HALOPERIDOL PRETREATMENT MODIFICATION OF COCAINE INDUCED LOCOMOTOR ACTIVITY

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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

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May 1989

ABSTRACT

Cocaine, a central nervous system stimulant, is known to produce behavioral arousal. It reduces levels of the neurotransmitters dopamine and norepinephrine in the rat brain and increases locomotor activity levels. When dopamine levels in the brain are reduced, cocaine has little or no effect on locomotor activity. Haloperidol, an antipsychotic drug with potent antidopaminergic properties, decreases dopamine content in the brain. A single dose of haloperidol produces a decrease in locomotor activity while chronic doses produce the opposite effect. Haloperidol also has been reported to reverse cocaine induced locomotor activity changes. The present study compares the effects of three haloperidol pretreatment durations on cocaine induced locomotor activity.

Thirty-six rats, approximately 160 days of age, served as subjects in one of three gender balanced groups. One half of each group received haloperidol (.2 mg/kg in bacteriostatic water) while the remaining rats received only bacteriostatic water. The three groups were given pretreatment injections for 18, 12, and 6 days respectively, prior to the start of testing with cocaine. The rats received one of three dosages of cocaine (0.0, 7.5, 15.0 mg/kg) every other day during testing, while

To the Graduate and Research Council:

I am submitting herewith a Thesis written by Patricia Ann LeDuc entitled "Haloperidol Pretreatment Modification of Cocaine Induced Locomotor Activity." 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 Master of Arts, with a major in 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

ACKNOWLEDGMENTS

My gratitude is extended to Dr. Anthony Golden for his time and assistance during the course of this research. I would also like to thank my other committee members, Dr. Susan Kupisch and Dr. Garland Blair, for their support and guidance.

Most of all, I would like to thank my husband, Hoss, for the many times he picked up my spirit and our house when I was not able to.

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CHAPTER 1

Review of the Literature

History

According to Van Dyke and Byck (1977), the pharmacological effects of cocaine were initially studied in 1880 by Von Anrep. The first descriptions of cocaine's effect on the central nervous system were provided by Aschenbrandt in 1883 and Freud in 1884. By the early 1900's, cocaine could be found in many medications and was accepted as a local and regional anesthetic. As the effects of cocaine on behavior became increasingly uncertain, governments began to restrict its use (Van Dyke & Byck). Cocaine now is classified generally as a CNS stimulant and falls into the group labeled behavioral stimulants (Julien, 1981). Many derivatives of amphetamine and methylphenidate also are labeled behavioral stimulants. Behavioral stimulants are known to elevate mood, increase alertness, and reduce fatigue. In high dosages, they can produce anxiety, irritability, and patterns of psychotic behavior (Julien).

Neurotransmitters

Norepinephrine, one of the brain's neurotransmitters, has been linked with arousal reactions (Azzaro & Rutledge, 1973; Carey, 1976). Julien (1981) has suggested that the

stimulant action of cocaine may be a result of its ability to potentiate or mimic the action of norepinephrine in the brain. Cocaine also may prolong the action of norepinephrine by slowing down re-uptake at the postsynaptic receptor sites, leaving the receptors stimulated longer (Leventhal, 1983).

Recent studies have suggested that dopamine, another major monoaminergic neurotransmitter and a precursor of norepinephrine (Leventhal, 1983), also may play a part in behavioral arousal (Ho, Taylor, Estevez, Englert, & McKenna, 1977; Scheel-Kruger, Braestrup, Nielson, Golembiowska, & Mogilnicka, 1977). Ho et al. found that repeated administration of cocaine reduced levels of both norepinephrine and dopamine in the rat brain while it increased locomotor activity. Wallach and Gershon (1971) reported that both d-amphetamine and cocaine administered to cats desynchronized their EEGs. EEG desynchronization, a shift in EEG patterns from synchronized, high voltage slow activity to desynchronized, low voltage fast activity, has been reported as an indication of both cortical (Starzl, Taylor, & Magoun, 1951) and behavioral arousal (Segundo, Arana, & French, 1955).

Cocaine and D-amphetamine

A comparative study of d-amphetamine and cocaine found that both drugs caused the release of dopamine in the brain

(Moore, Chiueh, & Zeldes, 1977). Moore et al. reported, however, that these two drugs were not equally potent. D-amphetamine increased the release of dopamine to a greater degree than did cocaine. These researchers suggested that the obtained differences may have been related to the two drugs' ability to block the uptake or facilitate the release of dopamine. Other studies have differentiated the effects of d-amphetamine and cocaine on the major neurotransmitters. An experiment with reserpine, a catecholamine depleting drug which acts upon existing stores, showed that the effects of cocaine are eliminated when the stores are depleted (Scheel-Kruger et al., 1977). It also was reported that d-amphetamine's effect was dependent upon newly synthesized catacholamines not existing stores (Van Rossum, Van Der Schoot, & Hurkmans, 1962).

Surgical manipulations of brain dopamine content have produced altered responsiveness to both d-amphetamine and cocaine. Lesions to the nigro-striatal dopamine pathway, which begins in the area of the substantia nigra, decrease dopamine content in the brain (Ungerstedt, 1971). Chandu-Lall, Haase, Zivanovic, and Szekely (1970) reported a 74% decrease in dopamine concentration in the substantia nigrae of cats following bilateral damage to the caudate nucleus, the opposite end of the nigro-striatal pathway.

Creese and Iversen (1975) reported that administration of cocaine to substantia nigra lesioned rats without functioning dopamine terminals in the striatum did not produce an increase in locomotor activity. Isaac and Kallman (1975) reported opposite findings using d-amphetamine on substantia nigra lesioned rats. They observed increases in locomotor activity levels of the lesioned animals when exposed to d-amphetamine. A recent comparative study of cocaine and d-amphetamine on vigilance performance, a more sensitive measure, also found that these drugs do not produce similar effects (Squire, 1989). While both drugs are CNS stimulants, Squire reported an overall increase in false alarm responding following d-amphetamine injections but an increase in detection rate following cocaine administration.

