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BRIEF COMMUNICATION

Acute and Chronic Single Dose Effects of LSD-25 on Visual Discrimination in Rats[1]

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FRIEDMAN, H. AND R. J. CAREY. *Acute and chronic single dose effects of LSD-25 on visual discrimination in rats.* PHARMAC. BIOCHEM. BEHAV. 5(2) 223–226, 1976. – Rats subjected to either a frontal cortex lesion or to a sham operation were trained to discriminate between a lighted and unlit alley to escape shock. Following intubation with either placebo or LSD-25 (1.0 mg/kg), they were given discrimination trials 2 hr, 1 week, and 1 month later, but with an increased level of task difficulty. Single dose effects of LSD-25 were observed acutely in a transient impairment of visual discrimination accuracy, and more chronically in slower running time. Although no significant drug-lesion interactions were noted, the results were in the direction of a combinatory effect. The value of increasing the level of post-treatment task was confirmed.

LSD Discrimination performance Brain-damaged animals Single-dose effects

IN a previous study [2], the possibility of a synergistic effect of a single dose of lysergic acid diethylamide (LSD-25) and pre-existing intracranial organic pathology upon behavior was investigated experimentally. This likelihood had been raised not only by clinical observations in humans, but also by some reports [3,5] of significant effects following the ingestion of a single drug dose of LSD-25 in subjects with pre-existing brain damage. Thus the analogue study examined the visual discrimination performance of rats subjected either to a frontal cortex lesion or to a sham operation under conditions of single dose LSD-25 (1.0 mg/kg) or placebo intubation. Evidence was obtained for a relatively long-term drug effect by decreased accuracy of performance and a drug-lesion interaction was reflected in slower running time. The latter finding, suggestive of a synergistic effect, was observed, however, only when the task difficulty was increased, and this strategy of uncovering drug effects which might otherwise be obscured was in keeping with the methodology used by other investigators [1,8,9]. Since, in the prior study, the change in task difficulty was instituted following two sets of trials 24 hr and 1 week postintubation using no increase in level of discrimination difficulty, it was not possible to determine whether any acute effect existed. The present study, using the strategy of an immediate postintubation increase in task level difficulty, is concerned with acute, as well as the longer lasting single-dose drug effects upon visual discrimination performance of animals both with and without pre-existing brain-damage. Further, it attempts to replicate the previous observation of a drug-lesion interaction.

METHOD

Animals

A total of 112 experimentally naive Sprague-Dawley rats, approximately 100 days old, were used, with 80 in the main experiment and 32 in an ancillary control experiment. Upon arrival each was housed separately and allowed one week of ad lib food and water prior to assignment to surgery. Following surgery, and throughout testing, water intake was monitored as a check on well-being.

Apparatus and Procedure

The animals were subjected to either bilateral frontal cortex lesion or to sham operation, allowed 2 weeks of postoperative recovery, and then received 11 prediscrimination training trials, followed by discrimination training consisting of 2 successive blocks of 10 trials each daily to a criterion of 9 correct choices for each 10-trial block. The discrimination box, with a shock grid floor and two alleys

[1] This study was performed as part of VA Research Project No. 2935-02. LSD tartrate solution was supplied by the Biomedical Research Branch-NIDA.

in the choice chamber, used a light bulb of 281 millilamberts luminance as a cue for correct choice.

Inasmuch as the apparatus, surgery and histology, prediscrimination and discrimination training were all identical with that reported in the previous study [2], further details will not be repeated here.

Testing procedure

On the first day after the week of discrimination training, each animal was given 20 retest trials to assure adequate retention. As in the previous study, immediately following the retest trials, the animals, under light ether anaesthesia, underwent intragastric intubation with either LSD-25 or placebo at the dosage level of 1.0 mg/kg body weight and at the concentration of 0.1 mg/ml. The dosage level was the same as used in the previous study [2] where it had been determined as the lowest effective single dose after preliminary screening with squads of animals receiving four lower concentrations. (Again, it should be noted that intubation rather than injection was used in order to approximate more closely the oral type of administration commonly reported with human subjects as well as the route used almost exclusively by drug-dependent patients.) Throughout the investigation, there was no evidence of toxic effects as determined by water intake and observation of behavior.

