but not correct detections.

CHAPTER 2

Method

Subjects

Twelve male and 12 female CD derived rats born at Austin Peay State University, approximately 245 days of age at the beginning of training, served as subjects. Rats were housed individually with food available ad lib. Water was available for 5 minutes daily one hour after testing. A LD 12:12 lighting schedule (lights on 6 a.m. to 6 p.m. CST) was maintained throughout the study.

Apparatus

The rats were tested in 24.7 x 18.0 x 18.0 cm galvanized cages. The front of the cage was wood with a 5.8 cm diameter opening centered 4.0 cm above the mesh floor. An acrylic panel located in the opening and hinged at the top served as the manipulandum. The panel required a displacement of .8 cm for detection. The rats were tested in individual sound attenuated cubicles which were closed on all sides. Illumination of 765 lx was provided by a 20w fluorescent lamp mounted at the top of each cubicle. The stimulus was a tone of 4kHz produced by solid state circuitry (Delay, Golden, & Steiner, 1978). This stimulus, measuring 3-4 db SPL (A scale, re: 20 $\mu N/M^2$) above the ambient noise level of 48 db SPL, was presented

to the rats through speakers mounted on the front of each cage. A reinforcement of .1 ml of water was delivered to a pedestal located directly adjacent to and right of the panel. Presentation of the trials and collection of the data was controlled by a micro computer located in another room.

Procedure

Training. Training began with a continuous tone, and the length of the tone on period was gradually decreased across training sessions to a duration of 2 seconds. Tone off periods were gradually lengthened across training sessions to a duration ranging from 40-162 seconds. A hold time was gradually introduced across training sessions, increasing from 2 to 10 seconds. The hold time had to elapse without a false alarm response before the tone was presented. When responding stabilized, training was continued using the actual contingencies to be used for testing.

Testing. The programmed tone off periods during testing sessions ranged from 80-180 seconds with a mean of 130 seconds. A tone on period of 2 seconds with a 2 second hold was used during testing sessions. A hold time of 10 seconds was used during training. This ten second hold ensured that detections were due to increases in vigilance performance and not to an increase in overall responding. The animals were allowed to receive only one reinforcement

per trial. Another measure of false alarm responding was produced by subtracting programmed false alarm time from actual false alarm time. This measure helped to determine if there was an increase in overall responding. Twenty-seven trials were completed during each testing session. Each testing session lasted approximately one hour.

Drugs. Half of the males and half of the females were assigned to one of two pretreatment groups which received 18 days of intraperitoneal injections of either 0.0 or 0.2 mg/kg of haloperidol (in bacteriostatic water, 1 ml/kg) which was generously supplied by McNeill Laboratories. Pretreatment injections were administered immediately following the last training session and daily thereafter. Test sessions were conducted every other day for 18 days. Drug days occurred every other day to ensure that no carry over effects of the cocaine would confound the data. Immediately prior to the start of each testing session the rats received intraperitoneal injections at a volume of 1 ml/kg in isotonic saline, of one of three levels of cocaine hydrochloride (Sigma Chemical, 0.0, 1.0, 2.0 mg/kg, measured as the salt). Dosages were presented in a semi-randomized order such that no rat received the same dosage of cocaine on two consecutive drug days. Training and testing took place between 6:30 am and 11:00 am CST.

Following these testing procedures, a fourth replication was conducted. On drug days, the rats received either 0.0, 1.0, or 2.0 mg/kg cocaine in the same manner as above, but instead of being tested on the vigilance task, the rats were given water for 5 minutes. The amount of water intake was measured in cc's.

CHAPTER 3

Results

Analysis of variance was used to determine significant main effects and interactions for the reinforcement data, the false alarm data, and the extended false alarm time. Due to 1 fatality, an animal from each group was dropped from the data for the final analysis. Twenty rats, 5 in each gender balanced group, were used for the final analysis. The data were collapsed into 5 blocks of 5 trials to observe within session changes. Simple effects analysis and the Studentized Range Test (SRT) were used to determine differences between means. Probabilities reported for the SRT have been adjusted for the number of comparisons.

Analysis of the reinforcement data indicated a significant main effect for blocks $F(4,64) = 6.62$, $p<.001$. The amount of reinforcements earned was significantly higher in blocks 1 and 2 than in blocks 4 and 5, SRT, $p<.05$, (see Figure 1). A main effect for replications was also observed, $F(2,32) = 10.57$, $p<.001$. As shown in Figure 2, more reinforcements were earned in the second and the third replication than in the first, SRT, $p<.05$. A main effect for pretreatment was found to be significant but in a manner that was not independent of replications or

Figure 1. Reinforcement Responding Across Five 5 Trial Blocks.