Haloperidol

Haloperidol, a widely used antipsychotic drug has potent antidopaminergic activity (DiPalma, 1971). Researchers have suggested that haloperidol acts as a dopamine antagonist by decreasing dopamine content in various regions of the brain (Bhattacharyya, Aulakh, Pradhan, Ghosh, & Pradhan, 1979). Bhattacharyya et al. also reported that administration of haloperidol reverses cocaine induced neurochemical and locomotor activity changes. Rastogi, Singhal, and Lapierre (1982) obtained

opposite effects on locomotor activity comparing acute and chronic administration of haloperidol. These researchers found that rats injected once with haloperidol showed a decrease in locomotor activity levels and an increase in dopamine synthesis. Animals subjected to 20 consecutive days of haloperidol injections demonstrated a 20% increase in activity and a decrease in dopamine synthesis.

Gender

A number of studies have shown that drugs which interact with dopamine produce gender related behavioral differences. Male and female rats trained on an operant task and exposed to haloperidol displayed differences in response rates (Van Hest, Van Haaren, & Van De Poll, 1988). These researchers reported that male rats were more sensitive to the inhibitory effects of haloperidol than females. The response rates of males were much lower than those of the females. They suggested that female hormones may influence post-synaptic dopamine receptor activity. Murphy and Golden (1982) also obtained gender differences in rats exposed to haloperidol under different illumination conditions. They found that haloperidol eliminated illumination effects on activity levels of male rats. This effect was not seen with females. Studies measuring locomotor activity changes in rats given CNS stimulants also have found gender differences. Wood (1987) reported

that female rats were more active than male rats when exposed to cocaine and alternating noise quiet conditions. Golden and LeDuc (1988) reported similar gender differences among rats injected with d-amphetamine.

Summary

It has been found that cocaine acts upon stored pools of brain catacholamines (Scheel-Kruger et al., 1977). Haloperidol has been shown to decrease dopamine content in various regions of the brain (Bhattacharyya et al., 1979). Different dopamine synthesis and locomotor activity levels have been obtained using chronic and acute administration of haloperidol (Rastogi et al., 1982). At the present time, the effects of combining haloperidol pretreatment with cocaine on locomotor activity levels are unclear. The present study was designed to examine the effects of three different haloperidol pretreatment durations on cocaine induced locomotor activity. It was expected that lower locomotor activity levels would be obtained for the haloperidol pretreated rats. Furthermore, the haloperidol pretreated rats would exhibit a reduced locomotor activity response to the cocaine. It also was anticipated that the magnitude of the pretreatment effect would correspond to the length of the pretreatment period.

CHAPTER 2

Method

Subjects

Eighteen male and 18 female CD derived rats of approximately 160 days of age, born in the Austin Peay State University animal behavior laboratory, served as subjects. The rats were housed individually under a LD 12:12 schedule (lights on 6am to 6pm CST) and had food (Wayne Lab Blox) and water available ad lib. The average weights on the first day of pretreatment were 425g for the males and 254g for the females. On the last day of the study, the average weight for the males was 461g and 270g for the females.

Apparatus

The rats were tested in 20.5 x 22.5 x 44.0 cm clear plastic cages (Hazelton Systems) covered with 6 mm hardware cloth tops. The cages were placed into individual sound attenuating cubicles which measured 56 x 50 x 70 cm and were open at the front. Illumination (1,076 lx) was provided by 20 watt fluorescent lamps (F20T12/CW) mounted 25 cm above the top of each cage. An infrared beam generated by an infrared emitting diode (GE-LED25C) and detected by a phototransistor (FPT120B) bisected the length of each cage 3 cm above the floor. Beam breaks were

amplified by an LM324N comparator and recorded in 5 minute intervals for 40 minutes by an Advanced Digital SuperSix Computer located in another room. Ambient noise measured in the test cubicles was 45-50 db SPL (A scale, re: 20 $\mu N/m^2$).

Procedure

Six males and six females were assigned to each of three haloperidol pretreatment groups. One half of each group received intraperitoneal injections of haloperidol (.2 ml/kg in bacteriostatic water, 1 ml/kg) which was generously supplied by McNeill Laboratories. The remaining rats received injections of the vehicle alone. The three pretreatment groups received daily haloperidol injections for 18, 12, and 6 days, respectively, prior to the beginning of testing. Following the pretreatment period, daily haloperidol injections were continued and testing with cocaine began.

Immediately prior to the start of each test session, the rats received intraperitoneal injections (1 ml/kg) of one of three dosages of cocaine hydrochloride (Sigma Chemical, 0.0, 7.5, 15.0 mg/kg) in isotonic saline. Dosages were presented in a semi-randomized order, every other day, such that no rat received the same dosage on two consecutive drug days and all of the rats received all dosages before one was repeated.

On the intervening non-drug days, all rats received intraperitoneal injections of isotonic saline (1 mg/kg) and were tested in order to measure any residual cocaine effects. Pretreatment injections took place between 3pm and 4pm (CST). Testing was conducted between the hours of 11am and 2pm (CST).

