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LSD-Induced Alterations of Investigatory Responding in Rats

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Abstract. The effects of lysergic acid diethylamide (LSD) on investigatory responses of rats in a novel hole-board were assessed in a series of experiments. LSD (40 – 160 μg/kg) altered the temporal distribution of 'nose-poke' responses during a 24-min session; LSD-treated rats responded less than controls initially, yet increased their response rates late in the session. This dose-dependent effect was not related to the time course of the drug's action nor to alterations in general locomotor activity. Only partial tolerance was found after eight daily injections of 100 μg/kg LSD. When handling stress was minimized by placing the animals in an anteroom for 10 min before starting the test, the distribution of responding was normal although the overall frequency was still reduced. Conversely, vigorous handling potentiated the LSD effect. These results are interpreted as indicating an increased sensitivity of the LSD-treated rats to the stimuli associated with being handled and placed into the novel hole-board rather than a direct effect on investigatory tendencies. This LSD-induced potentiation of defensive responses appears to compete with the active exploration of the novel environment.

Key words: LSD – Hole-board – Exploration – Habituation – Orienting response

An action common to the class of drugs called hallucinogens is their capacity to alter the perceptual impact of stimuli in a number of sensory modalities (Mandell and Geyer, 1976). Neurophysiological studies of sensory-evoked responses suggested that hallucinogens influence the reticular formation neurons that receive collateral sensory input, thus indirectly modulating the responsiveness of primary sensory pathways (Killam and Killam, 1958; Bradley and Key, 1958; Schmeigerdt et al., 1966). More recently, the midbrain serotonergic system, suggested to be somewhat congruent with the electrophysiologically defined reticular formation (Leontovich and Zhukova, 1963; Baumgarten and Lachenmayer, 1972; Morgane and Stern, 1974), has been invoked to explain the hallucinogens' effects on sensory-integrative function. In general, hallucinogens reduce the turnover of brain serotonin (Brawley and Duffield, 1972) and inhibit the firing of serotonergic raphe neurons (Aghajanian and Wang, 1978).

Both hallucinogens and raphe lesions increase startle responses to acoustic (Davis and Sheard, 1974a, b, c) or tactile (Geyer et al., 1976, 1978) stimuli. Thus, the effects of hallucinogens and raphe lesions are to some extent independent of sensory modality. However, these findings are based only on startle responses which are thought to represent the category of defensive responses. Unconditioned responses to sensory stimuli have been divided by Russian neurophysiologists into orienting and defensive responses on the basis of situational and physiological criteria (Sokolov, 1963). Orienting or investigatory responses to mild novel stimuli involve whole body movements directing the sensory apparatus toward the stimuli. Defensive responses are elicited by more intense startling stimuli. While orienting responses habituate rapidly as the stimuli become familiar, it would be maladaptive for the organism to habituate as rapidly to the potentially threatening stimuli that elicit defensive responses.

The following studies were designed to examine the influence of the prototypical hallucinogen lysergic acid diethylamide-25 (LSD), on orienting or investigatory

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responses of rats in a novel environment to assess further the generality of the heightened sensory responsivity observed with measures of defensive responses. The test apparatus used in these studies, a hole-board, is a simple chamber in which investigatory responses are quantified as the number of 'nose-pokes' into holes in the floor. A companion paper (Geyer et al., 1979) describes an alteration in the temporal distribution of nose-pokes by rats in a novel hole-board that is a characteristic effect of a variety of hallucinogens. The present paper describes studies intended to better characterize the nature of this alteration.

Materials and Methods

Except as noted below for specific experiments, all the procedures, analyses, and the apparatus were identical to those described previously (Geyer et al., 1979).

Experiment I. Forty rats were divided randomly into groups of ten. Each animal received an IP injection of either isotonic saline (1.0 ml/kg body weight) or 40, 80, or 160 µg/kg LSD. Following injection, each animal was placed in a single cage for 10 min before being placed in the hole-board for a 24-min test. To investigate the contribution of peripheral systems to the LSD effect, we tested 20 additional rats with either saline or 160 µg/kg 2-bromo-LSD (BOL).

