Pharmacology Biochemistry and Behavior, Vol. 3, pp. 151–155. ANKHO International Inc., 1975. Printed in the U.S.A.

LSD and Fixed-Interval Responding in the Rat[1]

J. L. ALTMAN[2,3] AND J. B. APPEL[4]

Departments of Psychology and Psychiatry, University of Chicago, Chicago, Illinois 60637

(Received 2 October 1974)

ALTMAN, J. L. AND J. B. APPEL. *LSD and fixed-interval responding in the rat.* PHARMAC. BIOCHEM. BEHAV. 3(2) 151–155, 1975. – A series of 6 doses of lysergic acid diethylamide-25 (LSD) altered the bar-pressing behavior of 6 rats maintained on a fixed-interval, 5 min (FI 5) schedule of reinforcement. High doses of LSD (0.16, 0.32 mg/kg) depressed overall rates of responding. Low response rates, which occurred during the first half of the interval between successive reinforcements, were increased by low (0.01, 0.02 mg/kg), moderate (0.04, 0.08 mg/kg), and high doses of LSD; high rates of responding which occurred during the final half of the interval were decreased only by high doses of LSD. All doses (except the lowest) decreased the Index of Curvature, a statistic describing the temporal distribution of responses. The results were discussed in terms of baseline rate of responding and the presence or absence of timing behavior.

Lysergic acid diethylamide Fixed-interval schedule Timing Index of curvature Rats

A METHOD commonly used to experimentally investigate timing behavior involves the programming of reinforcers to occur only after the completion of a temporal interval and the subsequent emitting of some response, that is a fixed-interval (FI) schedule of reinforcement. Responses emitted during the interval have no consequences. Eventually, the subject's pattern of responding becomes "scalloped" in appearance with little or no responding early in the interval and the frequency of the responding gradually increasing as the time during which reinforcement is available approaches [12]. The higher rate near the completion of the fixed-interval as compared with the lower rate at the beginning has been cited as evidence that a temporal discrimination occurs since no events other than the passing of the (fixed) interval differentiate the beginning from the end of the interval [12].

Despite the many published accounts of the interaction of various compounds with behavior maintained by FI schedules of reinforcement, there is little information available on the effects of the potent hallucinogen d-lysergic acid diethylamide-25 (LSD) on this temporal schedule [1,33]. This is rather surprising in view of (a) the many reports of the effects of LSD on other simple schedules such as fixed-ratio (FR) [2, 4, 5, 13], variable-interval (VI) [3, 13, 15, 21], and differential reinforcement of low rate (DRL) [3] in animals and (b) information that LSD alters "timing" behavior or the "sense of time" in humans [20].

When rates of responding are relatively stable, as is usually the case when FR or DRL schedules are used [12], behavior appears to be controlled primarily by the dose of LSD and by the base line (pre-drug) rate of responding [2,13]. Therefore, it is the purpose of the following experiment to analyze the effects of LSD upon the shifting rates of responding generated by a single schedule, the FI. A series of 6 doses of LSD were given to rats which were trained to work for food reinforcers on an FI 5 schedule. Data analyses involved assessment of overall response rates and rates for each half of the interval. The temporal distribution of responses as described by the Index of Curvature [14] was also calculated, and drug-induced changes in this statistic were evaluated.

METHOD

Animals

Six, adult male albino rats of Sprague-Dawley strain (Sprague-Dawley, Madison, Wisconsin), weighing 275–325 g were housed individually in a colony with constant temperature (72° F) and humidity (40–50%) and a

[1] Supported by USPHS Research Development Award 1-K2-MH-09355 from the National Institute of Mental Health and by Grant 102-13-RD from the Illinois Department of Mental Health to the second author.

[2] Please send reprint requests to Dr. J. L. Altman at: Alcohol and Drug Abuse Research Center, McLean Hospital, 115 Mill St., Belmont, Mass., 02178.

[3] This experiment was based on Chapter II of a dissertation submitted by J.L.A. to the faculty of the Graduate School of the University of Chicago in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[4] Present address: Department of Psychology, University of South Carolina, Columbia, S. C. 29208.

12 hr, day–night cycle. The food intake of the animals was restricted to 10–12 g of Purina Laboratory Chow each day in order to maintain relatively constant weight levels. Water was available ad lib.