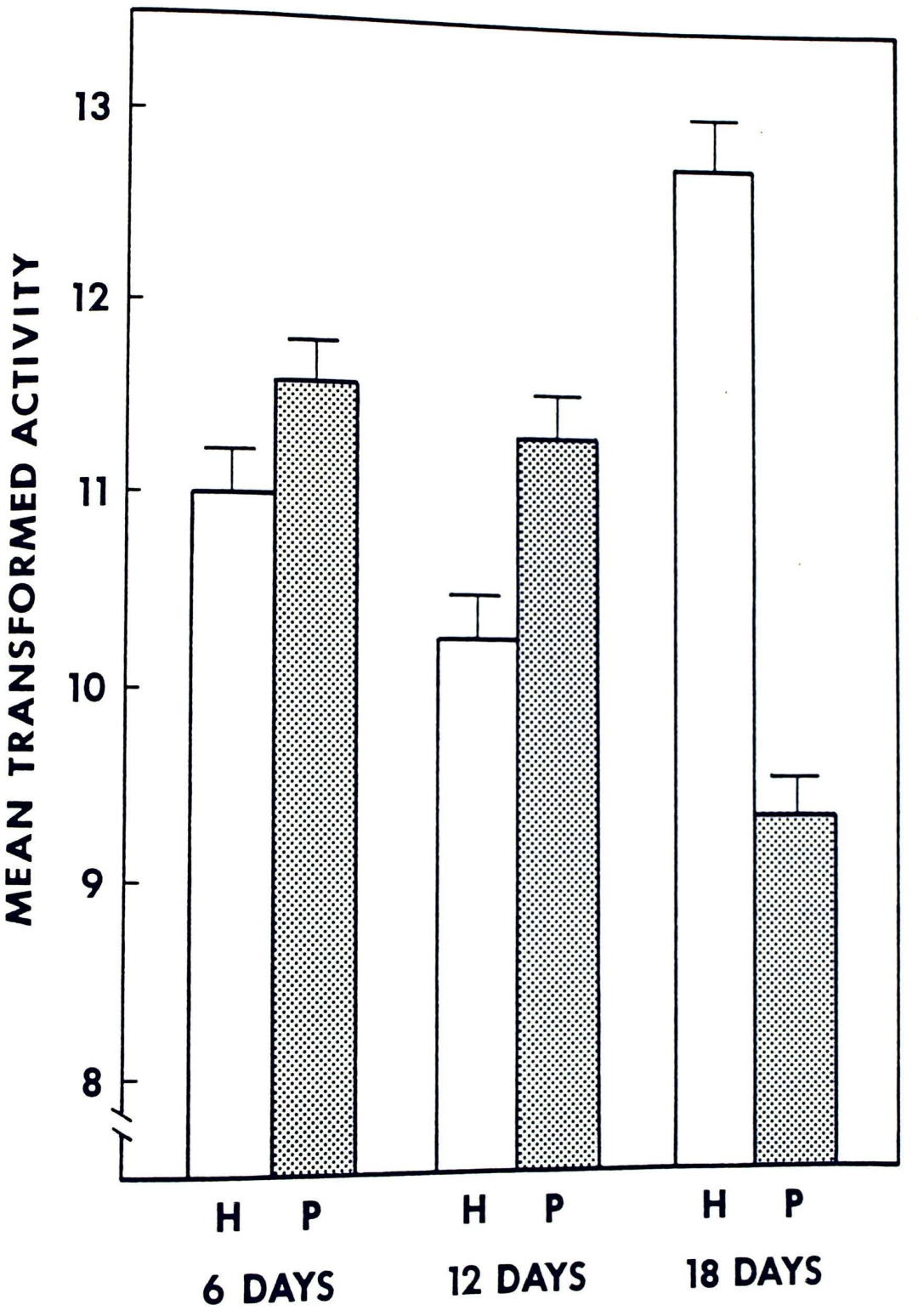
CHAPTER 3

Results

The data were collapsed into 5 minute blocks, transformed to the $\sqrt{X} + \sqrt{X+1}$ as recommended by Edwards (1985) for frequency data, and subjected to a 5 factor mixed model analysis of variance. Randomized groups were used for pretreatment length (3 levels) and gender (2 levels). Repeated measures were used for cocaine dosage (3 levels), 5 minute intervals within sessions (8 levels), and replications (6 levels). Simple effects analysis of variance and the Studentized Range Test (SRT) were used where appropriate for post hoc comparisons.

Analysis of the data from the drug days revealed no main effects for pretreatment duration or pretreatment dosage, $p>.05$. However, a pretreatment duration by pretreatment dosage interaction was obtained, $F(2, 24) = 6.23$, $p<.005$, (see Figure 1). The activity levels of the 6 day pretreatment groups did not differ. However, opposite effects were obtained for the 12 and 18 day pretreatment groups. The 12 day haloperidol pretreated animals were significantly less active than the placebo pretreated animals, SRT, $\alpha=.01$. In contrast, the 18 day haloperidol pretreated rats were significantly more active than the placebo group, SRT, $\alpha=.01$.

Figure 1. Effects of Haloperidol Pretreatment Duration on Locomotor Activity. (Open=Haloperidol, Shaded=Placebo)

