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Impairment by Lysergic Acid Diethylamide of Accuracy in Performance of a Delayed Alternation Test in Monkeys*

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With 4 Figures in the Text

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Introduction

One of the properties of lysergic acid diethylamide (LSD) is the remarkable ability of extremely small doses of this semisynthetic (about 0.001 mg/kg) to produce psychological changes in human beings, including hallucinations and delusions, as well as profound impairment of performance in intellectual tests (JARVIK, ABRAMSON and HIRSCH, 1955). Other mammals and birds require many times the human dose in order to exhibit behavioral changes (BLOUGH, 1957; COOK and WEIDLEY, 1959). In monkeys, EVARTS (1958) has shown that visual discrimination performance was not affected by doses of LSD as large as 9.95 mg/kg, but that delayed response performance was depressed. He noted that the LSD effect disappeared with continued testing, and he attributed this to overtraining. On the other hand, FUSTER (1957) has shown that performance on a tachistoscopic task by monkeys could be disturbed by doses of LSD as small as 0.005 mg/kg.

Performance on both delayed response and delayed alternation tasks has been shown to be impaired by frontal lobe and basal ganglia lesions in monkeys, but relatively unaffected by temporal lobe lesions (CHOW and HUTT, 1953; ROSVOLD, MISHKIN and SZWARCBART, 1958). Only a few experiments have dealt directly with the effect of drugs upon the performance of intact animals in delayed response tasks (HALL, WARREN and HARLOW, 1955) although a number of investigations have dealt with the effects of barbiturates and amphetamine upon the deficit in delayed response produced by frontal lesions (WADE, 1947; BLUM, CHOW and BLUM, 1951; and MISHKIN and PRIBRAM, 1953).

The present experiment was undertaken to determine whether LSD would impair delayed alternation performance in the monkey, to establish the presence or absence of tolerance, and to compare LSD with several other drugs in the same test situation. It was of particular interest to determine whether the confusional properties of LSD were related to a depressant action of this drug upon behavior generally, as reflected in

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rate of lever pressing, or whether the dichotomous choice situation of the delayed alternation task might be more sensitive than overall pressing rates.

Subjects. Eight immature Macaque monkeys were used in this experiment. They had some prior experience in the test situation and had been employed in a drug experiment several months previous to the present study. Their weights ranged from 3.4 to 5.8 kilograms.

Apparatus. The principal apparatus consisted of a modified refrigerator cabinet in which the monkeys performed the delayed alternation test. On one inner wall, were two plexiglass panels, each 10 cm × 10 cm and separated from one another by a distance of 3 cm. Timing and sequence control was obtained with appropriate relay circuitry and performance was recorded on counters which registered correct and incorrect responses. While being tested, the animals were restrained by a plastic collar in a chair constructed of aluminum and masonite as illustrated in Fig. 1. As can be seen, the animal when placed in the chamber was confronted by two panels and the reward dispenser, a flexible metal tube. The chamber was ventilated by a small blower which acted also as a source of masking noise. The animal was placed in the chair just before being tested and was returned to his home cage immediately afterwards.

Procedure. All animals were pretrained daily for several weeks on the delayed alternation task prior to drug administration. After being deprived of water for approximately 20 hours, the monkey was placed in the testing chamber. The correct response on the appropriate panel was rewarded by 0.03 cc sweetened water. At the same time, this response caused an overhead light (the "go" signal) to be extinguished and started the delay period. At the end of the delay interval (2 seconds), unless otherwise stated, the "go" signal reappeared, and the animal was required to press the opposite panel (the previously unrewarded one) in order to receive another 0.03 cc of fluid. If the animal pressed the incorrect (just previously rewarded) panel when the "go" signal appeared, the trial terminated without producing the reward, and the animal had to wait out the delay period before it could try again. This procedure was a delayed correction technique since the animal was forced to make a correct response (i.e. alternate) before being rewarded. The monkey was not rewarded so long as it perseverated in pressing the wrong side. Each time the animal responded during the delay interval (premature response), the delay timer automatically reset to zero, and the animal had to wait at least the prescribed time before it could make a rewarded response, or an error (both mature responses) again. It must be noted that this procedure differed from the fixed interval (FI) schedule shown to be susceptible to drugs (Dews, 1955) in that with FI the animal ordinarily is given no cue that the interval has ended.