Apparatus

The experiment was conducted in 2 experimental chambers which have been described in detail elsewhere [13]. Each box contained a single lever located in the center of one of its sides (about 5 cm above the floor); a force of 10–15 g activated the lever and defined a bar-pressing response. A dim, 28 V d.c. house light was mounted behind a white, translucent panel directly above the lever. White noise of moderate intensity entered the box from a 10.16 cm speaker mounted on the outside of the wall which contained both the lever and the light. To the right and slightly below the lever, a dipper delivered 0.05 ml of a liquid diet of sweetened evaporated milk and vitamins. Each box was housed in a wooden outer chest which provided sound and light attenuation. All experimental events were programmed by switching and timing circuits in an adjoining room. Responses were recorded on electromagnetic counters and cumulative recorders.

Behavioral Procedure

The animals were first trained to respond on a continuous reinforcement (CRF) schedule; the FI schedule requirements were then introduced and gradually increased. By the end of the first week, all rats were responding on an FI 5 schedule. The distribution of responses in the interval was recorded by dividing the total interval of 5 min into four 75 sec periods. This breakdown was used to calculate the average, overall rate of responding, the rate during each half of the interval, and the Index of Curvature, a rate-independent statistic previously used to dsecribe quantitatively the FI scallop [14]. All sessions lasted two hours.

Pharmacological Procedure

Drug administration occurred 30 min after the beginning of each session at which time the session timer was stopped. The animal was removed from the experimental chamber, injected intraperitoneally (IP) with either a saline vehicle (isotonic saline) or a specific dose of LSD, and returned to the chamber from the remaining 90 min of the session. (LSD was in the form of 0.1 mg/ml ampules manufactured by Sandoz Pharmaceuticals and obtained from the Center for the Study of Narcotic and Drug Abuse, National Institute of Mental Health.) Both control and drug data were based on the last 90 min of the session. Once stable response rates were obtained for four consecutive saline control days (the criterion used was less than 5 percent variation in the number of responses during the first half of the FI over the 4 days, since variability was greatest during the first half), the initial LSD dose was administered. Subsequent sessions were conducted with saline until stable baselines were again present for 4 consecutive days; then, the next LSD dose was injected. The LSD dosage regimen was 0.01, 0.02, 0.04, 0.08, 0.16, 0.32 mg/kg, and was repeated twice for each rat – in an ascending and then descending sequence for three rats, and in a descending and then ascending order for the other three rats. Control means were calculated from the data obtained upon the day immediately preceding the drug session.

RESULTS

Overall response rates averaged 0.27 responses/sec for the rats during saline control days (Fig. 1), 0.03 responses/sec occurred during the first half of the interval (Fig. 2) and 0.50 responses/sec during the final half (Fig. 3). On baseline (control) days, the mean Index of Curvature score was 0.577 (Fig. 1).

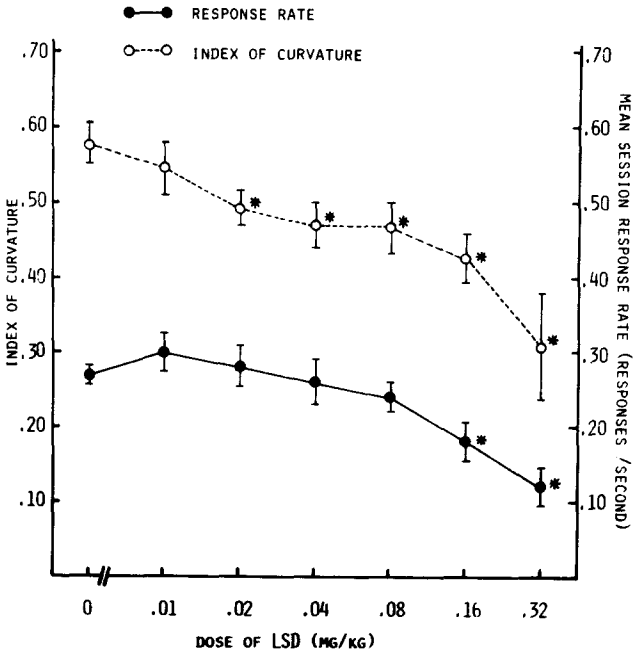

FIG. 1. Mean (and standard errors of the mean) Index of Curvature and overall response rates under control and LSD conditions. Asterisks denote significant changes at the 0.05 level.