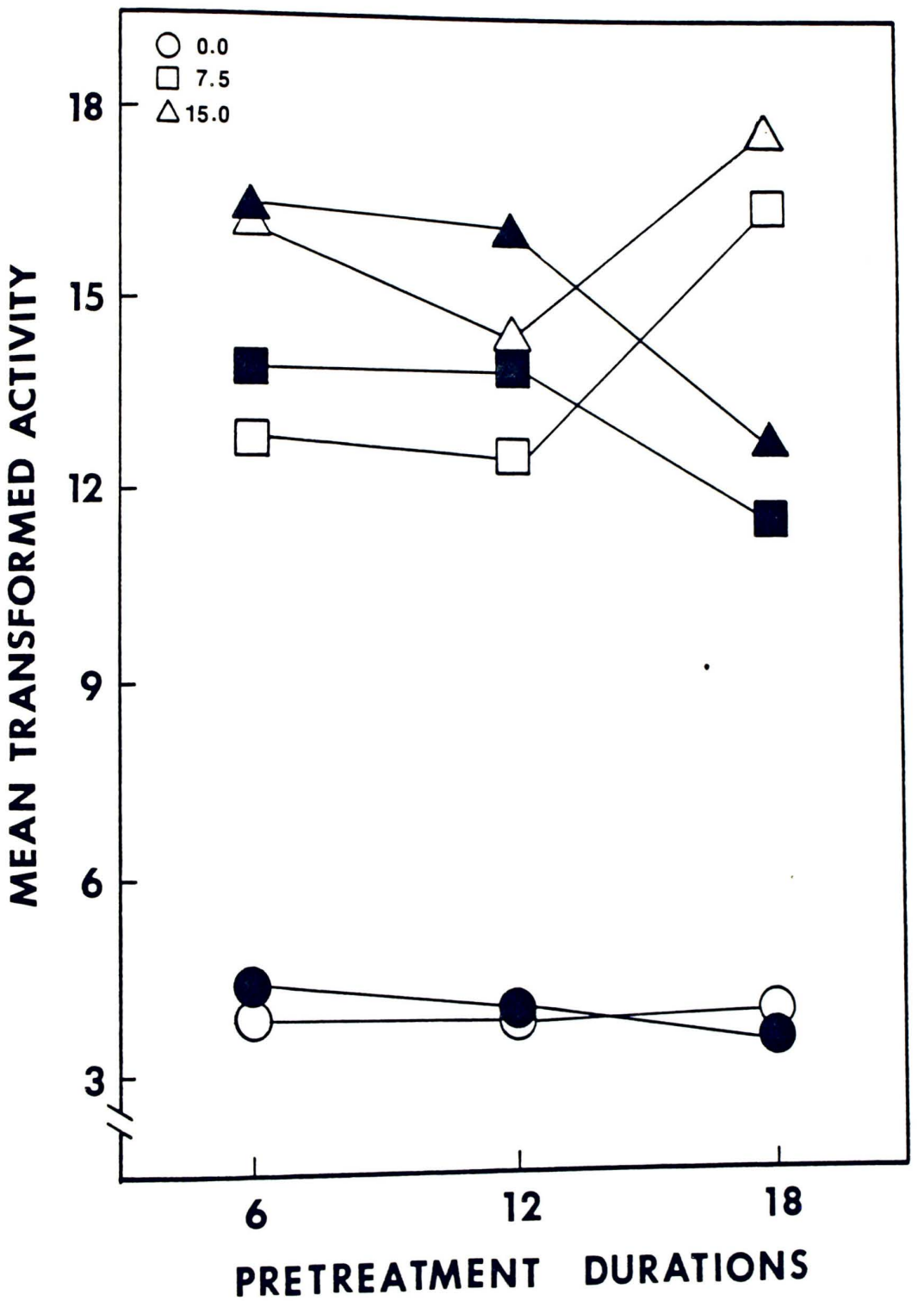

MEAN TRANSFORMED ACTIVITY
13
12
11
10
9
8
H
P
H
P
H
P
6 DAYS
12 DAYS
18 DAYS

As would be expected, activity increased with increasing cocaine dosages, $F(2, 48) = 688.02$, $p<.001$. However, the increases were not independent of pretreatment duration and pretreatment dosage, $F(4, 48) = 4.79$, $p<.005$, (see Figure 2). At the 7.5 mg/kg and 15.0 mg/kg cocaine dosages, activity levels of the 18 day haloperidol pretreated rats were significantly higher than those of the 18 day placebo pretreated rats, SRT, $\alpha=.01$. No other differences between pretreatment groups were obtained among the means for this interaction.

Locomotor activity declined significantly across the 5 minute intervals within sessions, $F(7, 168) = 235.72$, $p<.001$, in a manner which was not independent of pretreatment duration, $F(14, 168) = 2.64$, $p<.005$. Activity levels appeared to decline more rapidly with the 6 day pretreatment animals than with either the 12 or 18 day groups. An interaction of cocaine dosage with intervals also was found, $F(14, 336) = 22.42$, $p<.001$. The decrease in activity over time within the test sessions was less pronounced with increasing drug dosages.

No main effect was seen for the 6 day replications, $p>.05$, but a pretreatment dosage by replications interaction was obtained, $F(5, 120) = 2.43$, $p<.05$. Simple effects analysis revealed that rats receiving haloperidol became more active across replications, $F(5, 60) = 3.98$,

Figure 2. Effects of Haloperidol Dosage and Pretreatment Duration on Cocaine Induced Locomotor Activity. (Open=Haloperidol, Solid=Placebo)


0.0
7.5
15.0
18
15
12
9
6
3
MEAN TRANSFORMED ACTIVITY
6
12
18
PRETREATMENT DURATIONS

$p<.005$, while the placebo pretreated animals showed no such increase, $p>.05$. This interaction was not independent of gender, $F(5, 120) = 2.47$, $p<.05$, (see Figure 3). In the haloperidol pretreated group, activity levels of the female rats were significantly higher in the last 3 replications than the activity levels of the males, SRT, $\alpha=.001$, suggesting that the pretreatment dosage by replications interaction derived primarily from the female rats.

Analysis of the data from the non-drug days revealed no main effects for pretreatment duration, $p>.05$, or gender, $p>.05$. However, the combination of these two variables did produce a significant interaction, $F(2, 24) = 3.48$, $p<.05$. No gender difference was obtained with the 12 day pretreatment rats, however, opposite effects were seen for the 6 and 18 day pretreatment groups. In the 6 day pretreatment group, the males were more active than the females, SRT, $\alpha=.01$. In contrast to the 6 day group, the females in the 18 day pretreatment duration group were more active than the males, SRT, $\alpha=.01$.

The decline in activity across the 5 minute intervals within sessions observed on the drug days also was obtained on the non-drug days, $F(7, 168) = 180.32$, $p<.001$. This decline within sessions was not independent of pretreatment duration, haloperidol dosage, and gender, $F(14, 168) = 1.77$, $p<.05$, (see Figure 4). Simple effects analysis

Figure 3. Effects of Haloperidol on Activity Levels of Females (F) and Males (M) Across the Six 6 Day Replications. (Open=Haloperidol, Solid=Placebo)