Experiment II. To determine whether the altered distribution of responding following LSD was due to the time after drug administration or the time after the start of the test, 16 rats were divided randomly into two groups of eight. Each rat was injected IP with saline or 80 µg/kg LSD 30 min before testing. The middle of the first 8-min test segment therby corresponds to the same interval after injection as the middle of the third 8-min segment in Experiment I, with a 10-min pretest interval.

To assess the possible contribution of response-contingent-light (RCL) (cf. Geyer et al., 1979) to the LSD effect, 40 rats were divided into four groups of ten. Two groups were given saline or 100 µg/kg LSD 10 min before being tested with standard RCL presentations. The other two groups were treated similarly, but RCL was omitted.

Forty additional naive rats were used to examine the importance of handling stress in the characteristic pattern of hole-board responding produced by LSD. A 4-in portion at one end of each hole-board was walled off with sliding wooden door. Immediately after IP injection of either saline or 100 µg/kg LSD, each animal was gently placed in this anteroom for a 10-min pretest interval. For the nonstress condition (10 saline, 10 LSD rats), the test was begun by simply removing the sliding door. For the stress condition (10 saline, 10 LSD rats), the animals were picked up, held upside-down, and given a brief tail-pinch before being returned to the anteroom. Immediately after this 1-min handling period the door was opened to begin the test.

Experiment III. Thirty rats similar to those used previously were assigned randomly to groups of 15, each group receiving saline or 100 µg/kg LSD daily. Behavioral tests were made 10 min after the first, fourth, and eighth daily injections. Locomotor activity was monitored in the hole-boards through wide-angle lenses mounted in the ceiling of each chamber. The floor was divided into eight 15 × 12 cm sections with blue tape. At 30-s intervals, the section in which the animal was located was recorded. Locomotor activity was then defined as the number of sections the rat must have crossed to arrive at each new location.

Differences in locomotor activity between groups were assessed using Student's *t*-distribution, while differences between tests within each group were compared with paired *t*-tests. For correlations between locomotor scores and nose-pokes we used Pearson's *r*-test, and we assessed the significance of differences between *r* values by the method described by Hays (1963).

Results

Experiment I

When given 10 min before the test, LSD produced a dose-dependent decrease in the frequency of nose-pokes during the first 8 min ($F = 6.0$, $df = 3,36$, $P < 0.01$). The greatest effects were produced by 80 and 160 µg/kg LSD. Specific comparisons revealed significant decreases in the first 8 min [$t = 3.4-3.8$ (10,4), $P < 0.01$] and in the total number of responses [160 µg only, $t = 2.9$ (10,4), $P < 0.01$]. By observation through wide-angle lenses, we noted that LSD-treated animals appeared to spend more of their time near the walls of the hole-board, but did not seem to be less active.

In the mixed-design ANOVA, there was a significant drug-×-time interaction ($F = 4.9$, $df = 6,64$, $P < 0.001$). The source of this interaction is seen in Fig. 1 as a reduction in the rate at which responding decreased over time. This apparent impairment of habituation is most evident for the group treated with 80 µg/kg LSD, which continued to respond at a constant level throughout the 24-min session. Compared to controls, these animals made a significantly greater percentage of their total responses during the third 8 min (13 vs 39%; $U = 10$, $P < 0.01$). This altered distribution of responding during the 24-min test in the

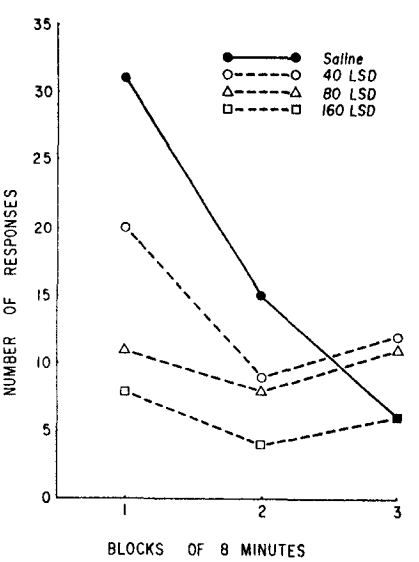

Fig. 1. The mean number of nose-poke responses in successive 8-min intervals in the hole-board is shown for groups of ten rats given either saline of graded doses (µg/kg) of LSD

