1966

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Recommended Citation

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SOME EFFECTS OF LYSERGIC ACID DIETHYLAMIDE ON VISUAL DISCRIMINATION IN PIGEONS

by

DANIEL I. BECKER

A Thesis Presented to the Faculty and the
Officers of the Yale University School of
Medicine in partial fulfillment of the
requirements for the degree of Doctor of Medicine

September 1966
Department of Psychiatry
Yale University School of Medicine

ACKNOWLEDGEMENTS

The author gratefully acknowledges his debt to Dr. James B. Appel and Dr. Daniel X. Freedman. Dr. Appel's continual contributions of instruction, guidance and encouragement were invaluable. The experiments were conducted under his supervision in the Psychopharmacology Laboratory, Departments of Psychiatry and Pharmacology. His influence is evident throughout this work. Dr. Freedman provided a perspective and many helpful suggestions which greatly furthered these investigations.

Thanks also are due to Dr. Malcolm Bowers, whose generous aid and careful editing were most welcome.

This research was supported in part by USPHS Research Grants MH-03363, MH-5942-14 and MH-5942-15 from the National Institute of Mental Health.

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INTRODUCTION

Experimental evidence, while often seemingly confused and contradictory, tends to confirm clinical reports that visual processes are uniquely sensitive to compounds of the general structure of lysergic acid diethylamide (LSD). Such agents have been called "hallucinogenic" or "psychotomimetic," perhaps because of bizarre visual sensations which sometimes occur in man following the ingestion of micro-quantities of drug.

Neurological investigations generally report an increase in the electrical activity of visual systems with LSD, but neither the exact character nor the precise location of these effects is clear. Current knowledge of the neurophysiological effects of LSD relating to vision will be briefly outlined, beginning with the retina and progressing centrally.

Jacobson and Gestring (1959) found that in 40% of cats given 50 micrograms per kilogram of d-LSD, spontaneous electrical potentials could be recorded from the eyeball which were abolished when the optic nerve was sectioned. Apter and Pfeiffer (1957) found that cats given 100 μg LSD/kg also demonstrated this effect. Schwartz and Cheney (1965a), also using cats, state that intra-peritoneal injections of high doses of LSD produce a retinal state analogous to stimulation with light flickering at high frequencies.

Apter and Pfeiffer conclude that LSD does not produce hallucinations in humans with section of the optic nerve. Jacobson and Gestring believe that the effects of LSD upon visual perception are central in origin, but Ostfeld (1961) feels that LSD in humans (75-100 μg) leads to hypoxic or toxic retinal changes. In a later paper, Krill, Alpert and Ostfeld (1963) found that LSD could indeed

induce hallucinations in humans without a functioning retina and decide that "LSD produces independent retinal and higher visual pathway effects."

In the visual pathways of the cat, LSD in doses of 100 to 250 μg/kg induced a general increase in tonic activity; the same effect could be produced by low frequency flickering light or changing light patterns (Schwartz and Cheney, 1965b). One of the most consistent alterations in the visual system following LSD is depression or complete block of synaptic transmission through the lateral geniculate body, an intermediate station in the visual pathway (Bishop, Field, Hennessy and Smith, 1958; Evarts, Landau, Freygang and Marshall, 1955). This effect, however, occurs at fairly high doses; with less drug, increased cortical responsiveness to visual stimulation has been found (Brazier, 1964; Evarts, 1957). This is a significant point in that clinical and behavioral evidence also suggests that, while high doses of LSD may totally inhibit behavior, lower doses seem to produce observable perceptual changes. Even with lateral geniculate block, the cortical response to stimuli applied to the optic radiations proximal to the block is unimpaired (Evarts et al., 1955).

Whether LSD results in stimulation or depression of the visual cortex is not certain at this time. Purpura (1956), using the unanesthetized, paralyzed cat, found that LSD in doses of 2 to 30 μg/kg facilitated the primary cortical evoked potential to both visual and auditory stimuli. At doses of 40 to 60 μg/kg, depression of the auditory and continued facilitation of visual evoked potentials were found. However, in the unanesthetized rabbit, 25 to 100 μg/kg seems to produce a depression of the photic evoked response (Khazan and McCash, 1965).

Khazan and McCash also found that 25-100 µg LSD/kg produce a shift of the EEG to the alert pattern in rabbits, a finding which others have also reported in other animals, including man (Brazier, 1964; Bradley and Elkes, 1957). However, Purpura (1957) cautions that this may actually be the result of activation of inhibitory synapses; this activity may simulate the alerting response when viewed from the cortex. Evarts, in a 1957 review, notes that in 7 out of 10 humans tested, LSD administration resulted in increased photic driving of the EEG, and in 5 out of these 7, irradiation of the photic response to the frontal region was recorded.

To summarize, then, LSD produces electrical changes in the visual system which seem to imply that some type or types (excitatory or inhibitory) of activity increases. The relationships between these changes and the behavioral effects of the drug are at present speculative.

Behaviorally, LSD produces some consistent effects which can be noted. Transient interruption of responding ("pausing") has been observed in rats (Appel and Freedman, 1964; Liberson, Ellen, Schwartz, Wilson and Gagnon, 1962; Olds and Olds, 1964; Ray, 1965), guinea pigs (Liberson _et_ _al._, 1962), pigeons (Berryman, Jarvik and Nevin, 1962) and rabbits (McGaugh, de Baran and Longo, 1963). The tasks involved included responding for food on simple schedules of reinforcement, hypothalamic self-stimulation, approach behavior and complex discrimination learning (matching to sample). Similarly, depression or lowering of response rate has been seen in monkeys (Jarvik and Chorover, 1960), rats (Jarrard, 1963; Ray, 1965), humans (Ostfeld, 1961) and pigeons (Blough, 1957a). As would be expected, increase in reaction time is another common finding

with LSD (Berryman et al., 1962; Edwards and Cohen, 1961; Fuster, 1957,1959). Tolerance to the behavioral effects of LSD has also been investigated (Freedman, Appel, Hartman and Molliver, 1964).

The fact that daily LSD administration leads to decreased food intake in rats (Hamilton and Wilpizeski,1961), and that performance under LSD is increased with extra food deprivation (Miltzer,1965) suggests that food may lose some of its reinforcement value under LSD; yet Jarrard (1963) found that 50 μg/kg in rats led to increased bar-pressing for food on certain schedules (VI). In experiments involving escape from shock, Hamilton (1960) reports that LSD increased the speed of running in the rat. He also found that LSD produced a higher percentage of avoidance in a conditioned avoidance situation; however, Appel (1965) found no such effect of LSD upon an unconditioned or conditioned escape wheel-turning response.

Perceptual changes following LSD administration include increase in the visual threshold in humans (Carlson,1958) and pigeons (Blough,1957b) and changes in the dark adaptation curve in humans (Ostfeld,1961). Peterson (1966) found that an increase in the apparent brightness of a visual stimulus occurred in monkeys given LSD. He also states that the shape of the visual discrimination curve was altered. Key (1961, 1964) also found that LSD produced an increase in auditory and visual stimulus generalization.

The results regarding the effects of LSD upon accuracy as opposed to rate of performance are equivocal. The drug impaired monkeys' performance of a delayed alternation task (Jarvik and Chorover,1960) and visual discriminations (Fuster, 1957,1959), but no change in accuracy was noted in auditory

discrimination in cats (Key, 1961) or in matching behavior in the pigeon (Berryman, et al., 1962). Finally, Blough (1957a) found an increase in accuracy of complex brightness discrimination in pigeons, an effect which outlasted the depression of response rate which followed drug administration.

Thus, LSD yields depression of response rate and transient interruption of responding as two general effects. The effects of LSD on running behavior (escape and avoidance) and accuracy of performance of a learned task are not nearly as clear.

Following Blough, the experiments to be described investigate a visual discrimination using the pigeon as the experimental subject. Relationships between LSD dose and accuracy of performance, depression of response rate and interruption of responding will be demonstrated. Since the period of experimentation was to last almost a year, the development of long-term tolerance to LSD might also be shown, and the effect of LSD on food consumption assessed.

The task chosen was designed so that the difficulty involved was primarily "perceptual." The pigeons were well-trained prior to drug administration and a minimum of "problem-solving" was needed for the bird to make the correct response. The discrimination was between flickering and steady light; the task difficulty could be altered by increasing the frequency of the flickering light.

It is apparent that, as the flicker frequency is increased, a point will be reached at which the flickering light appears steady. This is the critical flicker frequency (CFF), a phenomenon which has been extensively investigated. It should be noted that in the present study CFF values were not specifically relevant;

CFF of the flickering light only means that the discrimination between flicker and steady has become impossible.

Nevertheless, it is of interest that depressants of the CFF include barbiturates (Aiba, 1959), phenothiazines (Hoehn-Saric, Bacon and Gross, 1964; Karp and Pollack, 1963; Lloyd and Newbrough, 1964), nitrous oxide (Holland and Gooch, 1962), carbon monoxide (von Post-Lingen, 1964), electroconvulsive therapy (Mowbray, 1961) and brain damage (Taravella and Clark, 1963). Depression of the critical flicker frequency means, in these studies, that subjects discriminate between flicker and steady less well, while elevation of the CFF implies a better discrimination. Although the results of two recent experiments are contradictory (Holliday, Hall and Sharpley, 1965; Landis and Clausen, 1954) there is reason to believe that LSD should elevate the CFF. Two drugs related in some ways to LSD - d-amphetamine (Aiba, 1959) and psilocybin (Keeler, 1963) - both elevate this perceptual measure. Psilocybin is both chemically and clinically analogous to LSD, producing much of the same hallucinatory experiences and classed as a "psychotomimetic." Amphetamine yields some behavioral changes similar to those of LSD (Hamilton, 1960) and clinically, large, prolonged doses of amphetamine may also be "psychotomimetic."