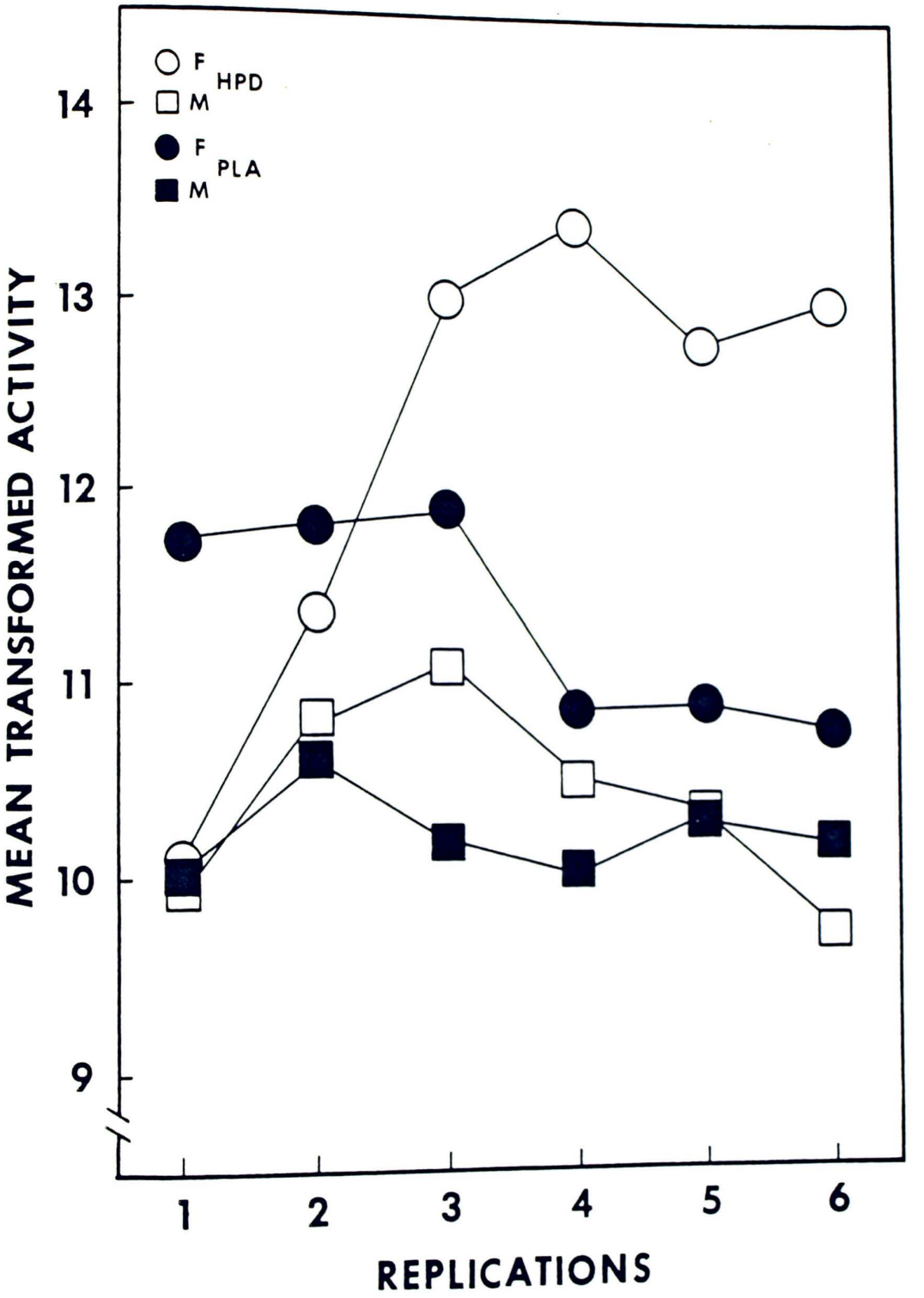
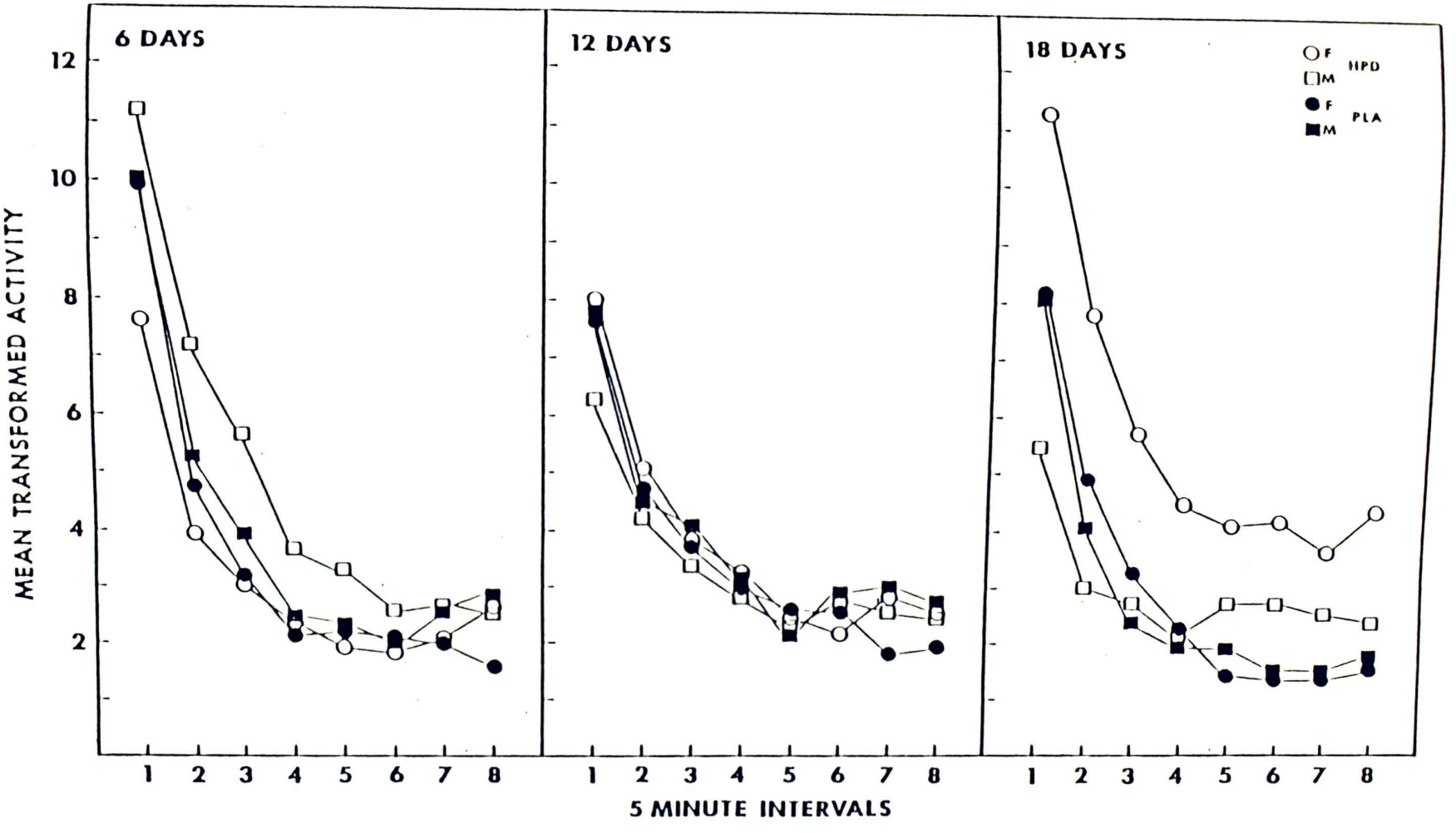