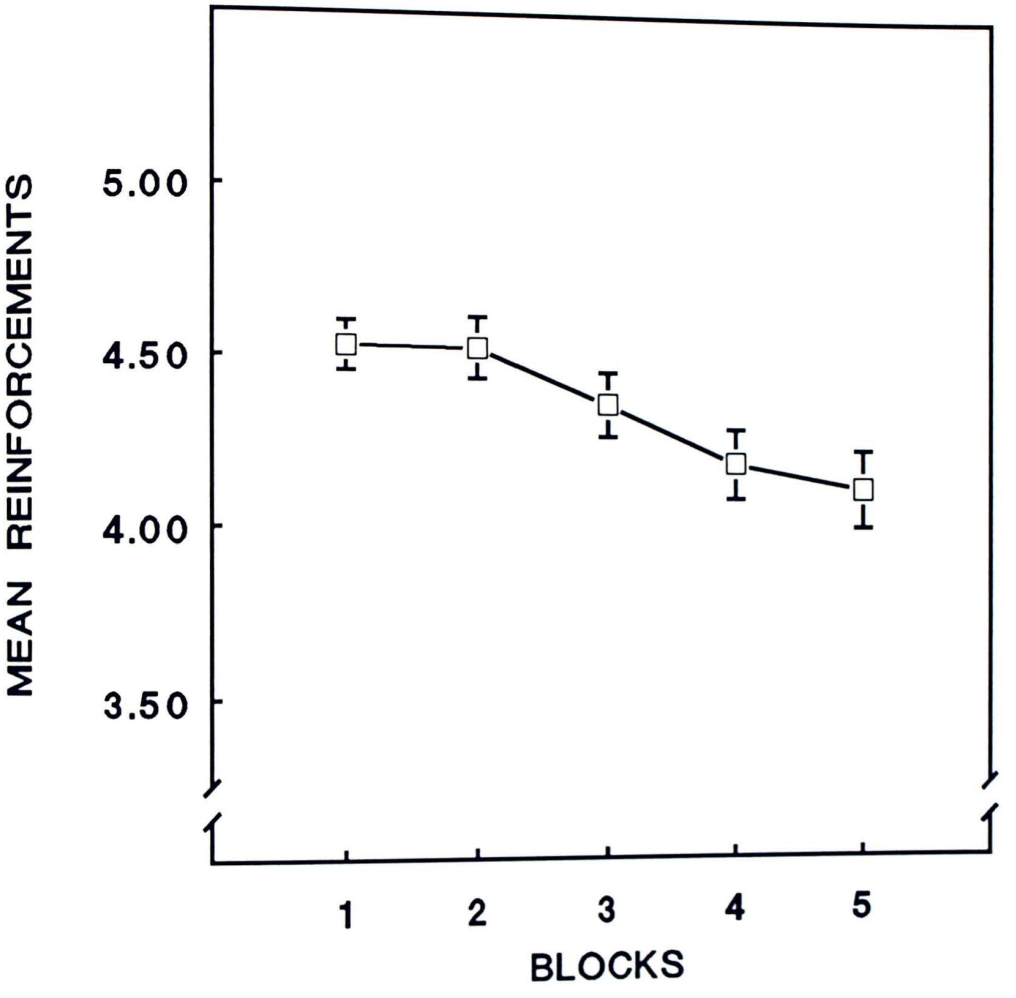
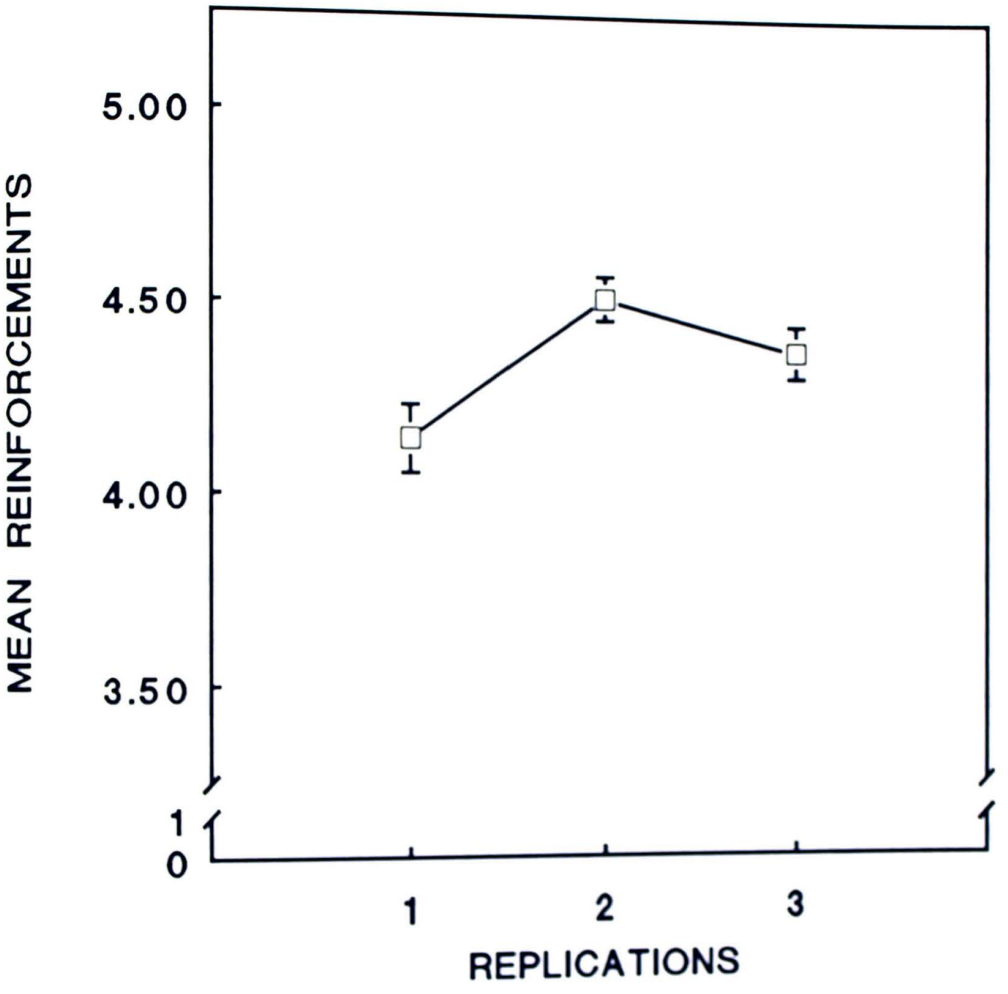