METHOD

Subjects: Six male White Carneaux pigeons, three months old, obtained from Palmetto Pigeon Plant, Sumter, S.C., were permitted to eat ad. lib. for five days in individual home cages, and a free-feeding weight was obtained for each bird. The pigeons were then reduced to 80% of this weight by feeding 5 grams daily of a mixture of 40% vetch, 50% Kaffir corn and 10% hemp seed. This was

the food mixture used throughout the entire period of study. Birds were maintained at 80% free-feeding weight by supplementary feeding in their home cages immediately following an experimental session. Water was always available in home cages which were housed in a room of constant temperature and humidity with a 12 hour light-dark cycle.

Apparatus: The experimental box was a modified version of that described by Ferster and Skinner (1957). Two keys which could be transilluminated were placed two inches apart and equidistant from the food magazine. When the magazine was opened to make food available to the birds a loud click occurred and the food was illuminated by a small light bulb placed high in the magazine structure. White noise was generated in the box to remove the distraction of external sound in the lab. The small house lights were gradually dimmed and finally extinguished before actual testing was begun, so that the only illumination in the box was provided by lights behind the translucent keys.

Two lights behind each key, General Electric Neon NE 51, were connected in parallel to the output of a tachistoscopic timer (R.C. Gunter Associates, Charlton, Mass.) which was driven by a square-wave stimulator (Bio-Electronic Laboratory, Div. of TALCO Engineering Co., Inc., Hamden, Conn.). The purpose of the above apparatus was to provide a controlled source of flickering light. The intensity and duration of the on phase were regulated by controls on the tachistoscopic timer. The frequency of the flicker, that is, the number of on pulses per second, was controlled by the square-wave stimulator.

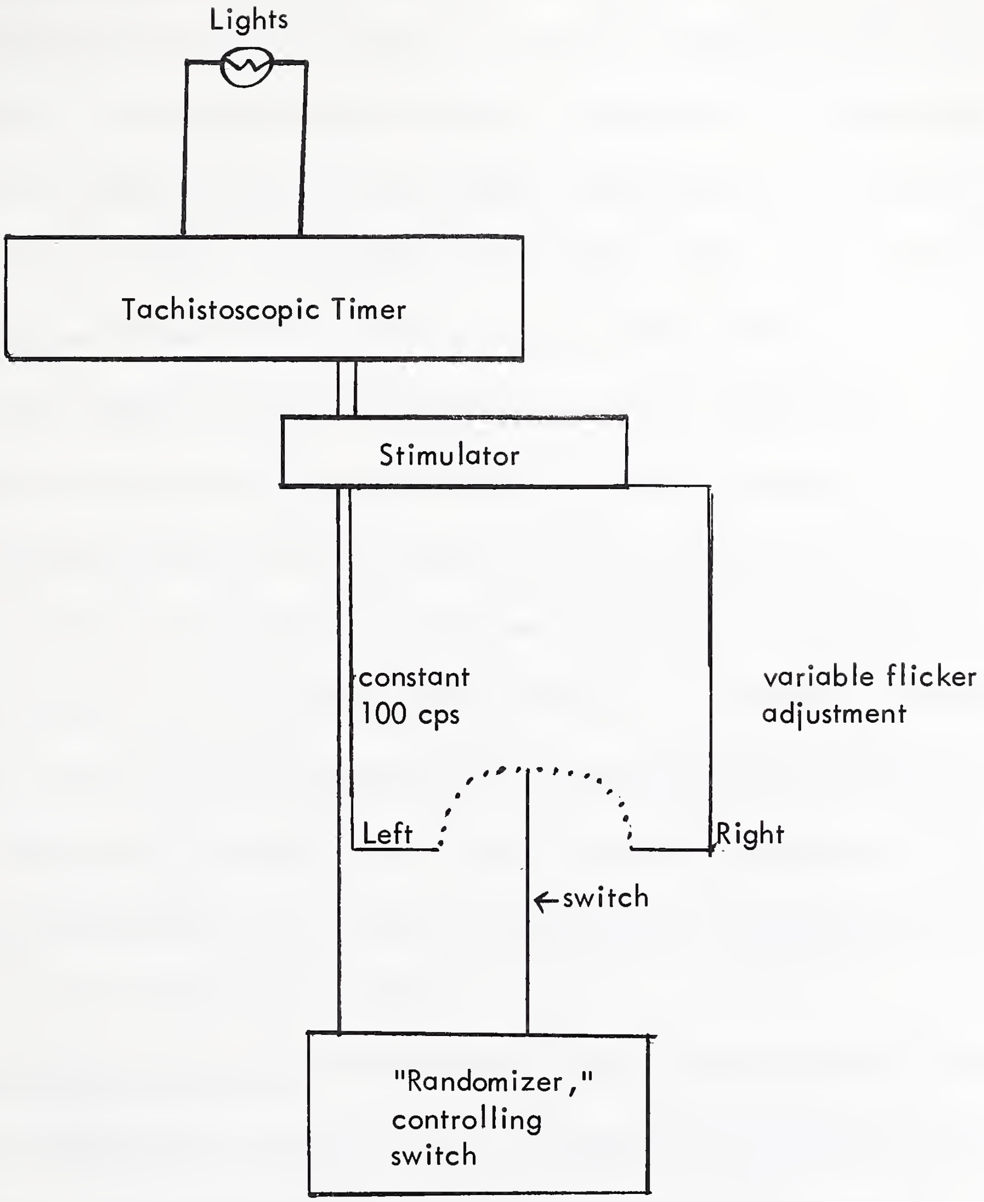
The intensity of the lights was maintained at a constant level throughout all experiments. In addition, for practical reasons, the duration of the on phase,

i.e., the pulse width, was kept at 4 milliseconds. The flicker frequency was varied as will be described below. It is apparent then, that as the frequency of flicker was increased, the total on time of the lights was increased also. For example, at a flicker of 30 cycles per second, the lights are on for 30 x 4 msec. or 120 msec. per second. At a flicker of 50 cps the on time is 200 msec./sec. Thus a discrimination between two flicker frequencies may involve the number of on pulses per second, the duration of the on phase or both. The advantage of using this type of task is that its difficulty can be easily and continuously varied by adjusting the flicker frequencies of the stimuli which are to be discriminated.

In practice, the pigeons were required to discriminate between a flickering and a "steady" light. (Actually, a flicker of 100 cps was used for the "steady" condition.) The lights behind both keys were operated together. When the lights were "steady," only pecks on the left key in the box were rewarded. At randomized, preset intervals, the condition was switched to "flicker." The lights then flickered at the desired frequency for the specific day's run, and only pecks on the right key were rewarded. (See Fig. 1.) The average length of each flicker or steady interval was 40 seconds.

The various conditions were programmed automatically by relay and timing circuits located in an adjoining room. Counters recorded responses on each key for both flickering and steady intervals. Two cumulative recorders were also used, one for correct responses (left key pecks on "steady," right key pecks on "flicker") and one recorder for errors.

Figure 1. Flicker Control Apparatus



When switch is at "Left," lights are "steady," left key is "correct," that is, pecks on the left key are rewarded. (See text.)

Figure 1

Behavioral Procedure: Since the birds were experimentally naive, a period of approximately five weeks was necessary for training. After being taught to eat food from the magazine, the pigeons learned to peck at the keys to obtain food. At this time, each peck was reinforced (CRF); later larger numbers of responses were required to obtain a reinforcement (fixed-ratio or FR). Finally, the birds were required to discriminate so that only "correct" pecks brought reinforcement.

Three experiments were run during the period July, 1965 to May, 1966. Throughout all experiments the number of correct responses necessary to obtain a reinforcement was 35 (FR35). The magazine was open and food was available for 3 seconds at each reinforcement. All experimental runs were terminated automatically as soon as 60 reinforcements were given. For the first experiment, the discriminations 30 cps *vs* steady, 50 cps *vs* steady and 70 cps *vs* steady were run. Experiment II was identical in all details except that flicker levels of 50, 55, 58, 62, 66 and 71 cps were employed; Experiment III investigated discriminations of 10, 20 and 30 cps *vs* steady.

Pharmacological Procedure: LSD in ampules of 0.1 mg/ml was obtained from Sandoz Pharmaceuticals, Hanover, N.J. The drug was administered in doses of 20 micrograms per kilogram, 40 μg/kg and 80 μg/kg to each bird at each flicker level. Each LSD day was preceded by a physiological saline control day run at the same flicker frequency and followed by a non-injection control day. Thus in the first experiment there were nine different 3-day runs for each of the six pigeons, one at each dose level for each flicker level. All saline and LSD doses were administered by intra-muscular (IM) injections approximately 1 cm lateral to the sternum, immediately before the start of the experimental session.