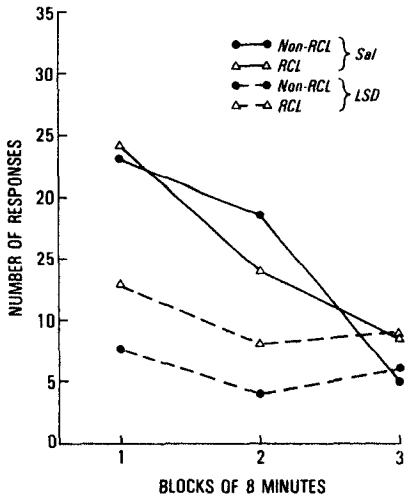

Fig. 2. The mean number of nose-poke responses is shown for groups of ten rats given saline or 100 μg/kg LSD, with or without presentations of response-contingent-light (RCL). Independent of RCL, LSD produced the characteristic alteration in the distribution of nose-poke responses over the 24-min test (Experiment II)

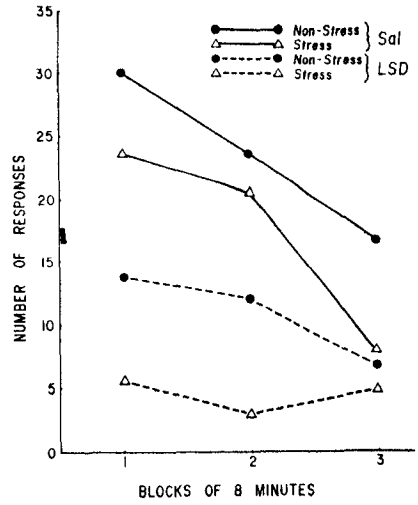

Fig. 3. The mean number of nose-poke responses by rats treated with either saline or 100 μg/kg LSD 10 min prior to a 24-min test. Each rat was placed in a 4-in anteroom for the 10 min between injection and start of testing. In the nonstress condition the test was begun by opening a sliding door while in the stress condition the rats were handled for 1 min immediately prior to the door being opened. The characteristic increase in responses from the second to third 8-min interval following LSD was not found when handling was separated from the onset of the test session (Experiment II). Each point represents the mean of ten animals

hole-board is a characteristic pattern not produced by other drugs or treatments that reduce the initial response frequency (Geyer et al., 1979); it can be differentiated from a 'floor effect' by the elevated response rate during the third segment. The finding that the mean number of nose-pokes is greater in the third segment than in the second (Fig. 1) is unique to the LSD group. Though the difference is small, a similar pattern has occurred in only one of 22 separate control groups (Geyer et al., 1979). The administration of 160 μg/kg BOL had no significant effect on the frequency of nose-pokes in any time segment or on the pattern of responding. The totals for the saline and BOL groups were 49.3 ± 12.1 and 37.5 ± 8.6, respectively ($F = 0.7$, $df = 1,18$, not significant).

Experiment II

When administered 30 min before the test, 80 μg/kg LSD produced essentially the same pattern of responding seen in Experiment I. As when LSD was given 10 min before testing (Experiment I, Fig. 1), these LSD-treated animals made significantly fewer nose-pokes than did controls during the first 8 min ($F = df = 1, 14$, $P < 0.01$) and a greater percentage of their responses during the third 8 min ($U = 14$, $N = 8, 8$, $P < 0.05$). Once again, the drug-×-time interaction was significant ($F = 4.0$, $df = 2, 42$, $P < 0.05$). In separate groups of rats given saline or 100 μg/kg LSD 10 min prior to a 48-min test we found that the increased activity produced by LSD continued for about 40 min, returning to control levels in the sixth 8-min segment.