Only the high doses of LSD (0.16, 0.32 mg/kg) produced a significant decrease in overall rate (Wilcoxon matched-pairs signed-ranks test, $p<0.05$). However, examination of each half of the fixed-interval (Figs. 2 and 3) revealed that significance drug effects were produced by low (0.01, 0.02 mg/kg) and moderate (0.04, 0.08 mg/kg) doses of LSD as well. During the first half of the interval, when response rates were low, there were significant increases in the rates following low (Wilcoxon matched-pairs signed-ranks test, $p<0.05$), moderate (Wilcoxon matched-pairs signed-ranks test, ($p<0.005$), and high (Wilcoxon matched-pairs signed-ranks test, $p<0.05$) doses of LSD. Thus, all doses of LSD significantly increased the low rates of responding found in the first half (150 sec) of the interval – the flat portion of the scallop.

LSD was not as effective in altering the high response rates which occurred during the last half of the interval. Low doses produced no changes in the rates, while the moderate doses approached but did not significantly decrease second half responding ($p<0.10$). Only the high doses of LSD significantly depressed high response rates (Wilcoxon matched-pairs signed-ranks test, $p<0.005$).

The Index of Curvature was significantly decreased (Wilcoxon matched-pairs signed-ranks test, $p<0.05$) by all doses of LSD except the lowest dose (Fig. 1). Additional analysis of the effects of LSD on the Index of Curvature

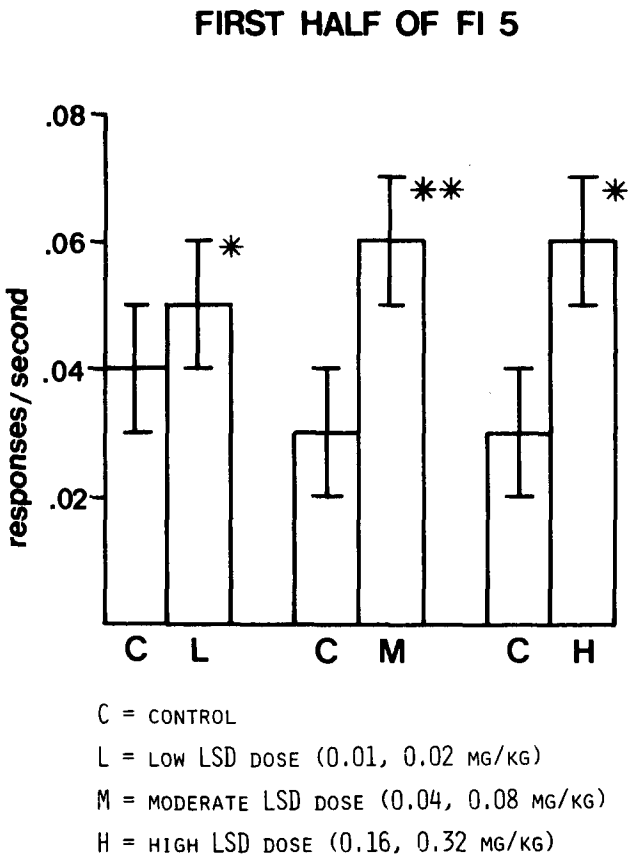

FIG. 2. Bar-graphs of mean (and standard errors of the mean) rate of responding during the first half of the FI under control and LSD conditions. Abbreviations: C = control; L = low LSD dose (0.01, 0.02 mg/kg); M = moderate LSD dose (0.04, 0.08 mg/kg); H = high LSD dose (0.16, 0.32 mg/kg); *significant at the 0.05 level, **significant at the 0.005 level.

