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# A Proposed Animal Model for Hallucinogens Based on LSD's Effects on Patterns of Exploration in Rats

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The utility of various measures of exploratory activity in rats was studied in order to develop an animal model of hallucinogens. A hole board chamber, connected by a door to a home cage, provided two test situations. Rats either were placed directly into the hole board with the door closed (forced exploration) or were placed in the home cage and, following adaptation, the door was opened (free exploration). The monitoring system provided both quantitative measures (crossovers, rearings, and hole pokes) and qualitative measures of locomotor patterns. A series of four experiments, with doses of 2–160 μg/kg LSD, revealed three major categories of effects, distinguishable on the basis of dose dependency, time course, or response to environmental manipulation: (a) increased avoidance of novel and central areas, (b) disruption of the spatial patterning of locomotion, and (c) suppression of rearing. All three effects exhibited partial tolerance 24 hr after one injection of 30 μg/kg LSD and complete tolerance after five daily injections. The possibility that LSD's enhancement of neophobia in rats may be a valid analogue model of its intensification of affective reactions in humans is discussed.

Attempts at deriving animal models of LSD's effects in humans have ranged from outright attempts to parallel hallucinatory activity (analogue models) to simpler physiological measures (assay models; see Stoff, Gillin, & Wyatt, 1978, for a review). By definition, analogue models of psychoactive drugs are distinguished from assay models on the basis of drawing parallels between psychological effects in humans and behavioral effects in animals, and they are frequently criticized for relying on anthropomorphic interpretations. On the other hand, assay models suffer from the fact that the behavior being modeled may bear no relation to the psychological effects of the drugs; for example, Isbell, Logan, and Miner (1959) found that some drugs could selectively block some of LSD's autonomic effects without attenuating its psychological effects. Similarly, DMT's potentiation of the H-reflex in humans was blocked by cyproheptadine with no attenuation of its mental effects (J. Metz, P. Teuting, N. Boutros, B. K. Rhoades, & H. Y. Meltzer, personal communication, 1984). Thus, the use of these particular behaviors in animals may not be valid for exploring the neurochemical basis of LSD's psychological effects in humans.

Because the utility of an animal model in providing an understanding of the neural basis of LSD's psychological effects is dependent on the extent to which the model behavior is a direct parallel of LSD's mind-altering effects, attempts should be made to draw such parallels wherever possible. Studies that have been focused on examining the responsiveness of animals to discrete, phasic stimuli have revealed alterations in both conditioned and unconditioned responding, such as enhanced reactivity to irrelevant stimuli (Key, 1964a, 1964b; Key & Bradley, 1960) and reduc-

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tions in rates of habituation of reflex responding (Geyer et al., 1978), which may be analogues of the human reports of increased sensory awareness and inability to selectively attend to stimuli. However, these particular effects in animals have not yet been demonstrated to be both common to a variety of hallucinogens and uncharacteristic of nonhallucinogens (Geyer et al., 1978; Stoff et al., 1978).

We previously reported the effects of LSD on rat exploratory activity, using the behavioral pattern monitor described here (Adams & Geyer, 1982). When tested in a free-choice situation, animals treated with 20–30 μg/kg LSD avoided the novel chamber during the first half of an hour session but exhibited normal rates of crossover, hole-poke, and rearing activity. Similarly, we had previously found that both phenylethylamine and indoleamine hallucinogens produced initial reductions in hole-poke responding (Geyer et al., 1979), an effect attributable to an interaction between the drug effect and the stress associated with handling and abrupt exposure to a novel chamber (Geyer & Light, 1979). These results suggested that effects of hallucinogens on neophobia in rats might be a suitable model behavior for analyzing their neurobiological effects, particularly in view of the obvious analogies to the enhanced responsiveness to threatening situations produced by hallucinogens in humans.

Thus, the present studies were designed to more directly compare the effects of LSD in free- and forced-exploration situations and to more systematically test whether LSD's potentiation of neophobia satisfied the criteria for an animal model of hallucinogenic activity. An additional characteristic of rats treated with LSD and tested in a free-exploration situation was a failure of the animals to establish the stereotyped excursion routes from the home cage to various parts of the novel chamber which is characteristic of controls (Adams & Geyer, 1982). Hence, these studies were also designed to explore the possibility that this effect might be related to the previously noted effects of LSD on habituation to sensory stimuli in animals.