Animals were assigned to 1 of the 4 treatment groups: drug-lesion (D-L), drug-sham (D-S), placebo-lesion (P-L), or placebo-sham (P-S). Each animal was then tested for visual discrimination in the same manner described in the discrimination training with test periods given 2 hr, one week, and one month postintubation. During all test periods in the main experiment, a light–dark discrimination more difficult than the preintubation discrimination training level (unlit alley vs 281 millilamberts luminance) was used. This was obtained by changing the unlit alley to a luminance of 50 millilamberts, i.e., the same differential as used for the initial increase in difficulty level in the previous study [2].

In order to highlight the efficacy of using a more difficult discrimination level to reveal possible acute experimental effects which otherwise might be obscured, an ancillary experiment with 32 animals (8 squads of 4 animals) was conducted. The format was identical to the main experiment but used only a single acute set of test trials with luminance unchanged from that of the discrimination training trials, i.e., offering no increase in difficulty level. (The effectiveness of increasing postintubation discrimination difficulty at other than acute periods had been pointed out in the previous study [2] with the same number of animals.)

RESULTS

In order to eliminate initial group differences and to take into account ceiling effects on scores, the analyses of results are based on data from animals matched in all 4 groups as closely as possible on the preintubation retention trials. For accuracy of performance, this, then, provided 15 squads of 4 animals matched for exact number of errors. For time scores, it was possible to obtain 14 squads matched within 1 sec on running time. An error score is the total number of errors made on a 20 trials test run by an animal, and a time score is the median number of seconds required to run from start chamber to goal box on the successful trials of the block of 20.

For the error-matched animals there was a mean body weight of 468.3 g (σ = 50.5), mean number of 4.3 (σ = 1.0) days from the end of discrimination training to retention trials, a mean of 54.7 (σ = 18.9) training trials to reach criterion, and a mean of 0.3 (σ = 0.4) errors on retention trials. There were no significant differences between the various subgroups in any of the above-mentioned variables. The time-matched animals had a mean body weight of 467.6 g (σ = 53.9), mean number of 4.3 (σ = 1.1) days from end of training to retention trials, a mean of 57.3 (σ = 18.1) training trials to reach criterion, and a mean time of 11.2 secs. (σ = 2.1) on the retention trials. Again there were no significant sub-group differences on these variables.

Both error and time scores were subjected to a three-factor analysis of variance with 2 between animal variables (drug, lesion) and 1 within animal variable (trial periods) as described in Winer [10]. As expected, and reflecting simply increased task familiarity, performance for the groups in both measures varied significantly as a function of trial periods: errors $F(2,112) = 17.40$, $p<0.001$; time, $F(2,104) = 15.99$, $p<0.001$.

In the error scores, a significant drug-trials interaction, $F(2,112) = 3.75$, $p<0.05$, was observed. Figure 1 plots the error scores of the combined drug groups and combined placebo groups by sets of trials and points to a transient acute (2 hr) drug effect. Analysis of the simple main effects at each time period confirmed this observation since only at the acute (2 hr) trials was the combined drug group significantly different from the combined placebo group, $F(1,168) = 6.69$, $p<0.05$.