Training sessions were conducted daily and lasted 30 minutes for each animal. Stable performance levels were established before drug administrations were begun. Injection of all drugs was intramuscular into the posterior thigh muscles (hamstrings) and preceded testing by 15 minutes. Doses of LSD ranged from 0.005 to 0.2 mg/kg. Compari-

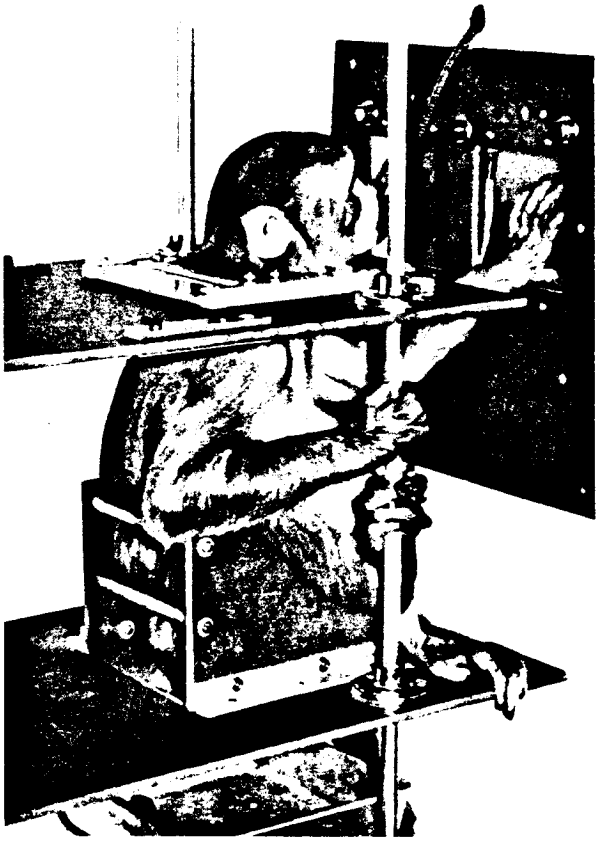

Fig. 1. Monkey pressing correct panel to receive liquid reward. When performing correctly, animal presses left and right panels alternately every 2 seconds

son with the effects produced by various doses of chlorpromazine, pentobarbital and amphetamine were made by administering these drugs to some of the animals several weeks after the termination of LSD.

Results

The depressant effects of LSD upon accuracy in the delayed alternation test is evident from Table 1. This shows both the accuracy and the total number of mature responses made by an animal during the half hour after receiving its first dose of LSD. Corresponding data are given

for the day prior to LSD — a representative control day. The four animals that received 0.025 mg/kg had at least a 30% fall in accuracy, whereas the scores of the four that received 0.005 mg/kg declined less than 21% of their control value on the previous day. The relative effect of the