F
M
HPD
F
M
PLA
14
13
12
11
10
9
MEAN TRANSFORMED ACTIVITY
1
2
3
4
5
6
REPLICATIONS

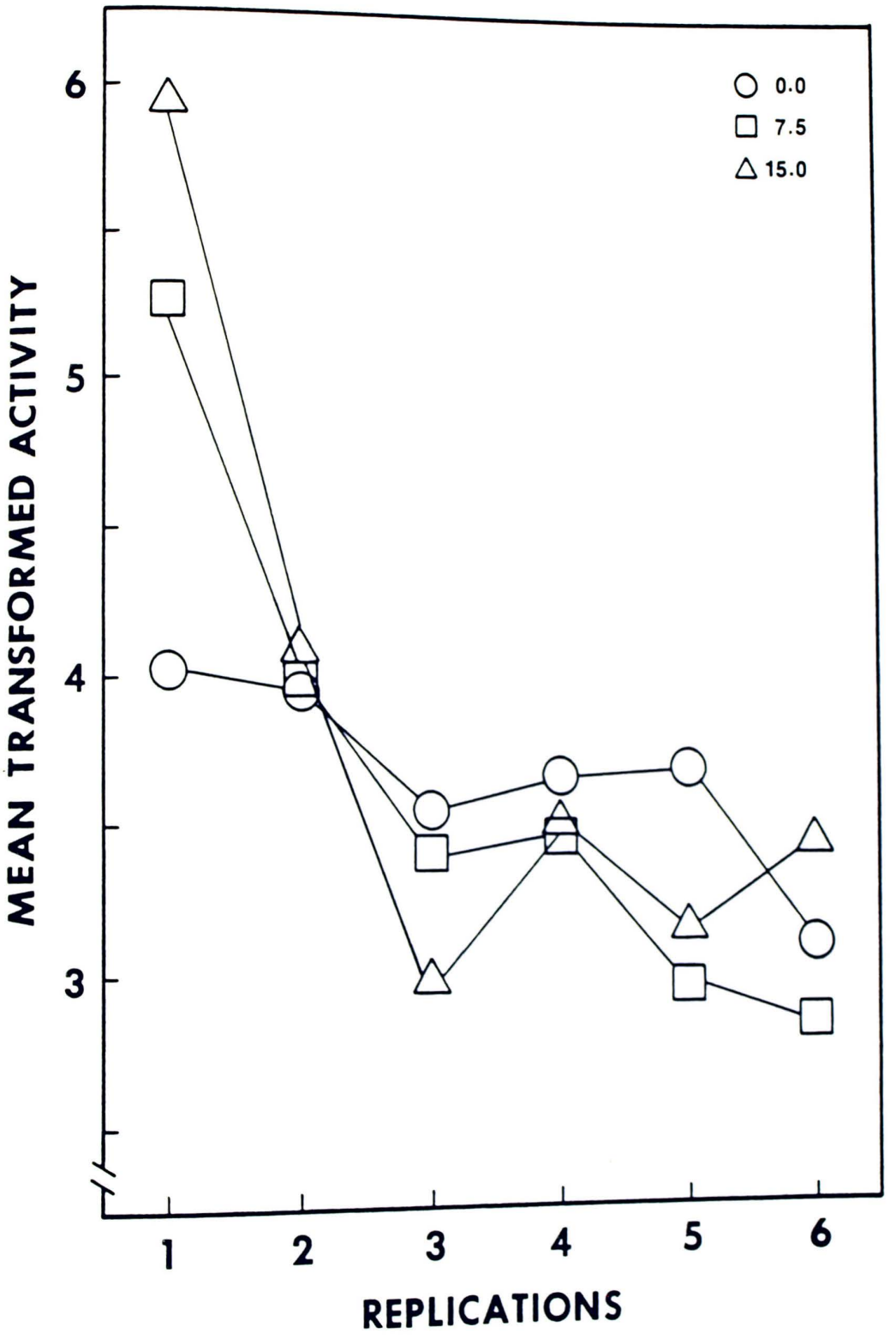
Figure 4. Effects of Haloperidol Dosage and Pretreatment Duration on Females (F) and Males (M) Across 5 Minute Intervals Within Sessions on Non-Drug Days. (Open=Haloperidol, Solid=Placebo)


6 DAYS
12 DAYS
18 DAYS
F
M
HPD
F
M
PLA
MEAN TRANSFORMED ACTIVITY
12
10
8
6
4
2
1 2 3 4 5 6 7 8
5 MINUTE INTERVALS

revealed that this interaction was not present with the placebo pretreated animals, $p>.05$. No gender differences were obtained for the 12 day haloperidol animals, $p>.05$. In the 6 day haloperidol pretreated group, males were significantly more active than females during the first 15 minutes of the test sessions, SRT, $\alpha=.001$. With the 18 day haloperidol group the opposite was seen, with females being more active than males during the first 20 minutes of the test sessions, SRT, $\alpha=.001$.

Activity levels also declined across replications on the non-drug days, $F(5, 120) = 17.90$, $p<.001$. This decline, though, was not independent of cocaine dosage, $F(10, 240) = 4.70$, $p<.05$, (see Figure 5). During the first 6 day replication, activity on the non-drug days following the 15.0 mg/kg cocaine dosage was significantly higher than on days following the other 2 dosages, SRT, $\alpha=.001$. Activity also was higher following the 7.5 mg/kg dosage than following the 0.0 mg/kg dosage, SRT, $\alpha=.001$. No carry-over effects were obtained beyond the first replication.

Figure 5. Cocaine Carry-Over Effects on Non-Drug Days Across the Six 6 Day Replications.