The results of the experiment comparing RCL with nonRCL are shown in Fig. 2. A three-factor ANOVA (drug, RCL condition, and time segments) revealed no significant effect of RCL conditions either on the number or responses overall or in each time segment ($F = 0.4$, $df = 1, 36$, not significant), nor did RCL interact significantly with the LSD effect ($F = 0.7$, $df = 1, 36$, not significant). Across both conditions, LSD significantly reduced responding during the first 8 min ($F = 8.3$, $df = 1, 36$, $P < 0.01$) and overall ($F = 7.7$, $df = 1, 36$, $P < 0.01$), and also resulted in a significant drug-×-time interaction ($F = 9.2$, $df = 2, 71$, $P < 0.01$). Thus, the altered pattern of hole-board responding produced by LSD is clearly independent of the presentation of RCL.

Figure 3 depicts the results of the experiment in which the animals were placed in an anteroom for the 10-min pretest interval so that the test could be started either with or without handling stress. Separate ANOVAs were performed for each condition. In the stressed groups, 100 μg/kg LSD produced the expected pattern of hole-board responding; a significant reduction in the first 8 min ($F = 10.0$, $df = 1, 18$, $P < 0.01$) and overall ($F = 8.0$, $df = 1, 18$, $P < 0.025$), and a significant drug-×-time interaction ($F = 7.0$,

$df = 2, 36, P < 0.005$), attributable in part to the mean increase in responding by the LSD group from the second to third segment (Fig. 3). In the groups in which handling stress was minimized, LSD still reduced responding in the first 8 min ($F = 4.6$, $df = 1, 18$, $P < 0.05$) and overall ($F = 4.4$, $df = 1, 18$, $P < 0.05$) but the altered distribution of responding was not found, since the drug- × -time interaction was not significant ($F = 0.7$, $df = 2, 36$). As shown in Fig. 3, the rate of decrease in responding over time is similar for the saline and LSD groups in the nonstress condition despite the reduced level of responding. Thus, both groups made about the same percentage of their total responses during the third 8 min (23.7 vs 20.6%). Therefore, the drug- × -time interaction seen in the stressed condition and in the previous experiments is not attributable to an impairment of habituation, but is more likely due to an increased sensitivity to handling stress produced by LSD. It is important to note that the handling stress was not sufficient to alter hole-board responding in control animals. An ANOVA comparing the two saline groups over time segments revealed no significant condition- × -time interaction ($F = 0.6$, $df = 2, 36$), and no significant effect of condition on overall response frequency ($F = 0.9$, $df = 1, 18$).

Experiment III

Figure 4 displays the results for the first test day in Experiment III in which we measured locomotor activity as well as nose-pokes to determine whether the characteristic pattern of responding produced by LSD was specific to the animal's investigation of the holes themselves or a correlate of general activity levels. With respect to nose-pokes, the LSD pattern of responding was evident: Reduced frequency in the first 8 min ($F = 14.6$, $df = 1, 28$, $P < 0.01$); increased frequency in the third 8 min ($F = 7.4$, $df = 1, 28$, $P < 0.025$); and a significant drug- × -time interaction ($F = 9.7$, $df = 2, 56$, $P < 0.01$) (Fig. 4a). In contrast to these effects on the frequency of nose-pokes, no significant differences in locomotor activity were found (Fig. 4b). In saline-treated animals significant correlations between each rat's nose-poke frequency and activity score ($r = 0.56 - 0.80$) were found in each 8-min segment. However, in the LSD-treated animals none of these correlations were significant. Furthermore, for the first 8 min the correlation coefficients for the saline group are significantly greater than those for the LSD group ($Z = 1.66$, $N = 15, 15$, $P < 0.05$ one-tailed). These results indicate that nose-poke frequency and locomotor activity levels are reliably correlated in control animals and treatment with LSD disrupts the relationship by selectively affecting the nose-poke behavior. These correlational analyses corroborate the