MEAN REINFORCEMENTS
5.00
4.50
4.00
3.50
1
2
3
4
5
BLOCKS

Figure 2. Reinforcement Responding Across 3 Replications.

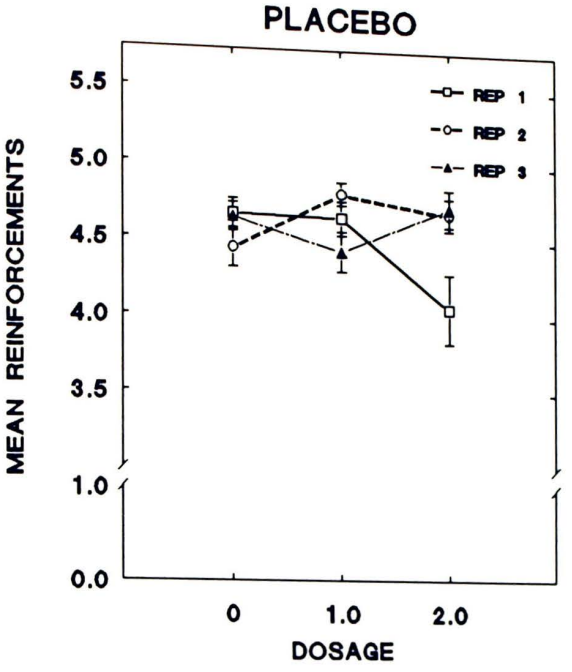

MEAN REINFORCEMENTS
5.00
4.50
4.00
3.50
1
0
1
2
3
REPLICATIONS

cocaine dose, $F(4,64) = 3.08$, $p<.05$ (see Figure 3). In the first replication, the haloperidol group under the influence of 0.0 mg/kg of cocaine received fewer reinforcements than the haloperidol group in the second replication and the placebo group in all replications under the same dose of cocaine, SRT, $p<.05$. The haloperidol group under the influence of 2.0 mg/kg of cocaine in the first replication received fewer reinforcements than the placebo group during the second and the third replication under the same dose of cocaine, SRT, $p<.05$.

Analysis of the number of false alarms revealed a main effect for the 5 blocks of 5 trials each, $F(4,64) = 9.01$, $p<.001$. As Figure 4 shows, more false alarms were observed in block 1 than in all other blocks, SRT, $p<.05$. The pretreatment groups differed in a manner that was not independent of blocks, $F(4,64) = 5.49$, $p<.001$ (see figure 5). The placebo group in the first block had more false alarms than the placebo animals in the remaining blocks or the haloperidol groups in all blocks, $p<.05$. Differences occurred among the 5 blocks that were not independent of gender, $F(4,64) = 2.98$, $p<.05$ (see Figure 6). Females in block 1 had more false alarms than did females in the remaining blocks or males in all blocks, SRT, $p<.05$.

An analysis of the false alarm extended time indicated an interaction among pretreatment group, gender, and blocks, $F(4,64) = 3.63$, $p<.005$. Simple effects analysis

Figure 3. Reinforcement Responding Across 3 Replications for Placebo and Haloperidol Groups Under the Effects of Cocaine (0.0, 1.0, 2.0).


PLACEBO
MEAN REINFORCEMENTS
5.5
5.0
4.5
4.0
3.5
1.0
0.0
REP 1
REP 2
REP 3
0
1.0
2.0
DOSAGE

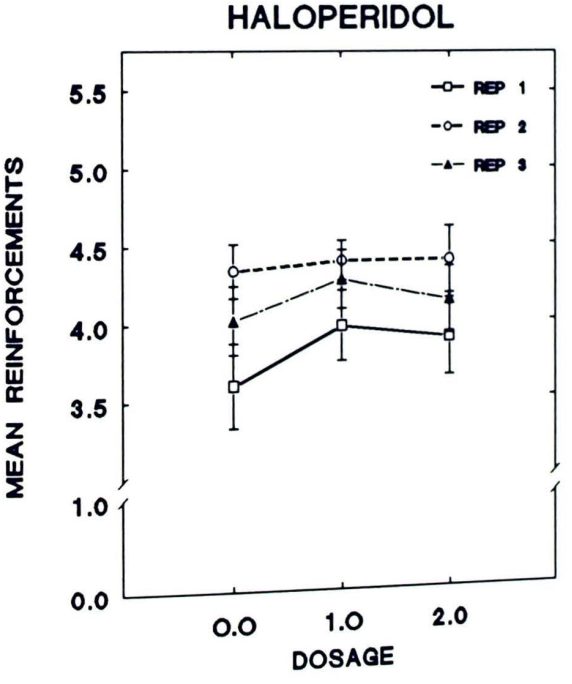

HALOPERIDOL
MEAN REINFORCEMENTS
5.5
5.0
4.5
4.0
3.5
1.0
0.0
REP 1
REP 2
REP 3
0.0
1.0
2.0
DOSAGE

Figure 4. False Alarm Responding Across Five 5 Trial Blocks.