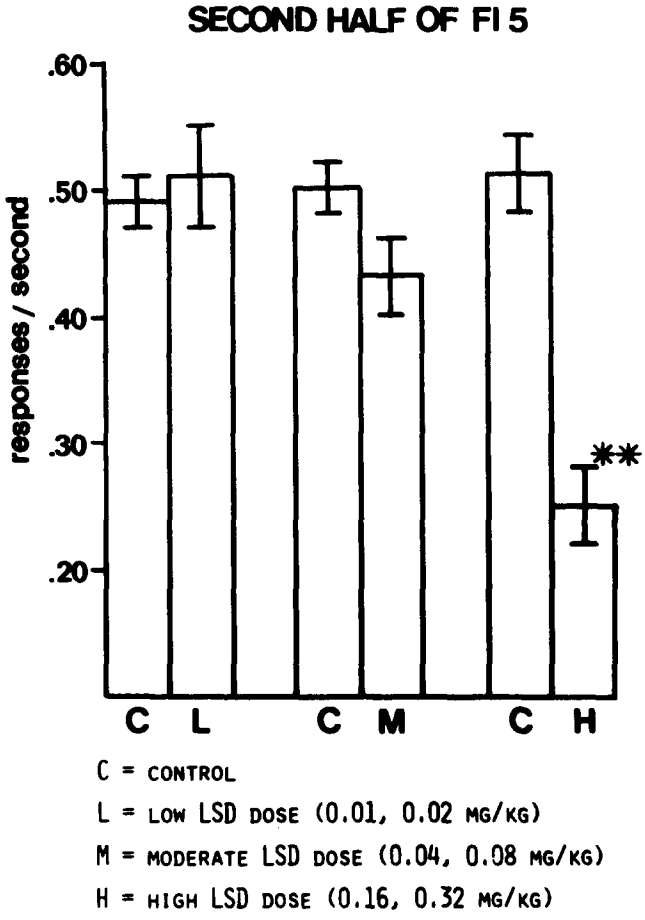

FIG. 3. Bar-graphs of the mean (and standard errors of the mean) rate of responding during the second half of the FI under control and LSD conditions. (Same abbreviations as Fig. 2).

indicated a significant linear trend, $F(1,30 = 43.5563$, $p<0.001$, or dose-dependent effect. That is, the greater the dose of LSD, the greater the decrease in the Index of Curvature. These shifts in the curvature statistic contrast with the lack of change (except at the high doses) in the overall response rates (Fig. 1) and tend to confirm that these two measures of performance are relatively independent [16].

DISCUSSION

Under control conditions, the behavior of all subjects exposed to the fixed-interval schedule showed the scallop pattern typically reported [12]. Rates were low early in the interval and accelerated positively towards the end of the interval as the time for the presentation of the reinforcer approached.

The effects of LSD were both dose and rate dependent. Examination of rate changes over the entire interval indicated that only high doses (0.16, 0.32 mg/kg) of LSD were effective in suppressing overall response rate. This tends to confirm the general finding that high doses of any drug will decrease ongoing behavior [22]. Also, it is known that LSD causes increased periods of pausing with increased doses on other simple schedules of positive reinforcement [4, 5, 13].

A more detailed analysis of the rates of responding in each half of the FI revealed significant interactions between the dose administered and the rate of responding. All doses of LSD increased the low response rates occurring in the first half of the interval, but only the high doses decreased the accelerated rates of responding of the last half. This finding is in agreement with previous experiments in which hallucinogenic drugs induced a disruption of the FI pattern of responding by facilitating the initial, low response rates and depressing, or leaving unchanged, the later, high rates [6, 17, 33]. Similar results have also been noted with other drugs in earlier studies of behavior maintained on fixed-interval schedules [9, 24, 29, 31, 36].

Reviews of the influence of drugs upon other simple schedules such as the FR, VI, and DRL [9, 10, 22] suggest that while the action of drugs may be mediated by multiple factors (e.g., genetic variables, environmental conditions), the most critical determinants are the dose of the drug and the characteristics of the on-going behavior, particularly the rate or frequency of occurrence of the response. The dosage administered is especially important since many drugs will

have opposite effects at different dose levels [19,25]. In general, drugs tend to facilitate low rates of responding and to depress high rates.

Every dose of LSD (except 0.01 mg/kg) significantly decreased the Index of Curvature, a statistic describing the temporal distribution of responding [14] and previously shown to be useful in analyzing the effects of drugs upon the FI response pattern [16,29]. The shifts in the Index of Curvature along with the marked changes in rate, particularly the early response rates, clearly demonstrate that LSD disrupts the FI scallop.