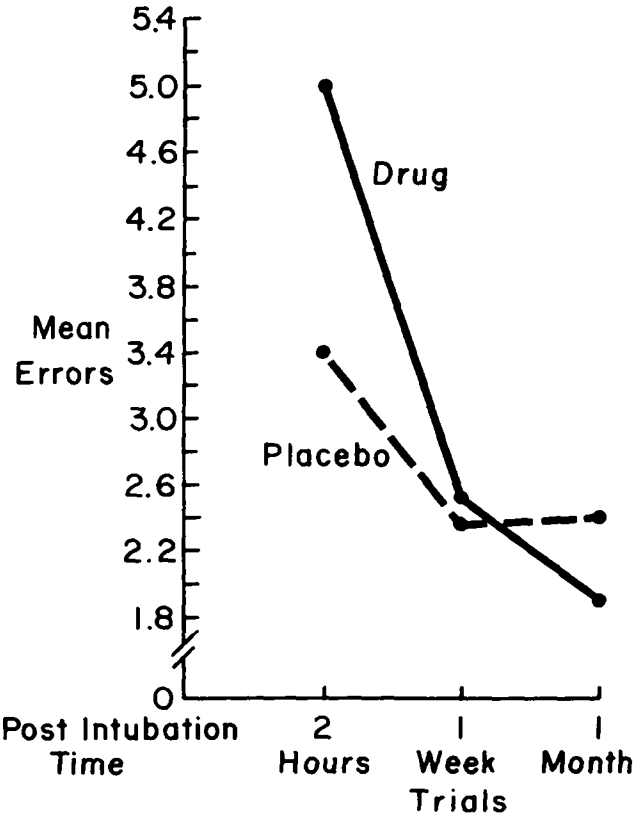

FIG. 1. Mean number of errors for all drug and all placebo animals at each postintubation time.

Analysis of time scores revealed again a significant drug-trials interaction, $F(2,104) = 4.26$, $p<0.05$, with no other significant findings. Figure 2 indicates that the effect was more chronic, beginning to appear at 1 week postintubation and increasing with trial periods to the last measurement period at 1 month. Simple main effects analyses indicated that the combined drug group showed a trend toward significant difference from the combined placebo group at 1 week postintubation, $F(1,156) = 3.49$, $p<0.07$, which increased in significance to an $F(1,156) = 5.15$, $p<0.05$, at 1 month. The relatively more abrupt improvement in error scores, as contrasted with time scores, may in large part be due to the design of the study in which only errors resulted, as in training, in continued grid shock. Although a significant "between groups" lesion effect appeared in error scores, $F(1,56) = 8.23$, $p<0.01$, there was no significant interaction with drug. Thus, the clearest evidence for a possible synergistic or combinatory effect, drug-lesion interactions, was not observed in either error or time scores. It is of interest to note, however, that in those sets of trials in which a drug effect was apparent, the ordering of the subgroups was in the expected direction. Figures 3 and 4 exemplify this.

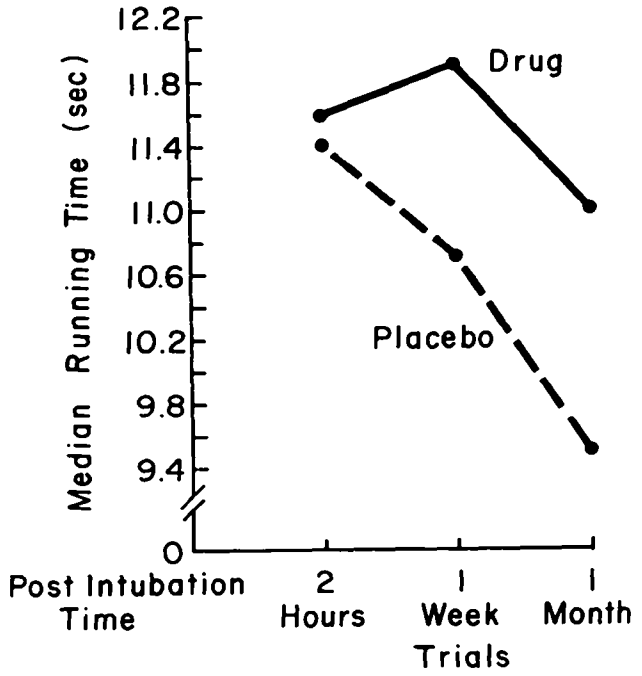

FIG. 2. Means of median running times for all drug and all placebo animals at each postintubation time.

In the ancillary experiment, the mean body weight of the animals was 444.4 g (σ = 50.1), the mean number of days from end of discrimination training to retention trials was 3.9 (σ = 0.8), the mean number of training trials to reach criterion was 55.9 (σ = 15.8), and there was a mean of 0.8 (σ = 0.7) in errors and a mean of 10.1 (σ = 2.6) secs. in running time for the retention trials. There were no significant subgroup differences on the above variables. It was apparent from the small mean pre-and postintubation subgroup changes in error scores, ranging from −0.4 to +0.1, and in running time scores, ranging from −1.6 to −0.3 secs., that the groups did not differ significantly.