The order of presentation of flicker cycle frequencies and drug dose levels for all experiments was determined by a Latin square design.

RESULTS

The accuracy of each pigeon's visual discrimination was assessed by dividing the number of incorrect responses per session (x 100) by the total number of responses emitted during the session, thus obtaining a per cent errors score. The effects of LSD upon accuracy of the visual discrimination will be considered first; other dose-response data will follow.

EXPERIMENT I:

A major purpose of this experiment was to explore the range of flicker frequencies the pigeon can discriminate from "steady" under the experimental conditions. To accomplish this, flicker frequencies of 30, 50 and 70 cycles per second were used.

Performance under LSD was always compared to the bird's performance on the identical task run the day before under NaCl. Reference to Fig. 2 shows that LSD at all three dose levels increased the accuracy of the discrimination 30 cps vs steady light. This increase in accuracy was not, however, statistically significant (t-test for differences, $p<.20$). Fig. 2 also reveals that the birds do worse on the 70 cps vs steady discrimination than they do on either the 30 or the 50 cps vs steady discrimination.

Table 1 shows the average error data obtained. Each value represents the average per cent errors (total incorrect responses divided by total responses) for 18 experimental sessions (one session per bird at each of the three LSD dose levels times six birds). These data suggested that the range between 50 and 70 cycles per second flicker would be worth exploring.

Figure 2. Experiment I: Per Cent Errors by LSD Dose and Flicker Frequency, Average of Six Birds

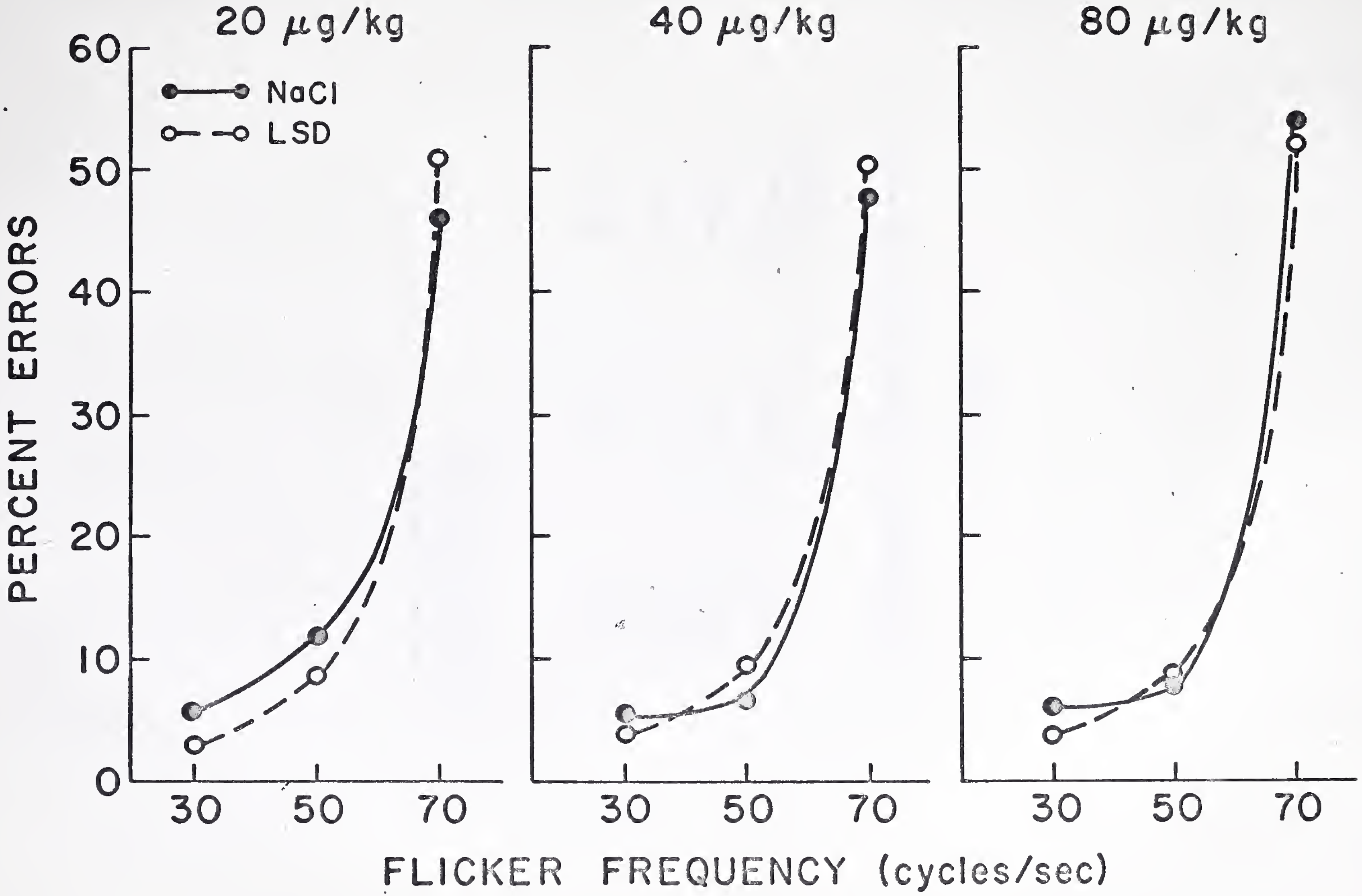

20 μg/kg
40 μg/kg
80 μg/kg
NaCl
LSD
PERCENT ERRORS
0
10
20
30
40
50
60
30
50
70
FLICKER FREQUENCY (cycles/sec)

Table 1

AVERAGE PER CENT ERRORS - EXPERIMENT I[+]

Flicker Frequency	NaCl	LSD
30 cps	5.9	3.5
50 cps	8.7	8.9
70 cps	49.4	51.1

[+] Each figure represents the average for 18 experimental sessions.

EXPERIMENT II:

Six closely spaced levels of flicker frequency were used: 50, 55, 58, 62, 66 and 71 cps; drug doses, as before, were 20, 40 and 80 µg LSD/kg. In order to determine the degree of covariance of increasing drug dose and increasing task difficulty (increased flicker frequency) with respect to errors, a Wilcoxon χ_r^2 interaction test (Wilcoxon, 1949) was performed; the degree of interaction was not significant ($p<.12$).

The effect of increased flicker frequency upon errors is shown in Fig. 3. The regular increase in errors manifested by the S-shaped function is significant by the Wilcoxon χ_r^2 rank test ($p<.001$).

The effect of LSD upon accuracy of discrimination was examined from two approaches. Fig. 4 shows the average errors at all flicker levels combined, for each bird at each drug dose. Twenty µg LSD/kg reduced average errors for five of the six birds; eighty µg/kg increased errors for five of the six birds. T-tests for differences were performed in both the above cases but were not significant ($p<.20$).

Figure 5 shows average errors combined for all birds, at each flicker frequency and each drug dose. It is evident that at each flicker level, 20 µg LSD/kg reduced the birds' average errors. The t-test for differences is significant here at $p<.02$. Eighty µg/kg raised errors at five out of six flicker levels but this effect was not significant ($p<.12$).

The major conclusions of this experiment regarding errors are:

1. As flicker frequency is increased, accuracy of visual discrimination between flickering and steady light decreases ($p<.001$).
2. 20 µg LSD/kg significantly improves visual discrimination in the flicker frequency range between 50 and 71 cps ($p<.02$).

Figure 3. Experiment II: Per Cent Errors by Flicker Frequency, Average of Three Saline Sessions for Each of the Six Birds