MEAN TRANSFORMED ACTIVITY
6
5
4
3
0.0
7.5
15.0
1
2
3
4
5
6
REPLICATIONS

CHAPTER 4

Discussion

The results of the present study indicate that the activity levels of rats pretreated with haloperidol differ according to the length of time the animals are exposed to the drug. The haloperidol and placebo groups with the shortest pretreatment duration, 6 days, did not show differences in activity levels. The 12 day haloperidol group was less active than the placebo group. In contrast, the haloperidol pretreated rats in the 18 day group were more active than the placebo group. The obtained increase in activity of the 18 day haloperidol animals is similar to that obtained by Rastogi et al. (1982) using chronic injections of haloperidol for 20 days. The increase in activity with increased cocaine dosages was similar to that reported by Wood (1987) for the same dosages. The decrease in activity within sessions also was similar to those found by Wood. The decrease within sessions was less pronounced with increasing drug dosages.

The effects of cocaine on locomotor activity were altered in animals pretreated with haloperidol. Rats exposed to haloperidol for 18 days before being given cocaine were much more active than those that did not receive the haloperidol. These results do not show the

reversal of cocaine-induced locomotor activity by haloperidol reported by Bhattacharyya et al. (1979) when cocaine was administered 30 minutes following haloperidol. The different findings in the present study may be a result of the chronic pretreatment with haloperidol prior to cocaine exposure, the 18 hour interval between haloperidol and cocaine injections, or a combination of both.

The activity levels of animals receiving haloperidol increased across the 6 replications while they did not in the placebo pretreatment groups. This increase in activity levels across replications may be a result of depleted dopamine pools in the rat brain caused by chronic haloperidol injections. This would support the findings of Rastogi et al. (1982) that chronic haloperidol exposure produces an increase in activity and a decrease in dopamine synthesis. Unfortunately, this explanation is in conflict with the increase in the cocaine effect obtained with the 18 day haloperidol pretreated animals. Since cocaine acts upon existing stores of dopamine (Scheel-Kruger et al., 1977) to produce an effect on locomotor activity, (Creese & Iversen, 1975; Ungerstedt, 1971), and haloperidol reduces brain dopamine content (Battacharyya et al., 1979), it is possible that one or more additional neurochemical mechanisms are involved.

The gender differences obtained across replications were not unexpected. Wood (1987) reported finding higher activity levels in female rats than male rats when exposed to cocaine. Golden and LeDuc (1988) reported similar findings in rats given d-amphetamine. Both of these drugs are known to have an effect upon dopamine levels in the rat brain (Ho et al., 1977; Moore et al., 1977). It would appear that haloperidol, which reduces dopamine levels, also produces gender related differences in locomotor activity.

On the intervening non-drug days, pretreatment duration and gender interacted to produce a reversal in activity levels. Male rats in the 6 day group were most active while the females in this group were the least active. The opposite was seen with the animals in the 18 day pretreatment group.

Unlike activity across replications on the drug days, activity declined significantly on the non-drug days across replications. A cocaine carry-over effect was seen in the first replication on the non-drug days. Activity levels of the animals which received cocaine were significantly higher than those of animals which received the placebo dosage on the previous day. This effect was no longer present after the first 6 day replication. Failure to find the carry-over effect in the later replications may be a

result of the animals habituating to the drug, to the test environment, or to both.

Results from the different haloperidol pretreatment groups after exposure to cocaine pose conflicting evidence. These results do not appear to be a function of haloperidol exposure alone. After two cocaine replications, the animals pretreated with haloperidol for 6 days before receiving their first dose of cocaine had received a total of 18 days of chronic haloperidol injections. At 18 days, these animals did not display an increase in activity. The 12 day haloperidol pretreated animals, after one replication, also had received the drug for 18 days. They maintained a reversal of cocaine induced locomotor activity throughout the study. An elevation of the locomotor response to cocaine was obtained only with the animals that had been given 18 days of haloperidol pretreatment prior to receiving cocaine. The one factor that seems to account for these differences is duration of exposure time to haloperidol prior to receiving cocaine. Further research in this area to investigate additional biochemical substrates which may be involved in the cocaine response is needed.

APPENDIX

TABLE 1

Analysis of Variance for Drug Days

SOURCE	SS	df	MS	F	
TOTAL	246189.16	5183			
Between Groups	19289.72	35	551.13		
DURATION (A)	205.45	2	102.72	0.24	
HALOPERIDOL (B)	424.86	1	424.86	1.01	
GENDER (C)	2859.15	1	2859.15	6.85	*
AxB	5200.60	2	2600.30	6.23	**
AxC	233.06	2	116.53	0.27	
BxC	176.55	1	176.55	0.42	
AxBxC	179.22	2	89.61	0.21	
Error	10010.80	24	417.11		
Within Treatments	226899.44	5148	44.07		
INTERVALS (D)	20331.35	7	2904.47	235.72	***
AxD	455.70	14	32.55	2.64	**
BxD	51.42	7	7.34	0.59	
CxD	580.53	7	82.93	6.73	***
AxBxD	114.76	14	8.19	0.66	
AxCxD	142.50	14	10.17	0.82	
BxCxD	40.47	7	5.78	0.46	
AxBxCxD	125.58	14	8.97	0.72	
Error	2070.04	168	12.32		
REPLICATION (E)	585.35	5	117.07	1.82	
AxE	1006.03	10	100.60	1.57	
BxE	777.78	5	155.55	2.42	*
CxE	240.37	5	48.07	0.75	
AxBxE	768.94	10	76.89	1.20	
AxCxE	670.81	10	67.08	1.04	
BxCxE	789.74	5	157.94	2.46	*
AxBxCxE	383.59	10	38.35	0.59	
Error	7689.33	120	64.07		
DOSAGE (F)	135293.33	2	67646.66	688.02	***
AxF	539.57	4	134.89	1.37	
BxF	296.47	2	148.23	1.50	

TABLE 1 (Continued)