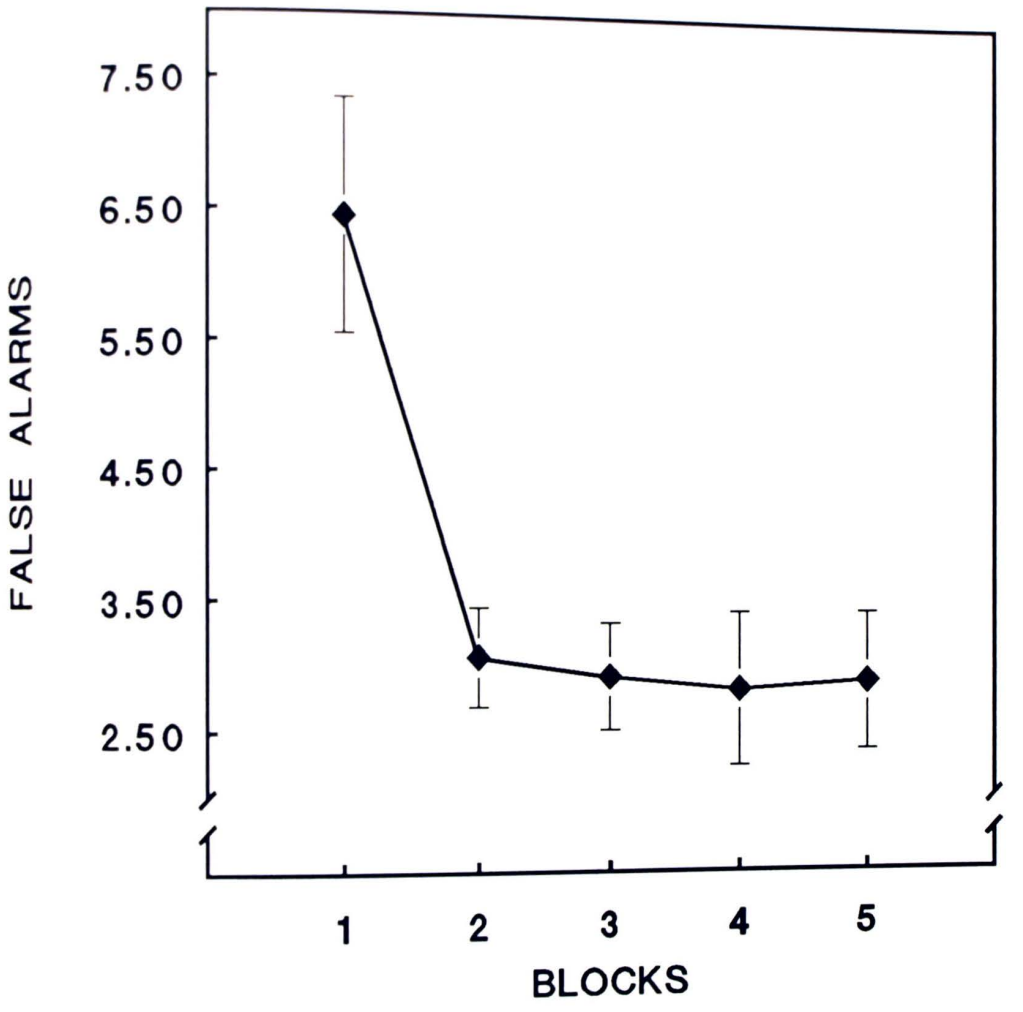

7.50
6.50
5.50
4.50
3.50
2.50
FALSE ALARMS
1
2
3
4
5
BLOCKS

Figure 5. False Alarm Responding Across Five 5 Trial Blocks for Placebo and Haloperidol Groups.