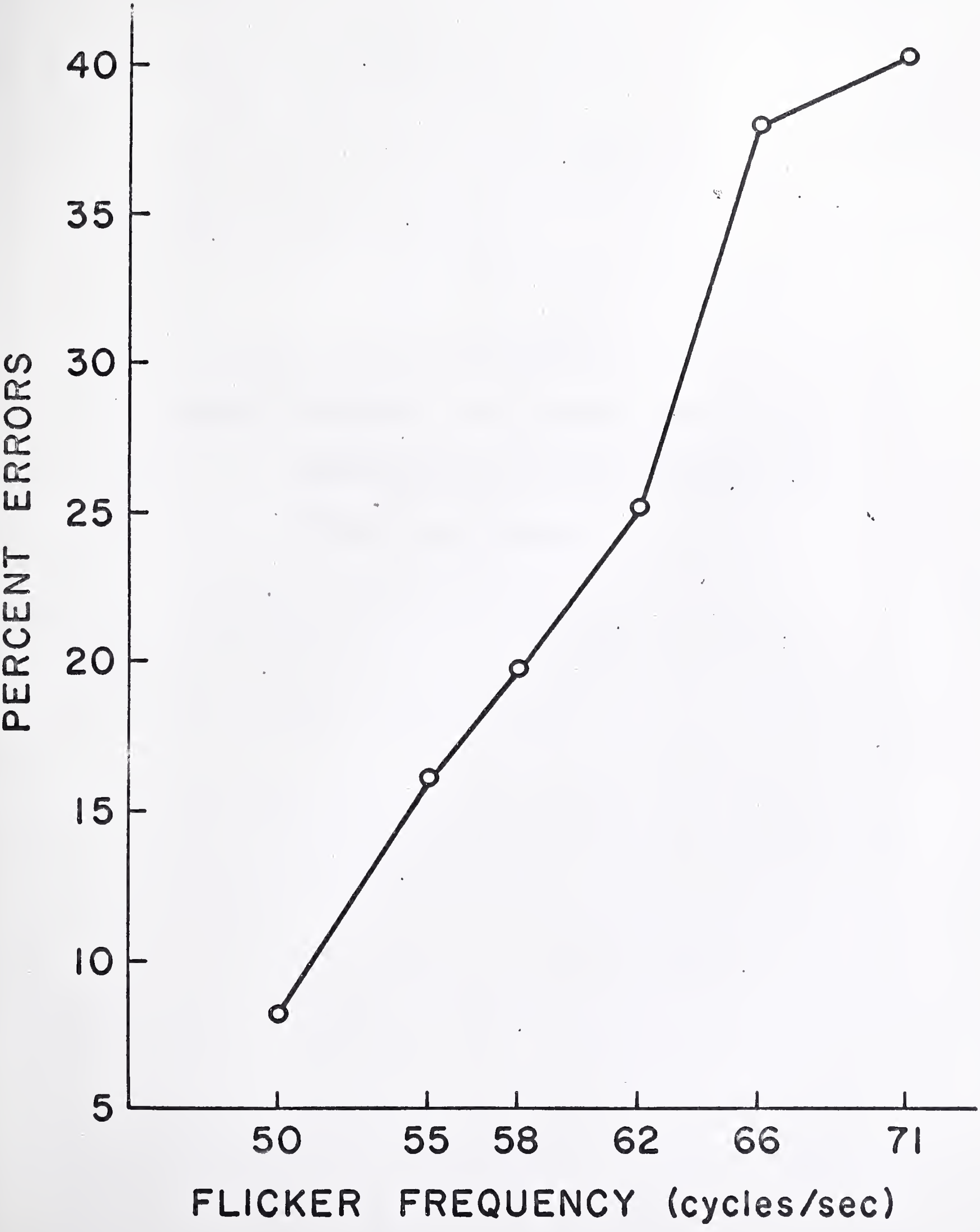

PERCENT ERRORS
40
35
30
25
20
15
10
5
50
55
58
62
66
71
FLICKER FREQUENCY (cycles/sec)

Figure 4. Experiment II: Per Cent Errors, Saline and Three LSD Doses, Shown for Each Bird, Average of Six Different Flicker Frequencies

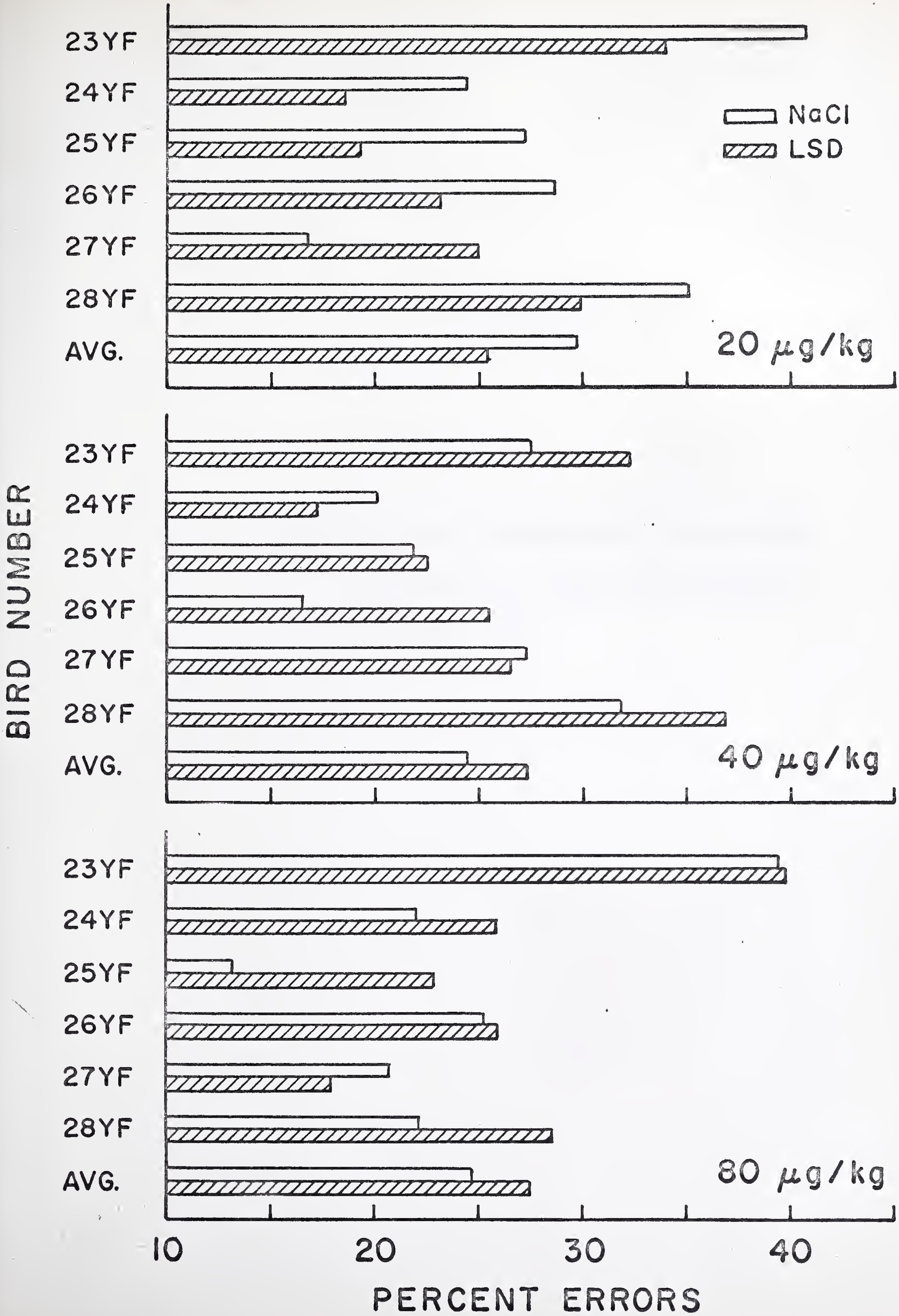
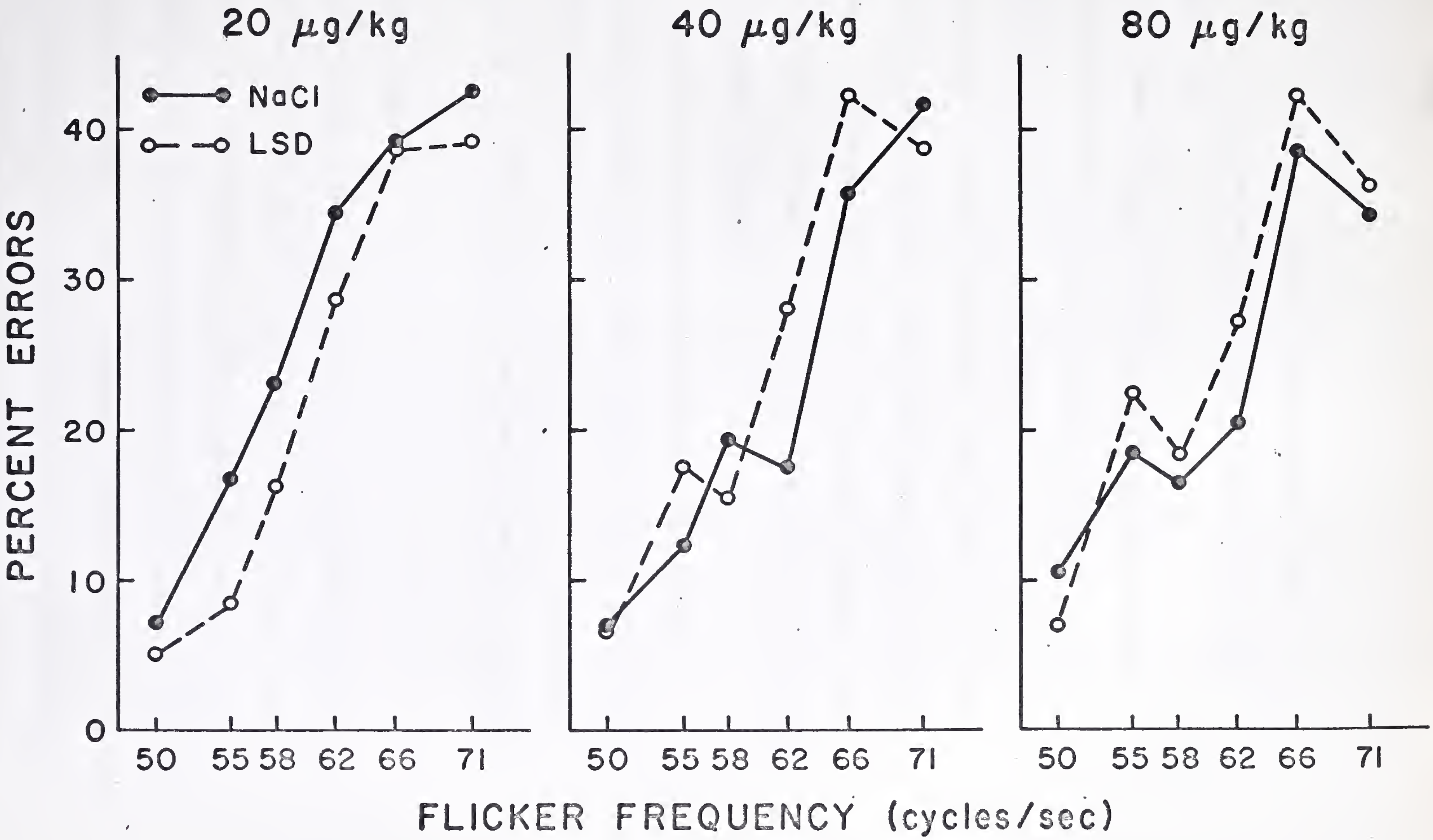