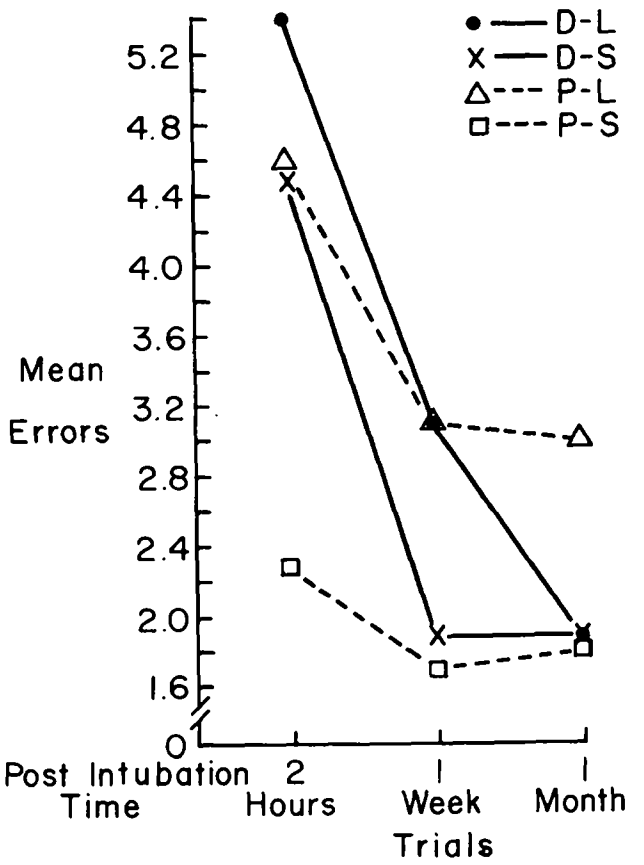

FIG. 3. Mean number of errors for all groups at each postintubation time.

Analysis of variance confirmed this with all F values < 1.0. This, then, also indicated that effects observed in the main experiment were not due simply to some type of ether-drug interaction.

DISCUSSION

The current study primarily reveals somewhat more clearly the effects of a single drug dose upon brightness discrimination than was apparent from a previous initial investigation [2] concerned with the possible synergistic effect of drug and pre-existing brain damage. Following a single dose of LSD-25 (1.0 mg/kg), there is an immediate (2 hr) decrement in accuracy of performance when the animals are required to cope with a somewhat more difficult level of discrimination than that to which they had been trained. This effect appears transient in that at 1 week and 1 month postintubation, drug per se was not differentially affecting error scores.

The effect of a single drug dose upon running times appears in a more chronic fashion. With successive time periods, the combined drug group demonstrated increasingly slower times than did the combined placebo group. The findings again confirm the conclusion of Rosen and Buga [7] that behavioral consequences outlast the drugged state. Although not dealing with the same issue as the current study, at least two other investigations [4,6] have also noted retardation in motor behavior following single dose administration of LSD-25.

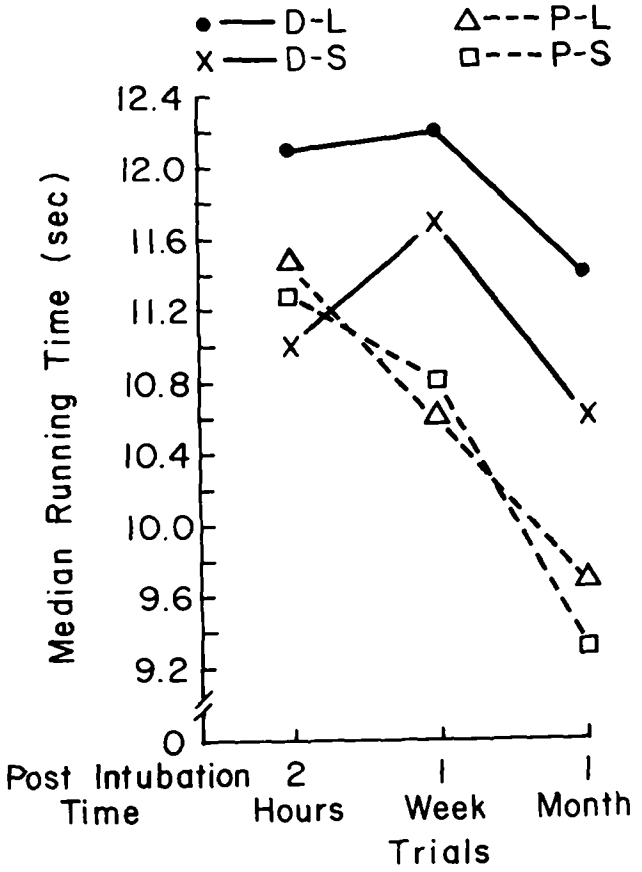

FIG. 4. Means of median running times for all groups at each postintubation time.