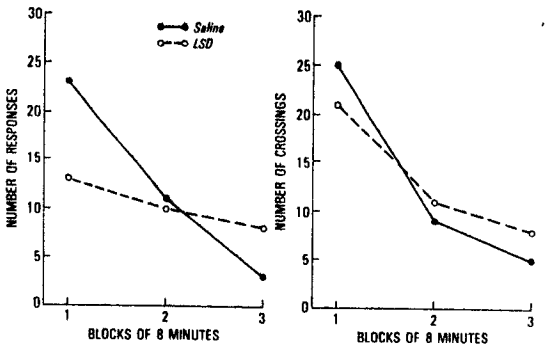

Fig. 4. *(Left)* The mean number of nose-poke responses per 8-min interval for groups of ten rats given either saline or 100 µg/kg LSD on the first day of the chronic experiment (Experiment III). The expected alteration of nose-poke responding was found, as evidenced by a significant drug- × -time interaction. *(Right)* The amount of general activity exhibited by these animals is shown as crossings from one sector to another (Experiment III). There was no significant effect of LSD on crossings, and no significant drug- × -time interaction

observation that LSD has no significant effect on locomotor activity in animals in which it alters the pattern of hole-board responding.

The effects of LSD on nose-poke behavior were only slightly diminished following eight daily injections of 100 µg/kg. In the final test (day 8) the response frequency during the initial 8 min was no longer significantly reduced by LSD, but the LSD-treated animals still made more nose-pokes than did controls during the third 8 min ($F = 4.2$, $df = 1, 28$, $P < 0.05$), and the drug- × -time interaction was still significant ($F = 5.2$, $df = 2, 56$, $P < 0.01$).

With respect to the locomotor activity scores, the only significant difference over the three test days was that the control group made fewer crossings during the third test than during the first test ($t = 2.5$, $df = 14$, $P < 0.02$). It is interesting that the significant correlations between nose-pokes and crossings observed on the first test day in control animals was not found in either of the subsequent tests.

Discussion

Hallucinogens have often been shown to increase behavioral and neurophysiological responses to sensory stimuli in a number of modalities, possibly because of their common actions on serotonergic neurons within the brain stem reticular formation. Measures of defensive responses such as startle are known to be increased by various hallucinogens and by reductions in brain serotonin. The present studies of the effects of LSD on investigatory responses are consistent with the notion that hallucinogens increase the perceptual im-

pact of sensory stimuli such that mild stimuli that normally elicit investigatory responses instead elicit defensive behavior. Thus the heightened sensory responsivity produced by hallucinogens may be reflected by either increases or decreases in a measured behavior depending upon the context (cf. Hughes, 1973).

More specifically, these experiments demonstrate that the effect of LSD on the behavior of rats in a hole-board is independent of general activity levels and related to an interaction between the drug effect and the stimuli associated with the animal's being handled and placed in the chamber. In a 24-min test session rats treated with LSD exhibit a different temporal pattern of responding to the holes than do controls. During the first 8 min in the chamber LSD-treated animals make fewer nose-pokes but are no less active than controls. While the response frequency in control animals consistently decreases over time, the LSD animals exhibit an increase in nose-pokes from the second to third 8-min segments. In some cases, the LSD group makes significantly more responses during the third 8 min than do controls, and always exhibit a greater proportion of their responses during the third segment. This characteristic pattern of responding in not simply due to the time course of LSD's action because different intervals between LSD injection and testing have similar effects. This effect of LSD appears to be related to the holes as specific stimuli since LSD had no significant effect on locomotor activity. Indeed, the positive correlation between activity and nose-pokes in control animals was not present in LSD-treated animals.