23YF
24YF
25YF
26YF
27YF
28YF
AVG.
NaCl
LSD
20 µg/kg
40 µg/kg
80 µg/kg
BIRD NUMBER
10
20
30
40
PERCENT ERRORS

Figure 5. Experiment II: Per Cent Errors, Saline and Three LSD Doses, Shown for Each Flicker Frequency, Average of Six Birds


20 μg/kg
40 μg/kg
80 μg/kg
NaCl
LSD
PERCENT ERRORS
0
10
20
30
40
50
55
58
62
66
71
FLICKER FREQUENCY (cycles/sec)

3. A disruptive effect of 80 μg LSD/kg upon visual discrimination is suggested by the above data ($p < .12$).

EXPERIMENT III:

The increased accuracy of the birds on the 30 cycles per second discrimination found at all drug doses in Experiment 1 prompted a further investigation of the area of the "easy" discrimination. For this experiment, flicker levels of 10, 20 and 30 cps were used. Fig. 6 demonstrates no major effect of LSD on errors, although at both 20 and 30 cps, 20 μg/kg improved performance. The lack of a clear-cut effect can perhaps be ascribed to the fact that the task was too easy, i.e., there was not much room for improvement.

THE EXPERIMENTS COMBINED

The most interesting result of the three experiments with regard to errors was the effect of 20 μg LSD/kg. These data are shown in Table 2. At nine of the eleven flicker level runs in the three experiments, LSD at this dose improved accuracy on the visual discrimination. The t-test for differences is significant ($p < .05$).

DOSE-RESPONSE DATA

The dose-response results were similar for all three experiments and will be considered together. Occasionally at the 20 μg/kg dose level, and often at the higher levels, the bird would stop responding altogether and remain immobile in the experimental box. This is the typical response to LSD shown by animals on FR schedules (Freedman *et al.*, 1964). The parameters of these "pauses" are discussed in the following section. Here, however, it is to be noted that two measures of time in the session can be obtained. One is *total time* in the experimental box

Figure 6. Experiment III: Per Cent Errors by LSD Dose and Flicker Frequency, Average of Six Birds

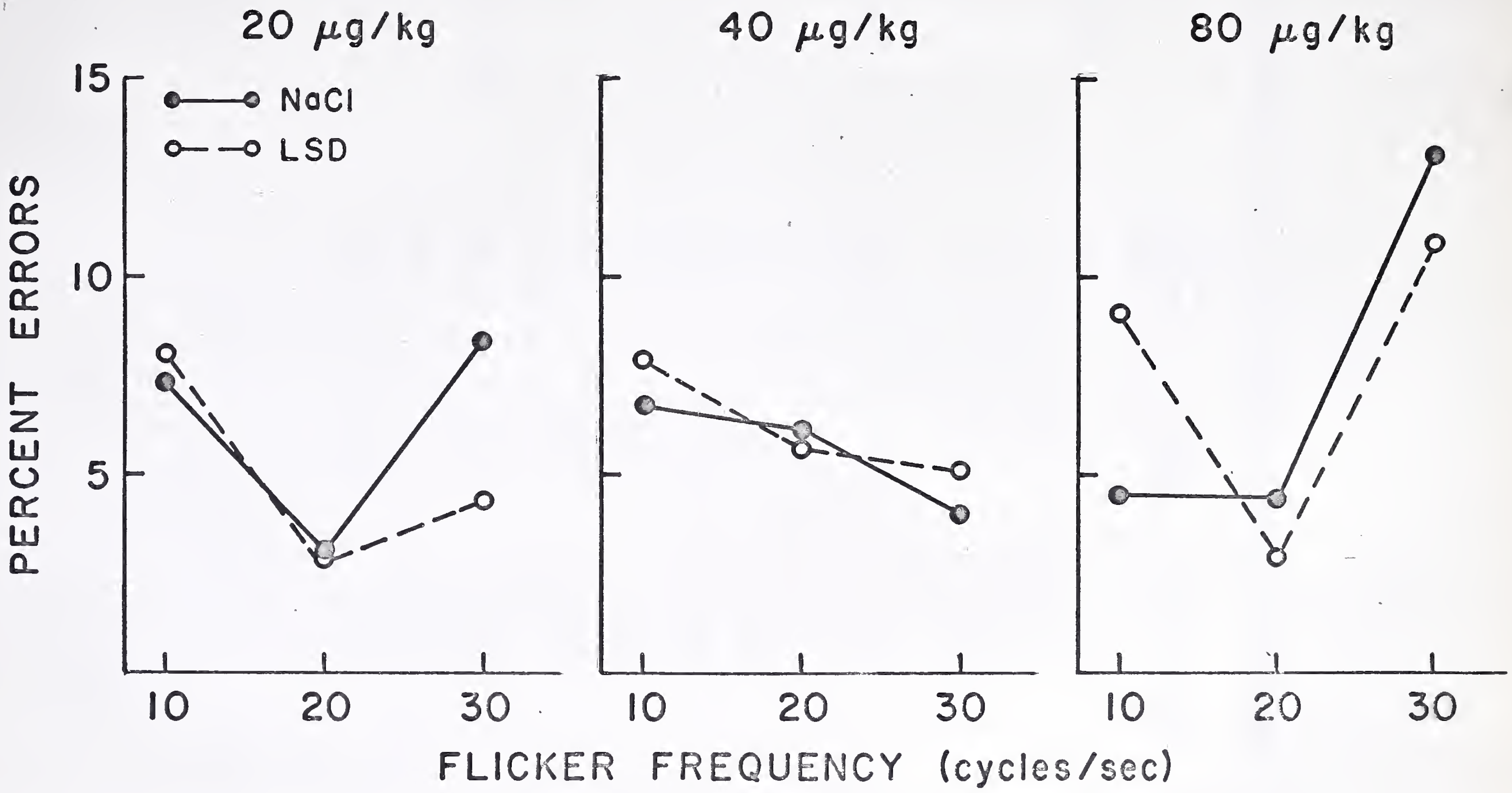

20 µg/kg
40 µg/kg
80 µg/kg
NaCl
LSD
PERCENT ERRORS
15
10
5
10
20
30
FLICKER FREQUENCY (cycles/sec)

Table 2

PER CENT ERRORS, NaCl vs 20 μg LSD/kg, AVERAGED OVER 6 BIRDS

	Flicker frequency (cps)	NaCl	20 μg LSD/kg
EXP. I	30	5.9	3.2
	50	11.9	8.5
	70	46.1	50.8
EXP. II	50	7.1	5.1
	55	16.9	8.6
	58	23.1	16.2
	62	34.6	28.9
	66	39.1	39.0
	71	43.7	39.2
EXP. III	10	7.3	8.0
	20	3.1	3.0
	30	8.3	4.4

required for the pigeon to complete the task of obtaining 60 reinforcements. This figure would take pause time into consideration. The other measure is running rate, computed by dividing total responses per session (including errors) by running time (total time minus pause time). The rate measure reflects the fact that a bird working at a difficult task might make more errors and therefore take longer to obtain 60 reinforcements than a bird working at an easy task. Also, if pause time were influenced by difficulty of the task (which, in fact, it is not) running rate would correct for that factor.

The dose-response curves for the two measures are shown in Fig. 7. Total time per drug session is divided by total time in the NaCl session the day before. At all dose levels, as shown, the quotient is greater than one since total time under LSD is greater than total time for saline. Running rate per drug session was divided by running rate for the NaCl session of the previous day. At all dose levels, this quotient was less than one since the birds respond less rapidly during the drug sessions. These results are dose-related and hold up through all three experiments, although the effect seems to be less in the third experiment than in the previous two. Thus LSD both increases the amount of pausing and decreases running rate; the degree of both of these effects depends on dose.

Interesting aspects of the pause data are shown in Tables 3 and 4. Table 3 illustrates the fact that there was no significant change in the number of pauses occurring in the three experiments, since Experiment II was twice as long as the others. The starting time data in Table 4 show no systematic change over the three experiments. There is a suggestion that increased drug dose leads to pauses beginning earlier in the session.