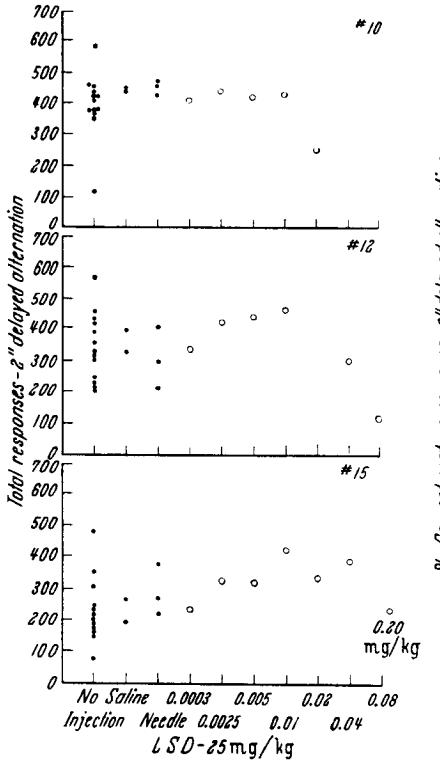

Fig. 2

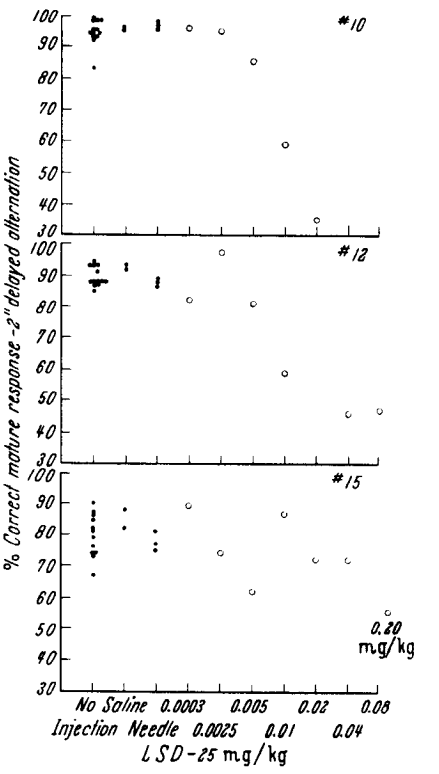

Fig. 3

Fig. 2. Dose-effect relationship, showing depression of pressing rate by LSD. The solid dots represent control values and the open dots results obtained with indicated doses of LSD-25. Each point is based upon a single day's experiment

Fig. 3. Dose-effect relationship, showing impairment of accuracy by LSD. The solid dots represent control values and the open dots results obtained with indicated doses of LSD-25. Each point is based upon a single day's experiment

two doses upon total number of responses was not as consistent as upon accuracy, but none of the animals receiving the small dose gave less than 100 mature responses in one half hour, whereas only one of the animals with the larger dose gave more than 100 presses (monkey 12 and, strangely enough, this was the animal with the biggest depression in accuracy).

Since there is no overlap between the control and experimental values, it is obvious that the differences for both percent correct and number

of responses are highly significant. The question of whether accuracy or rate was influenced more by LSD could not be answered from these data without instances in which one was affected and not the other. Consequently, some of the animals were given varying doses of the drug, so that dose-response relationships could be examined with respect to both accuracy and rate.

In Figs. 2 and 3 the dose-response relationships for three animals are plotted. Each point in Fig. 2 represents the total number of responses emitted by an animal in a 30 minute session while under the influence of the indicated dose. In Fig. 3 each point represents the accuracy achieved at that dose.

Table. 1. *Effect of First Dose of LSD on Accuracy and Rate of Delayed Alternation Performance*

Monkey	Day before LSD administration		Day of administration — LSD		
	Percent correct	No. of mature responses	Dose mg kg	Percent correct	No. of mature responses
10	99	427	0.025	58	45
12	89	410	0.025	46	242
13	88	200	0.025	56	16
15	74	306	0.025	50	11
14	80	201	0.005	70	160
17	92	301	0.005	71	111
18	91	262	0.005	74	198
20	91	299	0.005	77	245

It can be seen that the three animals show marked differences in sensitivity to LSD with monkey 15 relatively tolerant of high doses. It is evident that for both animals 10 and 12, there is a dose of LSD capable of depressing accuracy without affecting pressing rate (0.01 and 0.02 mg/kg, respectively). For animal 15, this is not so clear because the drug had relatively less effect. Nevertheless, for animal 15 too, despite the great amount of overlap with the control values, there is a downward trend in accuracy with increasing dose and, if anything, an upward trend in rate.

It must be emphasized that these data, unlike those in Table 1, are derived from repeated injections of the same animal with different doses of LSD. There were always at least three days intervening between injections, but the possibility of interactions between injections and days was present. Subsequently, in order to see what interactions might occur if they were deliberately encouraged, animals were injected with a given dose of LSD for several consecutive days. The procedure was repeated with different doses separated by control periods. This experiment lasted approximately three months. The effects of such treatment upon accuracy of performance can be seen in Fig. 3.