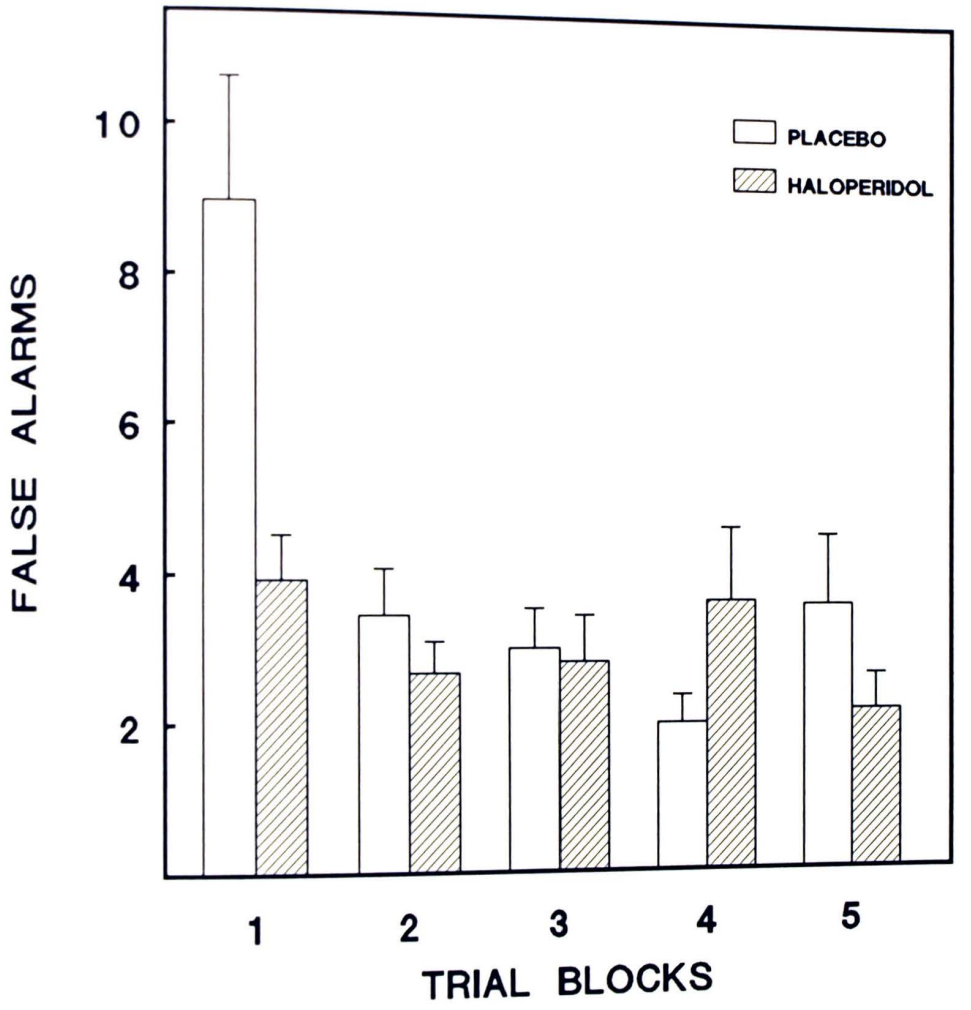
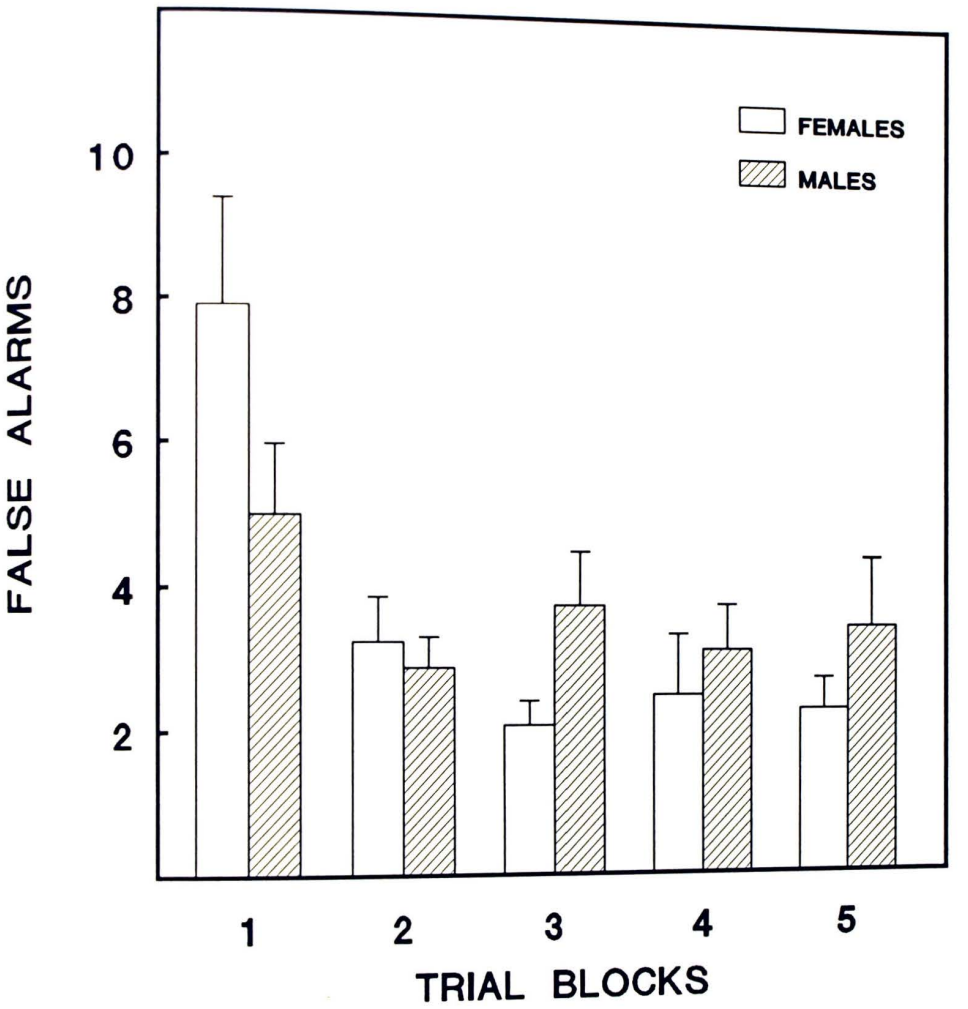