Figure 7. Dose-Response Measures: $\frac{\text{Rate of Response/LSD}}{\text{Rate of Response/NaCl}}$ and $\frac{\text{Total Time/LSD}}{\text{Total Time/NaCl}}$, By LSD Dose for Each Experiment, Average of Six Birds

Sessions Per Drug Dose Per Bird:

Exp. I: 3

Exp. II: 6

Exp. III: 3

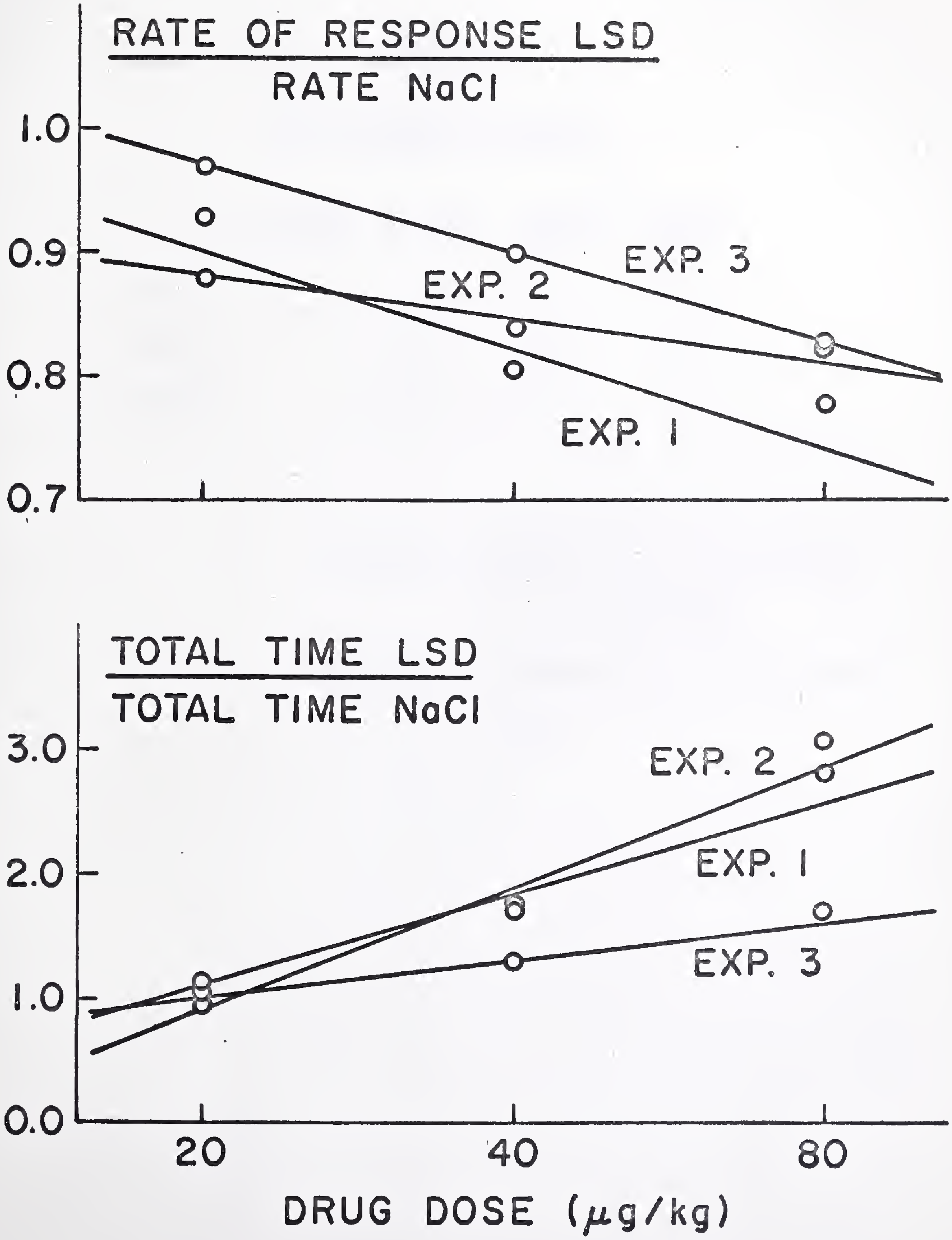
RATE OF RESPONSE LSD / RATE NaCl
1.0
0.9
0.8
0.7
EXP. 3
EXP. 2
EXP. 1
TOTAL TIME LSD / TOTAL TIME NaCl
3.0
2.0
1.0
0.0
EXP. 2
EXP. 1
EXP. 3
20
40
80
DRUG DOSE (μg/kg)

Table 3

TOTAL NUMBER OF PAUSES

LSD Dose:	20 μg/kg	40μg/kg	80μg/kg
Exp. I	3	12	17
Exp. II	11	32	56
Exp. III	8	12	17

Experiments I and III: 18 experimental sessions per drug dose.

Experiment II: 36 experimental sessions per drug dose.

Table 4

MEDIAN TIME OF PAUSE START (MS, in minutes after start of experiment)
AND MEDIAN DURATION OF PAUSE (MD, in minutes)

	Exp. I		Exp. II		Exp. III	
LSD Dose (μg/kg)	MS	MD	MS	MD	MS	MD
20	20.8	4.9	13.0	3.6	9.5	1.0
40	10.8	13.0	13.0	8.6	6.0	1.4
80	6.8	38.7	7.0	18.9	9.0	2.6

The median pause duration data are shown in Fig. 8. It will be noted that pause duration increases with dose in each experiment. In addition, the data show that at each dose, pause duration decreased from one experiment to the next. As stated previously, the total period of experimentation lasted approximately one year. Thus, the pause duration results demonstrate a dose-response relationship and also the long-term development of tolerance to LSD.

Another method of illustrating the pause results is demonstrated by Fig. 9. The frequency of occurrence of pauses per time interval after start is shown by LSD dose for each experiment. To count as a pause for a given time interval, a pause may begin during that time interval or it may have started previously and be continued into the time interval. For all experiments there is a peak of pause frequency at about 12 to 14 minutes after the start of the experiment. From one experiment to the next, however, the progressive decline in pause duration is illustrated by the decreasing frequency of pauses in the later time intervals.

FOOD CONSUMPTION

As noted in an earlier section of this paper, there have been suggestions both clinically and experimentally that LSD decreases food consumption. An attempt to verify these impressions was made.

Each bird was weighed immediately before and directly after each experimental session. Since each session contained exactly 60 3-second reinforcement periods, comparisons between sessions regarding food consumption during the session can be made. The data from Experiment II were examined since,by the time that Experiment was run, defecation by the birds during the discrimination test (presumably due to the novelty of the experimental environment)

Figure 8. Median Pause Duration in Minutes by LSD Dose, Shown for each Experiment, Average of Six Birds

Sessions Per Drug Dose Per Bird:

Exp. I: 3

Exp. II: 6

Exp. III: 3

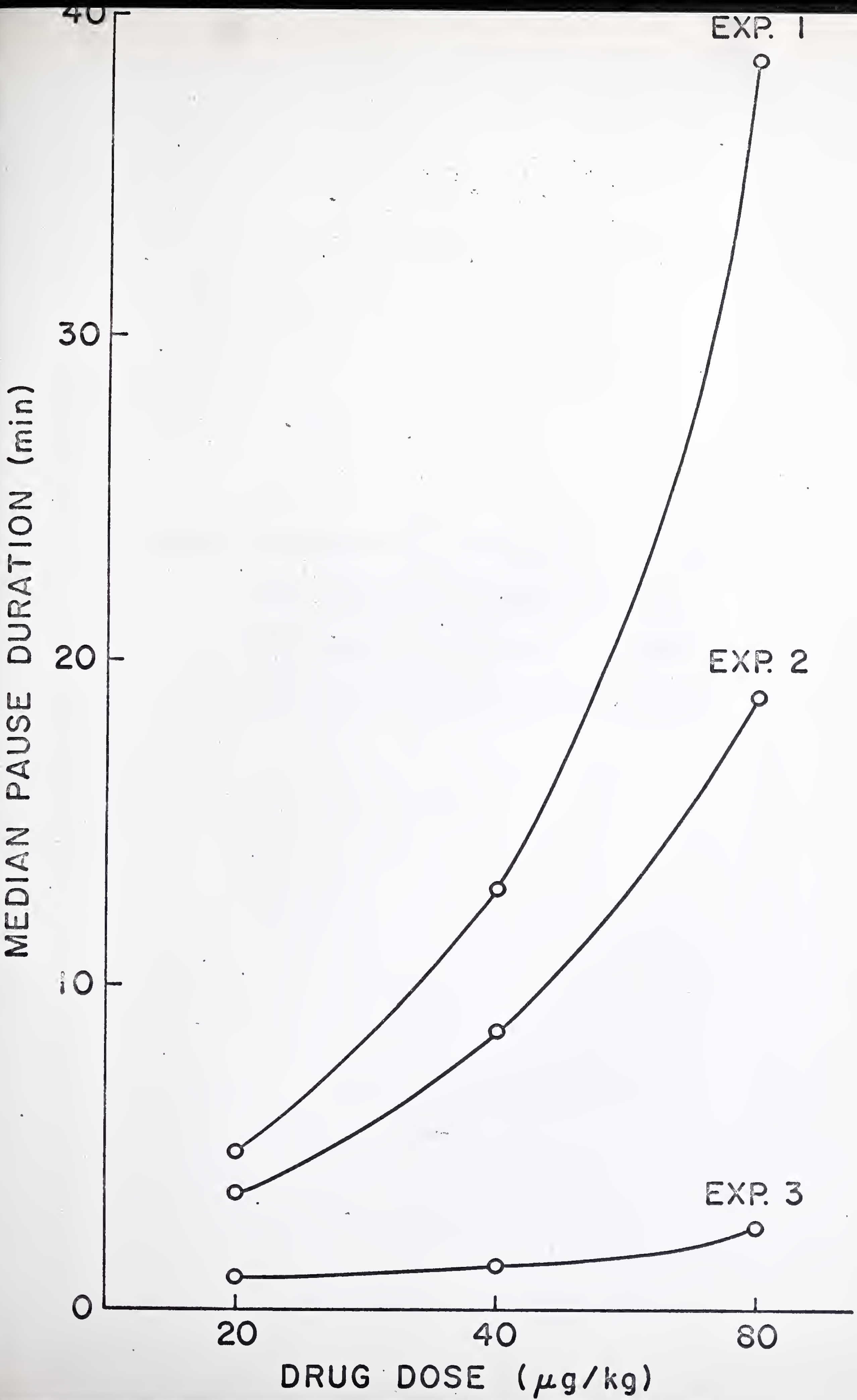
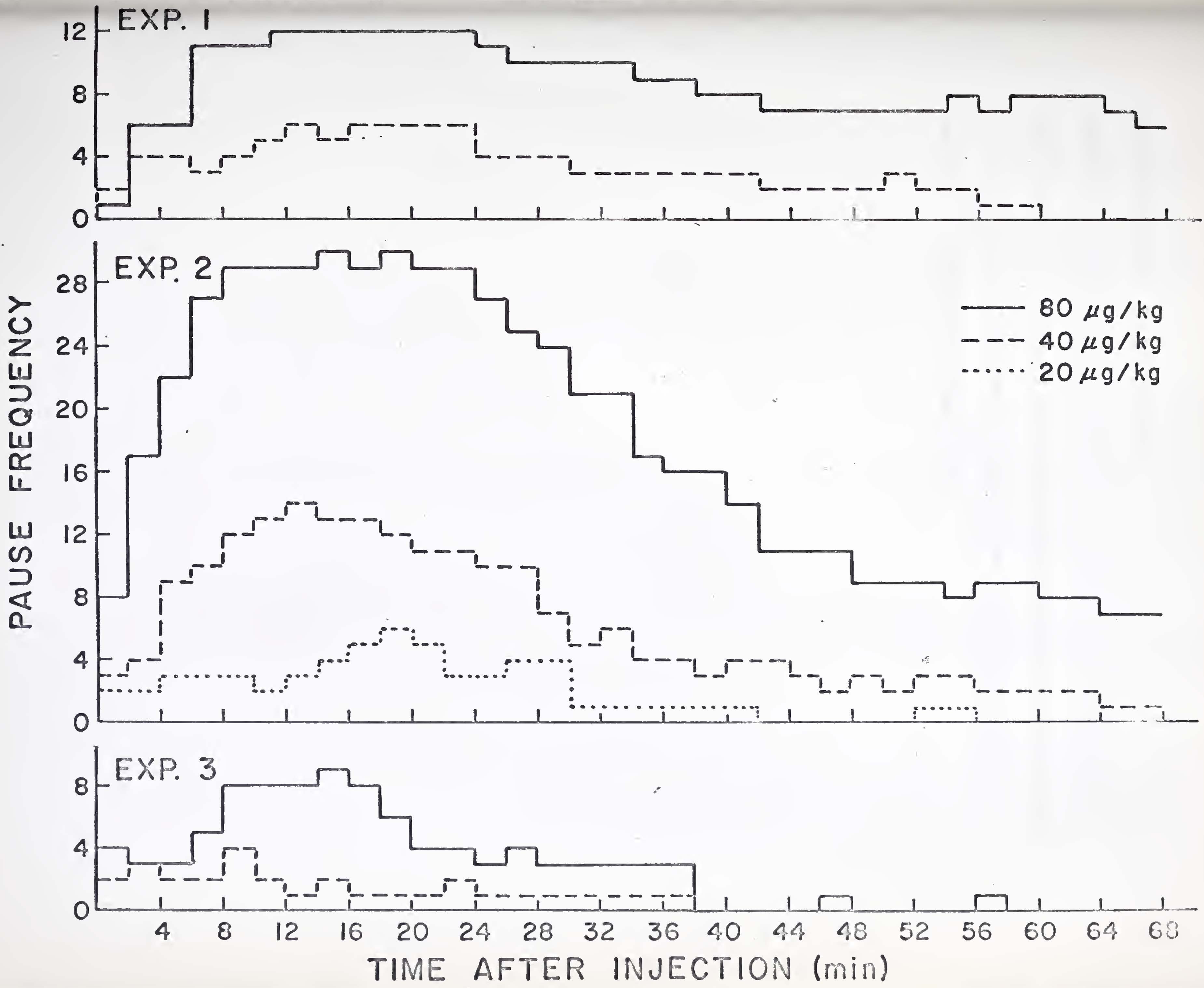
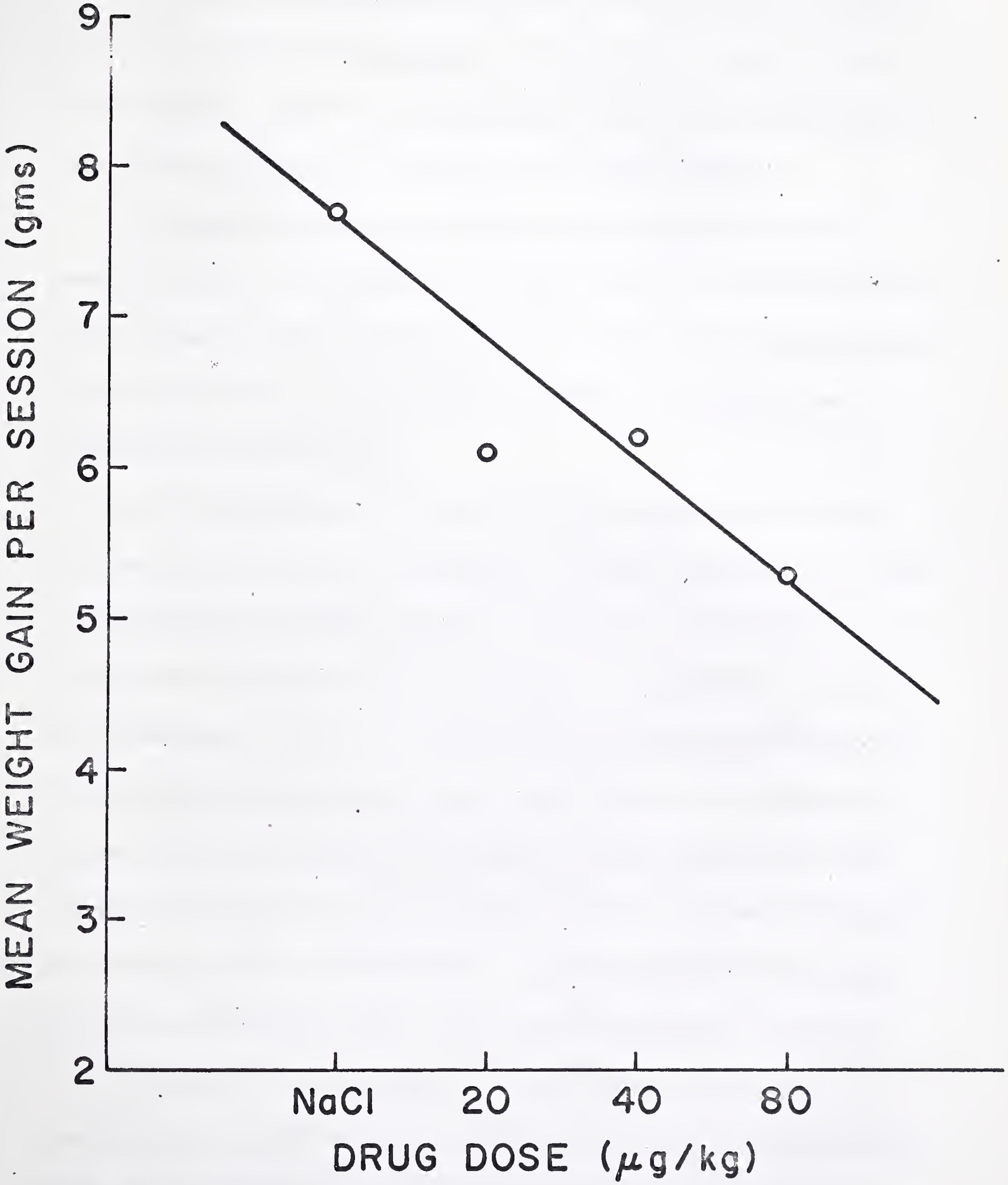

0
10
20
30
40
MEDIAN PAUSE DURATION (min)
EXP. 1
EXP. 2
EXP. 3
20
40
80
DRUG DOSE (μg/kg)

Figure 9. Frequency of Pauses Occurring Per 2-Minute Time Interval After Start of Experiment, Shown for Each Experiment and LSD Dose (20 μg LSD/kg Results Too Small to be Shown for Experiments I and III)


EXP. 1
EXP. 2
EXP. 3
12
8
4
0
28
24
20
16
12
8
4
0
8
4
0
PAUSE FREQUENCY
80 µg/kg
40 µg/kg
20 µg/kg
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
TIME AFTER INJECTION (min)

had ceased to occur. The results of the analysis are shown in Fig. 10. Average weight gain per session on saline days was 7.7 grams; for 80 μg LSD/kg days it was 5.3 grams. The t-tests for differences comparing LSD days to the preceding NaCl days were not significant, although the tests for 40 and 80 μg/kg were suggestive ($p<.07$ and $p<.08$ respectively).