Fig. 4 shows the daily performance of three animals with accuracy (percent correct) plotted against time (days). The steplike portions represent the effects of consecutive daily injections of LSD in the doses indicated on the graph. The steplike function is typical of the perfor-

mance of all of the animals and indicates the development of tolerance to the particular dose. It can be seen in Figs. 3A and B that a given dose (for example 0.02 mg/kg) given at the beginning of the experiment was more effective than the same dose administered later, after a degree of tolerance had been acquired. Original sensitivity to LSD was not regained even after drug-free periods of one to two weeks. In this case, the effect can be seen only with animals 10 and 12, and not with 15. For animal 15, none of the doses used produced a drop in accuracy significantly below control values, except 0.16 mg/kg. Even this large dose was effective only the first time it was given, as can be seen in Fig. 3C. Administration of the very same dose the following day did not prevent this animal from giving a very accurate performance.

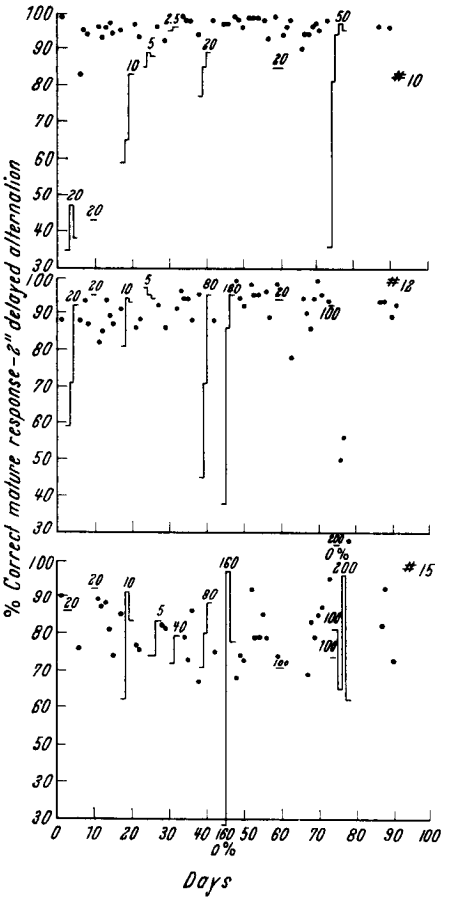

Fig. 4. Effect of repeated administration of LSD on accuracy in three animals. Note the rapid development of tolerance evidenced by the step-like improvement with a given dose, particularly prominent for animals 10 and 12. The small figures at the top of each step represent the dose of LSD, which was given for the period of consecutive days shown

Other drugs. In order to determine whether other drugs, which are known to affect the central nervous system, might produce a dissociation between accuracy and rate similar to that seen with LSD, selected doses of amphetamine, chlorpromazine, and pentobarbital were given to animals No. 10, No. 12, and No. 15. In Table 2, it is shown that in two of the animals, at least amphetamine was capable of markedly depressing the rate without particularly affecting accuracy. This is in contrast to LSD, which was capable of depressing accuracy without particularly affecting rate. The results in Table 3 with chlorpromazine and pentobarbital were gathered some months after the LSD experiments, and a

5 second instead of 2 second delay was used. Despite this change in procedure, some interesting contrasts with LSD emerged. Chlorpromazine in a dose of 0.5 mg/kg was capable of markedly depressing responding rate without influencing accuracy at all, quite the opposite effect of the lower dose of LSD. The effects of pentobarbital were more variable. In general, this appeared to depress rate, but in the doses used, its effect was much less marked than that of chlorpromazine and in one animal (No. 12) the number of responses actually increased. Monkey No. 15, in contrast to its resistance to LSD, was more susceptible than the other two monkeys to pentobarbital and was actually anesthetized by the larger dose (20.0 mg/kg).