FALSE ALARMS
10
8
6
4
2
PLACEBO
HALOPERIDOL
1
2
3
4
5
TRIAL BLOCKS

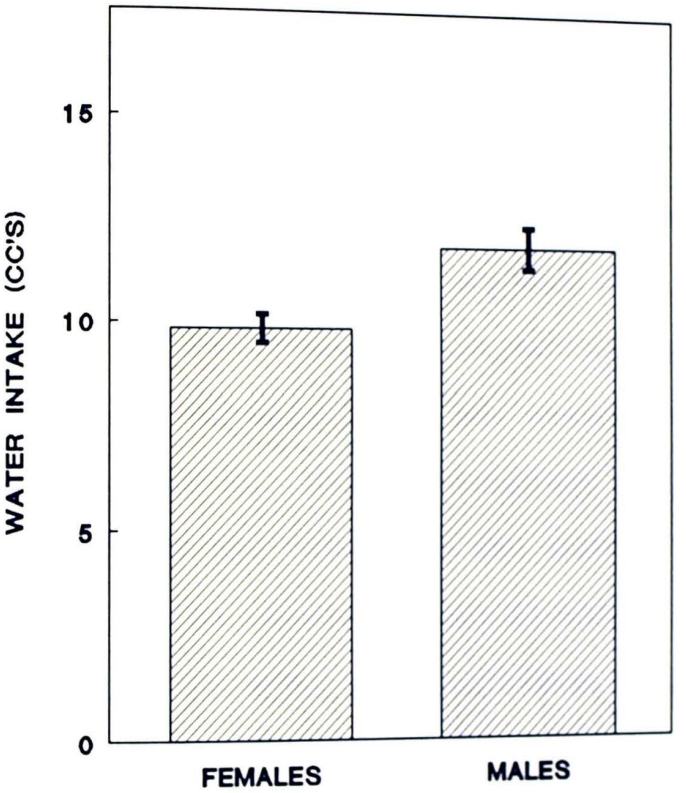
Figure 6. False Alarm Responding Across Five 5 Trial Blocks for Females and Males.


FEMALES
MALES
10
8
6
4
2
FALSE ALARMS
1
2
3
4
5
TRIAL BLOCKS

indicated that this interaction was due to a pretreatment by block interaction for females, $\underline{F}(4,32) = 3.04$, $\underline{p}<.05$. Placebo females in block 1 had longer false alarm extended times than did haloperidol females in blocks 3 and 5.

Analysis of the water intake data showed a significant main effect for gender, $\underline{F}(1,16) = 7.47$, $\underline{p}<.05$. As indicated by Figure 7, males drank more water than did females. No other effects were found to be significant.

Figure 7. Amount of Water Intake for Females and Males.


WATER INTAKE (CC'S)
15
10
5
0
FEMALES
MALES

CHAPTER 4

Discussion

The purpose of the present study was to compare haloperidol and placebo pretreated animals under various dosages of cocaine on a vigilance task. Based on the findings of Squire (1989), it was predicted that cocaine would enhance detection rates and that females would obtain more reinforcements than males. Haloperidol pretreatment was expected to alter cocaine induced responding. This prediction was based on the findings of LeDuc (1989).

The current study does not support the findings of Squire (1989). Cocaine did not significantly enhance detection rates, and therefore, the amount of reinforcements earned. This discrepancy could be due to the familiarity of the rats with the task. In the study by Squire (1989), males received significantly fewer reinforcements while under the influence of 0.0 mg/kg cocaine than did females receiving the same dosage of cocaine. In the present study both males and females responded in a manner that allowed them to obtain nearly all reinforcements. If cocaine did enhance performance, it would not have been evident in the present study.

In order to observe the enhancing effect cocaine may have on performance on a vigilance task, steps must be

taken to ensure that the rats are not receiving near maximum levels of reinforcement. This should not be done by reducing the training time of the rats because any improvement observed could actually be an enhancement in learning and not performance. Grilly and Grogan (1990) used a technique that required the animals to remain in a certain range of earned reinforcements. If rats started to receive more reinforcemts than allowed by the set range, the task was made more difficult by shortening the length of the stimulus. If the rats started to receive reinforcements less than the amount of the set range, the stimulus would be lengthened to make the task easier. This may be an answer to the problem of the current study. It could be argued that the rats are always relearning the task, and therefore, cocaine could be enhancing learning and not performance.

It may be more appropriate to use a vigilance task that is more difficult, but in which properties of the stimulus do not need to be altered each test session. One such task was used by Skjoldager and Fowler (1991). In this paradigm rats were required to respond to a visual stimulus and to refrain from responding to distractor visual stimuli. This task seems to be appropriate to look for performance enhancing properties of cocaine because even though the rats can learn the task, the task is too

difficult for them to receive the maximum number of reinforcements.

Similar to the findings of Squire (1989), cocaine did not increase false alarm responding or lengthen extended false alarm times. The present study indicates that cocaine did not increase overall responding. This substantiates the conclusion of Squire (1989) that enhancement of performance caused by cocaine was not due to an increase in overall activity.