SOURCE	SS	df	MS	F
CxF	1531.86	2	765.93	7.79 **
AxBxF	1885.27	4	471.31	4.79 **
AxCxF	1040.86	4	260.21	2.64 *
BxCxF	54.81	2	27.40	0.27
AxBxCxF	823.96	4	205.99	2.09
Error	4719.36	48	98.32	
DxE	410.87	35	11.73	1.89 **
AxDxE	345.79	70	4.94	0.79
BxDxE	232.62	35	6.64	1.07
CxDxE	206.31	35	5.89	0.95
AxBxDxE	430.39	70	6.14	0.99
AxCxDxE	356.24	70	5.08	0.82
BxCxDxE	204.36	35	5.83	0.94
AxBxCxDxE	355.55	70	5.07	0.82
Error	5203.89	840	6.19	
DxF	2375.27	14	169.66	22.42 ***
AxDxF	205.69	28	7.34	0.97
BxDxF	150.96	14	10.78	1.42
CxDxF	252.42	14	18.03	2.38 **
AxBxDxF	342.99	28	12.24	1.61 *
AxCxDxF	356.76	28	12.74	1.68 *
BxCxDxF	13.13	14	0.93	0.12
AxBxCxDxF	352.68	28	12.59	1.66 *
Error	2542.63	336	7.56	
ExF	2602.35	10	260.23	7.64 ***
AxExF	916.33	20	45.81	1.34
BxExF	548.14	10	54.81	1.61
CxExF	195.33	10	19.53	0.57
AxBxExF	461.21	20	23.06	0.67
AxCxExF	777.33	20	38.86	1.14
BxCxExF	298.86	10	29.88	0.87
AxBxCxExF	584.05	20	29.20	0.85
Error	8168.00	240	34.03	
DxExF	635.74	70	9.08	1.53 **
AxDxExF	801.34	140	5.72	0.96
BxDxExF	486.27	70	6.94	1.17

TABLE 1 (Continued)

SOURCE	SS	df	MS	F
CxDxExF	312.06	70	4.45	0.75
AxBxDxExF	840.78	140	6.00	1.01
AxCxDxExF	665.37	140	4.75	0.80
BxCxDxExF	470.94	70	6.72	1.13
AxBxCxDxExF	829.93	140	5.92	1.00
Error	9956.74	1680	5.92	

* $p<.05$
** $p<.005$
*** $p<.001$

TABLE 2

Analysis of Variance for Non-Drug Days

SOURCE	SS	df	MS	F	
TOTAL	71725.34	5183			
Between Groups	7736.38	35	221.03		
DURATION (A)	54.52	2	27.26	0.14	
HALOPERIDOL (B)	354.87	1	354.87	1.87	
GENDER (C)	31.31	1	31.31	0.16	
AxB	460.31	2	230.15	1.21	
AxC	1316.35	2	658.17	3.47	*
BxC	152.42	1	152.42	0.80	
AxBxC	825.14	2	412.57	2.18	
Error	4541.43	24	189.22		
Within Treatments	63988.96	5148	12.42		
INTERVALS (D)	20559.64	7	2937.09	180.32	***
AxD	614.36	14	43.88	2.69	**
BxD	144.80	7	20.68	1.27	
CxD	86.20	7	12.31	0.75	
AxBxD	76.24	14	5.44	0.33	
AxCxD	519.61	14	37.11	2.27	**
BxCxD	73.46	7	10.49	0.64	
AxBxCxD	402.91	14	28.77	1.76	*
Error	2736.39	168	16.28		
REPLICATION (E)	2312.15	5	462.43	17.89	***
AxE	257.02	10	25.70	0.99	
BxE	437.55	5	87.51	3.38	**
CxE	188.68	5	37.73	1.46	
AxBxE	110.72	10	11.07	0.42	
AxCxE	73.10	10	7.31	0.28	
BxCxE	36.55	5	7.31	0.28	
AxBxCxE	128.52	10	12.85	0.49	
Error	3100.74	120	25.83		
DOSAGE (F)	44.20	2	22.10	1.40	
AxF	37.89	4	9.47	0.60	
BxF	5.32	2	2.66	0.17	

TABLE 2 (Continued)

SOURCE	SS	df	MS	F	
CxF	85.44	2	42.72	2.72	
AxBxF	82.53	4	20.63	1.31	
AxCxF	60.05	4	15.01	0.95	
BxCxF	9.98	2	4.99	0.31	
AxBxCxF	34.14	4	8.53	0.54	
Error	753.62	48	15.70		
DxE	1140.41	35	32.58	5.53	***
AxDxE	287.51	70	4.10	0.69	
BxDxE	188.23	35	5.37	0.91	
CxDxE	252.22	35	7.20	1.22	
AxBxDxE	297.83	70	4.25	0.72	
AxCxDxE	457.67	70	6.53	1.11	
BxCxDxE	227.78	35	6.50	1.10	
AxBxCxDxE	495.00	70	7.07	1.20	
Error	4948.88	840	5.89		
DxF	196.16	14	14.01	2.32	**
AxDxF	113.58	28	4.05	0.67	
BxDxF	86.50	14	6.17	1.02	
CxDxF	71.47	14	5.10	0.84	
AxBxDxF	184.94	28	6.60	1.09	
AxCxDxF	107.75	28	3.84	0.63	
BxCxDxF	112.36	14	8.02	1.33	
AxBxCxDxF	167.18	28	5.97	0.99	
Error	2027.14	336	6.03		
ExF	704.36	10	70.43	4.70	***
AxExF	248.38	20	12.41	0.82	
BxExF	62.81	10	6.28	0.42	
CxExF	125.21	10	12.52	0.83	
AxBxExF	393.74	20	19.68	1.31	
AxCxExF	193.49	20	9.67	0.64	
BxCxExF	179.59	10	17.95	1.19	
AxBxCxExF	221.42	20	11.07	0.73	
Error	3593.63	240	14.97		
DxExF	346.55	70	4.95	0.93	
AxDxExF	864.62	140	6.17	1.17	
BxDxExF	386.33	70	5.51	1.04	

TABLE 2 (Continued)

SOURCE	SS	df	MS	F
CxDxExF	497.81	70	7.11	1.34 *
AxBxDxExF	933.52	140	6.66	1.26 *
AxCxDxExF	712.85	140	5.09	0.96
BxCxDxExF	325.40	70	4.64	0.88
AxBxCxDxExF	999.89	140	7.14	1.35 **
Error	8864.65	1680	5.27	

* $p<.05$
** $p<.005$
*** $p<.001$

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