Although the long-term single dose drug effect in error scores observed in the previous study [2] was not replicated, the current findings are not inconsistent. The design of the previous study utilized increasing levels of discrimination difficulty which thus may have uncovered chronic learning decrements, apparent only as the task subtly changed. The present simplified design with only a single post-intubation increase in discrimination difficulty does not provide the same opportunity to elucidate chronic performance decrements in accuracy, but instead offers information as to a more acute (2 hr) effect. These considerations, together with the results of the ancillary acute experiment, confirm the value of the technique of increasing task difficulty posttreatment. In the ancillary experiment the animals, rather than being exposed to a more difficult postintubation discrimination level, were given the identical task upon which they had been trained, and no effects were observed. Thus, it appears that the most sensitive design to uncover acute and chronic drug effects should involve posttreatment changes in task difficulty in order to avoid obscuring such effects by examining simply overlearned behavior.

Drug-lesion interactions, necessary evidence for conclusions regarding a synergistic or combinatory effect, were not replicated in the present study. It should be pointed out, however, that in both error and time scores the ordering of the various groups was in the expected direction for such an effect. As such, it is in keeping with the previous findings even though in the present study that degree of difference of the drug-lesion subgroup from all others was insufficient to establish this finding with confidence.

In general, the findings point to a transient acute impairment in accuracy of visual discrimination, and a relatively chronic effect upon running time, as the results of a single dose of LSD-25. There is also the suggestion of a combinatory effect of drug and pre-existing intracranial organic pathology such that the drug-lesion group tends to demonstrate the most striking drug effect, acute and chronic. Some insight, then, may be provided into the disparate clinical observations in human subjects wherein chronic impairment from a single dose of LSD-25 have very rarely been reported, and yet some association between single drug dose and pre-existing organic brain damage has been noted.

REFERENCES

1. Becker, D. I., J. B. Appel and D. X. Freedman. Some effects of lysergic acid diethylamide on visual discrimination in pigeons. *Psychopharmacologia* **11**: 354–364, 1967.
2. Friedman, H. and R. J. Carey. Effects of LSD-25 on performance of a visual discrimination task in brain-damaged rats. *Pharmac. Biochem. Behav.* **3**: 421–424, 1975.
3. Holden, J. M. and T. M. Itil. Lobotomized patients show increased response to LSD. *Roche Rep: Frontiers of Psychiatry* **1**: 1–2, 1971.
4. Hughes, R. N. Effects of LSD on exploratory behavior and locomotion in rats. *Behav. Biol.* **9**: 357–365, 1973.
5. Korein, J. and J. M. Musacchio. LSD and focal cerebral lesions. *Neurology* **18**: 147–152, 1968.
6. Lowe, G. and D. I. Williams. The effect of LSD-25 on light-reinforced behavior in the rat. *Psychopharmacologia* **27**: 255–263, 1972.
7. Rosen, A. J. and J. A. Buga. Effects of lysergic acid diethylamide on simple instrumental conditioning, extinction and discrimination learning in the rat. *Pharmac. Biochem. Behav.* **1**: 619–627, 1973.
8. Sharpe, L. G., L. S. Otis and R. J. Schusterman. Disruption of size discrimination in squirrel monkeys (Saimiri Sciureus) by LSD-25. *Psychon. Sci.* **7**: 103–104, 1967.
9. Uyeno, E. T. Lysergic acid diethylamide and novel stimulus. *Psychon. Sci.* **18**: 52, 1970.
10. Winer, B. J. *Statistical Principles in Experimental Design*. New York: McGraw-Hill, 1962.