It was predicted that haloperidol would modify cocaine induced vigilance performance. Even though the haloperidol group in the first replication under the influence of 2.0 mg/kg of cocaine received fewer reinforcements than the placebo group in the second and third replication under the same dose of cocaine, no consistent attenuating effects of cocaine were observed. Since the enhancing properties of cocaine could not be observed in this study, it is difficult to ascertain what effects haloperidol had on cocaine induced responding.

Haloperidol did initially attenuate overall responding. This is observed in the first replication in which the haloperidol group under the influence of 0.0 mg/kg cocaine received fewer reinforcements than the placebo group in all replications under the same dosage of cocaine. These findings are not consistent throughout the study. Since the haloperidol group only showed reduced

numbers of reinforcements in the first replication, it is possible that continued haloperidol pretreatment caused alterations that would reverse the initial attenuating effects of haloperidol. This is consistent with the findings of LeDuc (1989) and Rastogi, et al. (1982) in which chronic administration of haloperidol was found to increase locomotor activity. Rastogi, et al. (1982) suggest that this increase is do to supersensitivity of dopamine receptors. LeDuc (1989) found that cocaine enhanced the increaases in locomotor activity that were caused by chronic haloperidol treatment. The current study did not obtain similar results. This could be due to the nature of the task. The task used in this study does not require gross locomotor activity. Cocaine alone administered acutely increases locomotor activity (Ho, et al., 1977; Scheel-Kruger, et al., 1977; Wood & Golden, 1987; Kalivas & Duffy, 1990), but does not increase overall responding on a vigilance task (Squire, 1989).

Since the effects of drugs change with respect to time, it is important to observe within session changes in behavior (Lynch & Carey, 1986). In the present study, individual trials were grouped into 5 blocks of 5 trials each. More reinforcements were earned in the first two blocks than in the last two. Rats had more false alarms in the first block than in the remaining 4 blocks. These two findings could be caused by general fatigue of the rats, or

to the animals becoming satiated, or a combination of the two.

Fewer reinforcements were earned in the first replication than in the second or the third. This indicates that responses to haloperidol and to cocaine are not consistent across sessions. Changes due to drugs such as cocaine and haloperidol do not just occur and then stabilize, they continue to alter the organism's physiological state and behavior. This is evident from the different effects obtained with the varying length of haloperidol pretreatment (LeDuc, 1989) and to the continuing alterations of norepinephrine, dopamine, and serotonin caused by cocaine (Ho, et al., 1977; Bhattacharyya, et al., 1979; Hurd, et al., 1990; Scheel-Kruger, et al., 1977).

Based on Squire (1989), it was predicted that females would have higher detection rates than males. This was not observed in the present study. Gender differences in detection rates were probably not observed because all rats in the current study were responding at a high level of accuracy. In contrast, placebo males in the study by Squire (1989) obtained significantly fewer reinforcements than did placebo females. The only gender difference in the present study was observed in false alarm responding. Females in block 1 had significantly more false alarms than did males indicating that females in the first portion of

the session responded more than males did at any time during the test session.

The water intake data were collected to ensure that any pretreatment or cocaine dose effects were not due to the drugs altering the reinforcing properties of the water. Since no main effects for pretreatment or cocaine dose were observed, it is obvious that at the dosages employed in the present study, these drugs do not alter the reinforcing properties of water to water deprived rats, at least not in a manner that would confound any results due to drug treatment. Males did ingest more water than females. This is expected since males have more body mass than females.

In summary, any attention enhancing properties that cocaine may have could not be observed in the present study because the rats' detection rates were near maximum levels. Haloperidol did not attenuate cocaine induced responding, but did attenuate overall responding in the first replication. It is hypothesized that no attenuating effects were observed in subsequent replications because the effect of chronic administration of haloperidol can eventually lead to supersensitivity and increases in activity. This study supports the use of within session data and the use of both genders when studying the effects of centrally acting substances. Finally, this study indicates that when using vigilance paradigms, it is important to make the task difficult enough so that the

rats cannot obtain maximum detection rates and to ensure that any changes that are observed are changes in performance and not learning.

APPENDIX

TABLE 1

Analysis of Variance for Reinforcements

SOURCE	SS	df	MS	F
TOTAL	1475.96	899		
Between Groups	588.31	19	30.96	
Pretreatment (A)	44.44	1	44.44	1.45
Gender (B)	38.44	1	38.44	1.25
AxB	15.99	1	15.99	0.52
Error	489.43	16	30.58	
Within Treatments	887.64	880		
Blocks (C)	26.21	4	6.55	6.62 **
AxC	3.47	4	0.86	0.87
BxC	1.77	4	0.44	0.44
AxBxC	5.38	4	1.34	1.36
Replications (D)	20.94	2	10.47	10.57 **
AxD	5.04	2	2.52	2.54
BxD	2.24	2	1.12	1.13
AxBxD	5.00	2	2.50	2.52
Dosage (E)	3.04	2	1.52	1.53
AxE	2.62	2	1.31	1.32
BxE	0.85	2	0.42	0.43
AxBxE	0.40	2	0.20	0.20
CxD	4.37	8	0.54	0.55
AxCxD	1.86	8	0.23	0.23
BxCxD	3.84	8	0.48	0.48
AxBxCxD	11.57	8	1.44	1.46
CxE	5.63	8	0.70	0.71
AxCxE	4.38	8	0.54	0.55
BxCxE	8.06	8	1.00	1.01
AxBxCxE	7.47	8	0.93	0.94
DxE	5.31	4	1.32	1.34
AxDxE	12.22	4	3.05	3.08 *
BxDxE	4.15	4	1.03	1.04
AxBxDxE	8.88	4	2.22	2.24