Since the LSD-induced alteration in hole-board responding is one in which the percentage decrement in responding over time is reduced by the drug, this effect could be interpreted as an impairment of habituation. The habituation of defensive responses such as tactile startle is reduced by LSD (Geyer et al., 1978). However, the difference in the initial response frequencies makes difficult any interpretation of different habituation slopes and introduces other considerations. Since stress-induced fear or hyperarousal have often been shown to compete with the exploration of a novel environment (Montgomery, 1955; Hayes, 1960; Berlyne et al., 1966), we reasoned that the reduction in the initial response frequency might reflect an interaction between the drug effect and the stress associated with the animals' being handled and placed in the hole-board. The active exploration of a novel environment is thought to be attenuated by stimulus satiation, a term used to describe the development of sufficient familiarity with the stimulus so that it is no longer novel (Berlyne, 1966). Given an initially reduced amount of exploration due to the stress of handling, the concept of stimulus satiation suggests that a subsequent increase in exploration would ensue until the environment was sufficiently investigated. With minimal stress, LSD had no significant effect on the distribution of hole-board responding, yet it still reduced both the initial and overall response frequencies (Fig. 3). In contrast, with more handling stress than in the standard paradigm, LSD produced a more marked initial decrement in response frequency and a clearly altered distribution of responding. The addition of stress by itself did not change the distribution of responding by control animals (Fig. 3), confirming that the pattern seen after LSD derives from an interaction between the drug effect and handling stress. This view is strengthened by physiological evidence of a hypersensitivity to stressors in animals treated with LSD (Cohen, 1970).

Our results are incompatible with the hypothesis that the altered distribution of responding produced by LSD represents an impairment of habituation itself because no drug-$\times$-time interaction was found in the absence of handling. Both the initial decrease and the later increase in responding therefore appear to be attributable to an interaction of the effect of LSD with the stress accompanying handling and being placed in the hole-board. This effect, then, may indicate that animals treated with LSD are hyperreactive, as originally hypothesized, but that the predominating effect on the behavior measured derives from their heightened reactivity to stimuli other than the novel holes, namely handling. Whereas normal animals exhibit orienting or investigatory behavior in response to being placed in the novel chamber, LSD-treated animals respond more defensively, as though the stimuli were more intense and threatening. This effect of LSD may reflect a qualitative shift in the nature of the behavioral response when the stimulus intensity is near the threshold for the normal switch from orienting responses to defensive responses (Vinogradova, 1969). Analogous phenomena appear in a tactile startle pardigm. We have reported that while LSD has no effect on the first startle response to moderate stimuli, LSD increases the initial response to more intense stimuli and simultaneously impairs the habituation to those stimuli (Geyer et al., 1978). Such shifts may be due to an LSD-induced increase in the perceived stimulus intensity via the previously noted facilitation of sensory transmission through primary relay nuclei, perhaps secondary to hallucinogenic drug arrest of serotonergic cell function. Similarily, in an acoustic startle paradigm, the effects of LSD appear to depend upon the level of background noise stimulation prior to and during the test session (Davis and Sheard, 1974b). All these phenomena are consistent with the profound influence of the environmental setting on the quality of hallucinogenic experiences in animals and man (Adey et al., 1962; Hughes, 1973).

As documented in the companion paper (Geyer et al., 1979), this characteristic distribution of responding following LSD is reproduced by virtually every hallucinogen we have tested, including both indoleamine and phenylethylamine derivatives. Furthermore, a variety of other psychoactive drugs do not produce a similar pattern of responding over time in a hole-board. Of the nonhallucinogenic drugs tested so far, only apomorphine showed a significant interaction with response frequency over time. These findings suggest that hole-board measures may provide a useful animal model with which to study the neurochemical or neuroanatomical substrates of the common effects of hallucinogens.

However, this usefulness is diminished by our finding of little tolerance to the effect of LSD administered once daily for eight days (Experiment III). Although the LSD-induced reduction in nose-pokes was no longer significant after 8 injections, its effect on day 8 was not significantly different from that on day 1, and the drug-×-time interaction was still significant. Because rapid tolerance to the euphorogenic and hallucinogenic effects of LSD is the rule in man (Balestrieri and Fontanari, 1959; Isbell et al., 1956; Mandell and Geyer, 1976), an animal model in which tolerance is not observed is not generally considered to be an analog of those effects reported by humans (Lipton, 1970). However, not all the behavioral effects of hallucinogens exhibit tolerance (Smythies et al., 1966; Tucker et al., 1972; Bridger et al., 1973; Gillin et al., 1976). Indeed, Bridger et al. (1973) have suggested that the behavioral effects of hallucinogens that are found in stressful situations and do not show tolerance may provide the better animal model for the production of psychoses by hallucinogens in man.

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