Many investigators have postulated that the scalloped pattern of responding generated by the fixed-interval schedule represents an underlying temporal discrimination [23, 27, 30] since little responding occurs early in the interval when the probability of reinforcement is low, and high rates of responding are emitted near the end of the interval when reinforcement is most likely. Others, however, have suggested that the pattern is due to schedule "dynamics" – that is, the effects of reinforcement and delayed reinforcement upon responding – and not necessarily to any hypothetical temporal discrimination [11,26]. While such factors as the "dynamic" and differentiating properties [8] of the FI schedule or its "aversive" and "cost" effects [7, 28, 35] contribute to characteristic FI performance, they cannot adequately account for the "timing" behavior demonstrated in FI experiments where these factors have been eliminated or greatly reduced [18,34]. While timing may be present during FI, and may be at least partially responsible for the scallop, it cannot be assumed that drug-induced disruptions of fixed-interval performance necessarily indicate that any timing mechanism is being affected. Many other factors may be operating. Compounds such as LSD might alter the "time sense" of the organism [20], change other schedule influences, or do both.

In summary, the results of the present experiment indicate that LSD may affect the temporal responding of rats working on a fixed-interval schedule of reinforcement. The influence of other schedule factors prevents a more definitive conclusion about LSD and timing mechanisms or time sense. Future experiments concerned with the effects of drugs upon timing behavior or temporal discriminations should employ procedures which unequivocally involve the perception of time. Such procedures (described in detail [8, 32, 37] entail the presentation of different stimulus durations associated with reinforcement (or other explicit consequences for responding) only after the stimulus ends, and treat stimulus duration as a property of stimuli to be discriminated in the same way as other properties of stimuli such as frequency or intensity.

REFERENCES

1. Altman, J. L. and J. B. Appel. Effects of LSD on fixed-interval responding in the rat. In: *Proc. 79th a. Conv. Am. psychol. Ass.* 1971, pp. 628–629.
2. Appel, J. B. The effect of "psychotomimetic" drugs on animal behavior. In: *Psychopharmacology: A Review of Progress 1957–1967,* edited by D. Efron. Washington, D. C.: U. S. Government Printing Office, 1968, pp. 1211–1222.
3. Appel, J. B. Effects of LSD on time-based schedules of reinforcement. *Psychopharmacologia* **21:** 174–186, 1971.
4. Appel, J. B. and D. X. Freedman. The relative potencies of psychotomimetic drugs. *Life Sci.* **4:** 2181–2186, 1965.
5. Appel, J. B., W. E. Whitehead and D. X. Freedman. Motivation and the behavioral effects of LSD. *Psychon. Sci.* **12:** 305–306, 1968.
6. Boyd, E. S., E. D. Hutchinson, L. C. Gardner and D. A. Meritt. Effects of tetrahydrocannabinols and other drugs on operant behavior in rats. *Archs int. Pharmacodyn. Ther.* **144:** 533–554, 1963.
7. Brown, T. G. and R. K. Flory. Schedule-induced escape from fixed-interval reinforcement. *J. exp. Analysis Behav.* **17:** 395–403, 1972.
8. Catania, A. C. Reinforcement schedules and psychophysical judgements: A study of some temporal properties. In: *The Theory of Reinforcement Schedules,* edited by W. N. Schoenfeld. New York: Appleton-Century-Crofts, 1970, pp. 1–42.
9. Cook, L. and R. T. Kelleher. Drug effects on the behavior of animals. *Ann. N. Y. Acad Sci.* **96:** 315–335, 1962.
10. Dews, P. B. Drugs in psychology. A commentary on Travis Thompson and Charles R. Schuster's *Behavioral Pharmacology. J. exp. Analysis Behav.* **13:** 395–406, 1970.
11. Dews, P. B. The theory of fixed-interval responding. In: *The Theory of Reinforcement Schedules,* edited by W. N. Schoenfeld. New York: Appleton-Century-Crofts, 1970, pp. 43–61.
12. Ferster, C. B. and B. F. Skinner. *Schedules of Reinforcement.* New York: Appleton-Century-Crofts, 1957.
13. Freedman, D. X., J. B. Appel, F. R. Hartman and M. E. Molliver. Tolerance to behavioral effects of LSD-25 in rat. *J. Pharmac. exp. Ther.* **143:** 309–313, 1964.
14. Fry, W., R. T. Kelleher and L. Cook. A mathematical index of performance on fixed-interval schedules of reinforcement. *J. exp. Analysis Behav.* **3:** 193–199, 1960.
15. Gardner, E. L. Effects on LSD-25 on bar-pressing behavior in the hooded rat. *Psychon. Sci.* **3:** 507–508, 1965.
16. Gollub, L. R. The relations among measures of performance on fixed-interval schedules. *J. exp. Analysis Behav.* **7:** 337–343, 1964.
17. Greenberg, I. The effects of 1-(Δ)-9-trans-tetrahydrocannabinol on low and high response rates generated under two similar conditions. Unpublished doctoral dissertation, Syracuse University, 1972.
18. Harzem, P. Temporal discrimination. In: *Animal Discrimination Learning,* edited by R. M. Gilbert and N. S. Sutherland. New York: Academic Press, 1969, pp. 299–334.
19. Hearst, E. and J. R. Vane. Some effects of d-amphetamine on the behavior of pigeons under intermittent reinforcement. *Psychopharmacologia* **12:** 58–67, 1967.
20. Hollister, L. E. Human pharmacology of lysergic acid diethylamide (LSD). In: *Psychopharmacology: A Review of Progress, 1957–1967,* edited by D. Efron. Washington, D.C.: U. S. Government Printing Office, 1968, pp. 1253–1261.
21. Jarrard, L. E. Effects of lysergic acid diethylamide on operant behavior in the rat. *Psychopharmacologia* **5:** 39–46, 1963.
22. Kelleher, R. T. and W. H. Morse. Determinants of the specificity of behavioral effects of drugs. *Ergebn. Physiol.* **60:** 1–56, 1968.
23. Keller, F. A. and W. N. Schoenfeld. *Principles of Psychology.* New York: Appleton-Century-Crofts, 1950.
24. Marr, M. J. Effects of chlorpromazine in the pigeon under a second-order schedule of food presentation. *J. exp. Analysis Behav.* **13:** 291–299, 1970.
25. McMillan, D. E. and R. J. Campbell. Effects of d-amphetamine and chlordiazepoxide on spaced responding in pigeons. *J. exp. Analysis Behav.* **14:** 177–184, 1970.