TABLE 1 (Continued)

SOURCE	SS	df	MS	F
CxDxE	7.54	16	0.47	0.47
AxCxDxE	14.23	16	0.88	0.89
BxCxDxE	5.92	16	0.37	0.37
AxBxCxDxE	8.16	16	0.51	0.51
Error	696.96	704	0.99	

* $p<.05$
** $p<.001$

TABLE 2

Analysis of Variance for False Alarms

SOURCE	SS	df	MS	F
TOTAL	55757.52	899		
Between Groups	9335.44	19	491.33	
Pretreatment (A)	300.44	1	300.44	0.54
Gender (B)	0.36	1	0.36	0.00
AxB	201.63	1	201.63	0.36
Error	8832.99	16	552.06	
Within Treatments	46422.08	880	52.75	
Blocks (C)	1786.31	4	446.57	9.01 **
AxC	1089.07	4	272.26	5.49 **
BxC	590.98	4	147.74	2.98 *
AxBxC	215.06	4	53.76	1.08
Replications (D)	163.48	2	81.74	1.65
AxD	295.01	2	147.50	2.97
BxD	3.25	2	1.62	0.03
AxBxD	28.28	2	14.14	0.28
Dosage (E)	137.86	2	68.93	1.39
AxE	200.68	2	100.34	2.02
BxE	148.44	2	74.22	1.49
AxBxE	180.72	2	90.36	1.82
CxD	496.26	8	62.03	1.25
AxCxD	343.72	8	42.96	0.86
BxCxD	341.32	8	42.66	0.86
AxBxCxD	181.47	8	22.68	0.45
CxE	355.54	8	44.44	0.89
AxCxE	251.26	8	31.40	0.63
BxCxE	304.74	8	38.09	0.76
AxBxCxE	645.43	8	80.67	1.62
DxE	156.75	4	39.18	0.79
AxDxE	197.43	4	49.35	0.99
BxDxE	250.75	4	62.68	1.26
AxBxDxE	298.68	4	74.67	1.50

TABLE 2 (Continued)

SOURCE	SS	df	MS	F
CxDxE	620.59	16	38.78	0.78
AxCxDxE	899.65	16	56.22	1.13
BxCxDxE	807.02	16	50.43	1.01
AxBxCxDxE	561.98	16	35.12	0.70
Error	34870.20	704	49.53	

* $p<.05$
** $p<.001$

TABLE 3

Analysis of Variance for Extended False Alarm Times

SOURCE	SS	df	MS	F
TOTAL	7623.83	899		
Between Groups	535.36	19	28.17	
Pretreatment (A)	45.83	1	45.83	1.70
Gender (B)	40.57	1	40.57	1.50
AxB	18.51	1	18.51	0.68
Error	430.44	16	26.90	
Within Treatments	7088.46	880		
Blocks (C)	70.67	4	17.66	2.14
AxC	14.49	4	3.62	0.44
BxC	16.12	4	4.03	0.48
AxBxC	119.76	4	29.94	3.63 *
Replications (D)	2.83	2	1.41	0.17
AxD	28.78	2	14.39	1.74
BxD	0.54	2	0.27	0.03
AxBxD	8.06	2	4.03	0.48
Dosage (E)	12.45	2	6.22	0.75
AxE	6.74	2	3.37	0.40
BxE	14.04	2	7.02	0.85
AxBxE	0.48	2	0.24	0.02
CxD	14.52	8	1.81	0.22
AxCxD	23.99	8	2.99	0.36
BxCxD	48.31	8	6.03	0.73
AxBxCxD	46.74	8	5.84	0.70
CxE	31.79	8	3.97	0.48
AxCxE	83.80	8	10.47	1.27
BxCxE	33.40	8	4.17	0.50
AxBxCxE	67.83	8	8.47	1.02
DxE	26.73	4	6.68	0.81
AxDxE	6.23	4	1.55	0.18
BxDxE	29.92	4	7.48	0.90
AxBxDxE	40.36	4	10.09	1.22

TABLE 3 (Continued)

SOURCE	SS	df	MS	F
CxDxE	146.52	16	9.15	1.11
AxCxDxE	203.86	16	12.74	1.54
BxCxDxE	104.58	16	6.53	0.79
AxBxCxDxE	83.75	16	5.23	0.63
Error	5801.04	704	8.24	

* $p<.005$

TABLE 4

Analysis of Variance for Water Intake

SOURCE	SS	df	MS	F
TOTAL	382.98	59		
Between Groups	186.31	19	9.80	
Pretreatment (A)	0.41	1	0.41	0.05
Gender (B)	58.01	1	58.01	7.47 *
AxB	3.74	1	3.74	0.48
Error	124.13	16	7.75	
Within Treatments	196.66	40	4.91	
Dosage (C)	16.13	2	8.06	1.54
AxC	8.13	2	4.06	0.77
BxC	3.73	2	1.86	0.35
AxBxC	1.60	2	0.80	0.15
Error	167.06	32	5.22	

* $p<.05$

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