Table 2. *Effect of Amphetamine Upon Delayed Alternation Performance (2 sec Delay)*

Monkey	Control			Amphetamine	
	Percent correct	No. of Mature responses	Dose mg/kg	Percent correct	No. of Mature responses
10	96	408	0.1	98	446
			0.25	94	231
			0.5	—	2
12	83	382	0.1	85	442
			0.25	79	112
			0.5	76	33
15	81	417	0.1	77	427
			0.25	85	180
			0.5	74	292

Table 3. *Effect of Chlorpromazine and Pentobarbital Upon Delayed Alternation Performance (5 sec Delay)*

Monkey	Control		Chlorpromazine			Pentobarbital		
	Percent correct	No. of Mature responses	Dose mg/kg	Percent correct	No. of Mature responses	Dose mg/kg	Percent correct	No. of Mature responses
10	97	246	0.5	96	25	5.0	99	171
						10.0	96	213
						20.0	83	145
12	90	192	0.5	96	27	5.0	88	225
						10.0	95	204
						20.0	89	232
15	79	266	0.5	79	198	5.0	67	239
						10.0	70	248
						20.0	66	3

Discussion

Of the drugs which were used in this experiment only LSD seemed capable of affecting the accuracy of performance of the delayed alternation task without affecting the rate. In this respect, the results which were obtained following LSD administration resemble those seen in monkeys with frontal lobe lesions. However, it has not yet been determined whether the automatic apparatus, which was employed in the

present study, tests the same functions as manual testing methods which have been used in ablation studies. With the present automatic apparatus, it is possible for an animal to make premature responses since the manipulanda are available during the intertrial interval in contrast to those in the traditional Wisconsin General Test Apparatus. The reason for the relative increase in errors with LSD is still a mystery, but appears to be dissociable from factors responsible for a decrease in rate of responding. As WIKLER (1957) has noted, "In spite of the many difficulties encountered in attempting to reconcile the data on the neurophysiological mechanisms of action of 'psychosomimetic' agents, it appears quite clear that they are capable of altering profoundly the patterns of corticipetal afferent impulses originating in the periphery, in a manner quite different from those of other drugs ... That such alteration of sensory input may produce marked changes in 'mental' and 'motor' output has been suggested by several investigators ... and this is supported by evidence independent of pharmacological data ..." It is possible that under the influence of LSD individuals are rendered more susceptible to the distracting effects of both internal and external stimuli, as has been suggested by BRADLEY and ELKES (1957) and are less capable of handling a delay type of situation.

The results of this experiment demonstrate that tolerance to LSD develops rapidly and, in addition, may persist for long periods (at least two weeks) when no drug is given. The rapid development of tolerance to LSD has previously been noted in rabbits and humans (GOGERTY and DILLE, 1956; ISBELL, FRASER, WIKLER and BELLEVILLE, 1955) and is a major source of variance when repeated doses of this drug are used in the same subject.

The cumulative effects of LSD and the variability in susceptibility make it difficult to establish threshold doses which will uniformly and repeatedly affect delayed alternation performance in different animals. In general, it would appear from the present study that a previously untreated animal will respond to an initial dose of LSD with impaired accuracy, and a moderately depressed rate of responding, but that on immediately subsequent days, the same dose will be less effective in modifying its responses.

It has been shown that accuracy of choice of equally appearing alternatives is a function which is much less susceptible to generalized physiological influences, such as motivational changes, than is the rate of responding (MEYER, 1951; and MILES, 1959). The rather unexpected finding that LSD can, under certain circumstances, depress accuracy on a delayed alternation test without affecting rate suggests that, under these conditions, it must work primarily on some nervous mechanism other than those controlling the simple instrumental response of pressing for water.

Summary and Conclusions

Monkeys were found to show impairment in performing the delayed alternation problem following injections of LSD in initial doses as low as 0.005 mg/kg. The effect of this drug was primarily reflected in a decrease in accuracy of response, although increasingly large doses tended also to depress the rate of performance. Tolerance to the effects of LSD rapidly developed and persisted for several days, at least.

Unlike LSD, amphetamine, pentobarbital and chlorpromazine either did not produce changes in accuracy, or when they did, these changes were relatively small compared to the effects of these drugs on the pressing rate. The possibility is suggested that the partial similarity of the effects of LSD to those obtained in monkeys following bifrontal lesions may reflect the operation of some common factor.

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