Figure 10. Experiment II: Weight Gain Per Session in Grams by LSD Dose, Average of Six Birds, Six Sessions Per Bird at each Drug Dose and Eighteen Sessions Per Bird with Saline


MEAN WEIGHT GAIN PER SESSION (gms)
9
8
7
6
5
4
3
2
NaCl
20
40
80
DRUG DOSE (μg/kg)

DISCUSSION

The significant increase in accuracy following 20 μg LSD/kg is perhaps the most important finding of the experiments. While previous research on critical flicker frequency suggested that an improvement in discrimination might be seen with LSD (see introduction), interpretation of the data is difficult.

One suggestion might be that the drug, since it decreases the rate of responding, leads to a more deliberate choice by the bird. However, this notion is hard to support; while slowing of responding is an effect which is seen more and more strongly as dose is increased, accuracy, which is raised by low doses, declines with increasing dosage.

It will be recalled that the duration of the total <u>on</u> period for the lights increased as flicker frequency was increased. Perhaps a light which is on for 400 milliseconds per second appears brighter to a pigeon than a light which is on for 200 msec/sec, even though the absolute intensity of the light when it is on is the same in both cases. Peterson (1966), as mentioned earlier, did find that 20-35 μg LSD/kg increased apparent brightness of a visual stimulus. If, for example, the apparent brightness of the lights were doubled, then LSD might have the effect of making the 400 msec/sec stimulus appear as bright to the pigeon as a flickering light whose <u>on</u> period was 800 msec/sec. The 200 msec/sec light might appear as bright as a 400 msec/sec light. Thus, the absolute difference in brightness between the two stimuli might appear to be equivalent to an <u>on</u> period of 400 msec/sec rather than 200 msec/sec, increasing the ease of discrimination between them. But this hypothesis is in conflict with the increases in generalization for

brightness found with LSD (Key, 1964), where stimuli of various intensities appeared less different from one another than they did normally, and therefore seems of dubious value.

It is possible that the results are specific to a flicker discrimination and therefore are of little general interest. The neurophysiological evidence indicates that LSD treatment yielded electrical responses not unlike those found when the retinas were stimulated with flickering light (Schwartz and Cheney, 1965a, 1965b). Perhaps there is an additive effect operating, where a high frequency flicker, e.g., 71 cps, which may appear steady to a bird given saline, is imparted with an extra "flicker" due to LSD. The 100 cps flicker presumably is at a high enough frequency so that it continues to appear steady after LSD administration.

Yet this interpretation does not seem plausible. For one thing, LSD decreased errors at flicker frequencies where the birds were making only 7% errors when given saline. It is hard to imagine that this discrimination is so "borderline" for the pigeon that an additive mechanism could operate. In fact, if the action of the drug were to raise the flicker fusion "threshold," one would expect to see increased accuracy of discrimination only for the frequencies which, under saline, are above "threshold" and which the drug has shifted to below "threshold."

The fact that LSD, at 20 μg/kg, increased accuracy generally over the whole range of flicker frequencies examined, suggests that the effect is some type of perceptual facilitation broader than just elevation of the CFF. Blough (1957a) tested pigeons on a task which required responding on one or the other of two keys,

depending upon whether a light in the box was on or off. The accuracy of performance under these conditions was improved by LSD. It is unlikely that the drug made it easier for the pigeon to tell whether the light was on or not. What is possible is that the drug somehow increased the "importance" of the light; that is, responses to distracting stimuli were less likely to be emitted under the drug. Thus in the present series of experiments, LSD may have given flicker a "sensory impact" which it did not possess or possessed to a lesser degree under saline, making it impossible for the change from steady to flicker to go unnoticed. This correlates well with clinical observations that humans taking LSD report great increases in perceived intensity of visual stimuli (Cohen, 1964).

The data suggest that two effects may be operating after the pigeon has been given LSD. First, perception of sensory input is intensified (above). With relatively low doses of drug, _e.g._, 20 µg/kg, this increase in perceived intensity has the effect of improving accuracy of performance on visual discrimination tasks which are already well-learned.

It is apparent that this same effect of the drug, if of sufficient magnitude, might result in a behavioral change quite opposite to that of low doses. Thus 80 µg LSD/kg may intensify all stimuli to such a degree that perceptual disorientation is the result. The bird is unable to distinguish between the flickering and steady light stimuli since all sensory input is of literally staggering impact. High doses may therefore result in a _decrease in_ accuracy.

Blough used oral doses of 200 and 500 µg LSD/kg (1957a). Since drugs taken orally are absorbed more slowly and less completely than the same drug injected intramuscularly, Blough's doses may be more comparable to those used

here than would at first appear. His testing sessions ran as long as 5 hours. The sessions in the present study lasted about 20 minutes if the bird were given saline or 20 µg LSD/kg, about 40 minutes if given 40 µg/kg and about 80 minutes if given 80 µg/kg. Perhaps if the sessions had been of greater length, an increase in accuracy would have become evident in the latter portion of the high-dose sessions, as "disorientation" subsided. Another possibility is that the stage of perceptual disorientation may be initiated by the rapid delivery to the brain of a large amount of the drug, with oral administration tending to decrease this sudden effect.

In the present study, depression of response rate after LSD administration continued uniformly (except for the "pause" periods of no responding) throughout the experimental session. Blough found that this phase lasted about 2½ hours. The explanation for these results may lie with a second effect of the drug. One suggestion dealing with decreased rate would be that LSD results in general motor incoordination; however, the behavioral data on wheel-turning (Appel, 1965) and running responses (Hamilton, 1960) do not support this hypothesis. Decreased response rate may more probably be due to a decreased "interest" of the animal in the task, and specifically to a decrease in the reinforcing value of food.

The evidence that the pigeons in this study eat less in LSD sessions, despite the fact that 60 reinforcements were presented in all sessions, might be construed as indicating a decrease in actual motor ability to get to the magazine during the 3-second periods in which food is available. However, Hamilton and Wilpizeski (1961) indicate that food consumption is decreased in a dose-related fashion by LSD

in circumstances where rapid motor ability is not a factor. It is this decrease in motivation which may largely account for the slowing and interruption of responding seen in this study.

Finally, the progressive decline in pause duration over the year during which the experiments were run must be explained. The median starting time and the time of maximum pause frequency (12-14 minutes after start) did not change appreciably. These may be related to physiological "constants" such as length of time necessary for the drug to reach its "active site" in the brain. The decrease in pause duration, however, may reliably reflect the development of long-term tolerance to the effect of LSD on food as a reinforcer.

The mechanism of this development of tolerance is unknown at present. It is possible to speculate that perhaps continued administration of LSD leads to alteration in the molecular configuration at the "active sites" of the receptors for the drug, or that repeated LSD treatments deplete some vital intermediate necessary for the drug's continued action. One might suggest that LSD acts by releasing physiologically active compounds which then actually cause the changes which can be observed behaviorally. If, say, at the start of the experiments, 80 μg LSD/kg released enough of these compounds to cause the bird to "pause" for 40 minutes, one might imagine that at the time of the third experiment, only enough of these active intermediates were available to result in a pause duration of 3 minutes.

A simpler hypothesis might be that the decreases in rate and the periods of pausing were responses by the pigeons to the novelty of the drug state, and that as this novelty was diminished by repeated drug administration, so the responses to it

declined. Perhaps being in the experimental environment after LSD treatment was aversive to the birds and the decline in pause duration over the experiments reflects the pigeons' learning that the experimental session could be terminated more quickly by more rapid responding. It is not possible to choose among the above mechanisms with the data available.

In conclusion, then, the behavior shown by the birds after LSD is consonant with postulating two drug effects. One is an increase in perceptual "receptivity." At low doses of the drug, the behavioral manifestation is an increase in accuracy of performance on a task where relatively simple responses to perceptual stimuli are required. At high doses the unchecked flood of perceptual input may lead to total disorientation and a resultant decrease in the apparent discrimination ability.

The other major result of LSD administration seems to be a decrease in the value of food as a reïnforcer and a decreasing rate of responding to obtain food in a dose-related fashion. This explanation does not preclude some degree of motor inhibition or incoordination as an additional effect of the drug.

SUMMARY

Six pigeons were tested on a visual discrimination between light flickering at various frequencies and a steady light, under saline and LSD. The birds were required to respond for food reward by pecking on the left key in the experimental box at FR35 if the light was steady, and at FR35 on the right key if the light flickered. Incorrect responses were never rewarded. Each experimental session continued until the bird obtained 60 reinforcements.

The doses of LSD were 20, 40 and 80 μg/kg, administered by IM injection. Twenty μg/kg produced a significant increase in accuracy of performance and the results with 80 μg/kg suggest a decrement in accuracy. Consumption of the food reinforcer was decreased in LSD sessions, despite the fact that all sessions contained 60 reinforcements. Depression of the rate of responding and periods of complete cessation of responding were found to occur in dose-related fashion. Tolerance to the rate and pause effects apparently developed over the testing period of about one year.

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