26. Morse, W. H. Intermittent reinforcement. In: *Operant Behavior: Areas of Research and Application*, edited by W. K. Honig. New York: Appleton-Century-Crofts, 1966, pp. 52–108.
27. Reynolds, G. S. *A Primer of Operant Conditioning*. Glenview, Illinois: Scott, Foresman and Company, 1968.
28. Richards, R. W. and M. Rilling. Aversive aspects of a fixed-interval schedule of food reinforcement. *J. exp. Analysis Behav.* **17**: 405–411, 1972.
29. Richelle, M. Combined action of diazepam and d-amphetamine on fixed-interval performance. *J. exp. Analysis Behav.* **12**: 989–998, 1969.
30. Skinner, B. F. *The Behavior of Organisms.* New York: Appleton-Century-Crofts, 1938.
31. Smith, C. B. Effects of d-amphetamine upon operant behavior of pigeons: Enhancement by reserpine. *J. Pharmac. exp. Ther.* **146**: 167–174, 1964.
32. Stubbs, A. The discrimination of stimulus duration by pigeons. *J. exp. Analysis Behav.* **11**: 223–238, 1968.
33. Tilson, H. A. and S. B. Sparber. Similarities and differences between mescaline, lysergic acid diethylamide-25 (LSD) and d-amphetamine on various components of fixed-interval responding in the rat. *J. Pharmac. exp. Ther.* **184**: 376–384, 1973.
34. Wall, A. M. Discrete-trials analysis of fixed-interval discrimination. *J. comp. physiol. Psychol.* **60**: 70–75, 1965.
35. Weiner, H. Some effects of response cost upon human operant behavior. *J. exp. Analysis Behav.* **5**: 201–208, 1962.
36. Weiss, B. and V. G. Laties. Comparative pharmacology of drugs affecting behavior. *Fedn Proc.* **26**: 1146–1156, 1967.
37. Woodrow, H. Temporal discrimination in the monkey. *J. comp. Psychol.* **8**: 395–427, 1928.