## General Method

### *Subjects*

Male Sprague-Dawley rats weighing 275–300 g (Charles River Laboratories) were used. In order to conduct behavioral testing during the active phase of these nocturnal animals, the housing facility was kept on a reversed 12:12 hr light/dark cycle (lights off from 1000 to 2200 hours). Animals were allowed a 7-day period for acclimation to the animal room and then handled every other day (between 1300 and 1600) during the week prior to testing.

### *Apparatus*

Each of the four activity monitoring chambers consisted of a 30.5 × 61 cm chamber with walls 38 cm high and a stainless steel floor ("hole board"). The walls were black plastic except for a 15-cm-high stainless steel touchplate that detected wall rearings. The chamber had three floor holes and seven wall holes, each 2.54 cm in diameter. Hole pokes were detected by an infrared photobeam in each of the 10 holes. Connected to the chamber by a 7.6 × 12.7 cm sliding door was a 17.8 × 25 cm metal cage, identical to those in which the animals lived (home cage) and enclosed in its own 30.5 × 30.5 cm anteroom. A 4 × 8 perpendicular array of photobeams 1.9 cm above the floor was used to locate the animal's position with 3.8-cm resolution, as illustrated elsewhere (Adams & Geyer, 1982). The home cage was equipped with a 2 × 2 array of photobeams which were sampled together with those in the activity chamber. The presence of the animal in the doorway was detected by an additional photobeam. Each assembly was enclosed in a ventilated wooden box. A microprocessor system checked the state of all beams every 100 ms. If any change had occurred in that interval, a data reading was taken, together with the time since the preceding event.

### *Procedure*

For an experimental session, 4 animals were brought to the test room under black cloth 1 hr before the start of the session. Testing never began sooner than 90 min after the transition to the nocturnal period. For free-exploration tests, each animal was injected and placed in one of the four home cages. After 10 min, the sliding door for that chamber was opened remotely. For forced-exploration tests, the sliding door was sealed shut. Each animal was injected, returned to a holding cage for 10 min, then placed in the chamber for a 60-min test.

### *Data Analysis*

The raw data were translated into frequencies and durations of events cumulated over 10-min blocks. X-Y position was calculated and used to define the animal's position in 1 of 8 equally sized sectors and 1

of 9 unequally sized regions (cf. Adams & Geyer, 1982). For free-exploration tests, the 9 regions were collapsed into front, middle, and rear thirds (with respect to the home cage). The centermost region was also analyzed separately. For forced-exploration tests, the regions were pooled into center, corner, and wall regions (cf. Flicker & Geyer, 1982).

*Activity measures.* The two locomotor activity measures derived from these data were photobeam breaks (the total number of X-Y beam breaks) and crossovers (the number of sector entries). For free-exploration tests, both measures were cumulated and analyzed separately for the hole board and the home cage. However, for clarity and brevity, only measures cumulated within the hole board are presented. For hole pokes and rearings, a distinction was made between repeated and varied events. A repeated hole poke is the second of two consecutive hole pokes into the same hole, which has not been preceded by an interposed crossover from one sector to another, a rear, or a hole poke into a different hole. All others are varied hole pokes. Repeated rearings have a similar definition.

*Additional measures.* For free-exploration tests, the amount of time spent in and the number of whole-body entries into the hole board were cumulated over 10-min blocks. In order to correct for individual differences in the time spent in the hole board, rate measures were computed for each subject by dividing the number of responses per 1-hr session by the time spent in the novel chamber. In addition, the ratio of repeated to varied entry beam breaks (those followed by either full entry into the hole board or retreat to the rear of the home cage) provided a measure of vacillatory behavior in the entryway. Such measures have been shown to reflect the degree of conflict behavior resulting from the competing tendencies of approach and avoidance elicited by a novel environment (Montgomery, 1955).

### *Pattern Analysis*

*Video and hard-copy plots.* The X-Y position data were used to produce video displays of the animal's X-Y position changes, rearings, and hole pokes, which could be viewed from 20 to 1 time real-time speed (with relative temporal relation preserved). The same data files were also used to produce hard-copy plots with a Zeta plotter.

*Transition analysis.* The X-Y position data were translated into a sequence of transitions between any two of five hole-board regions: two end regions, center, and two long wall regions (cf. Geyer, 1982). The transitions were calculated and summarized in a 5 × 5 matrix with 16 permissible cells. The coefficient of variation (*CV*) was computed by dividing the standard deviation by the mean of each set of relative transition frequencies (Geyer, 1982). To the extent that an animal preferentially repeats certain transitions, the *CV* increases, whereas a more random distribution produces a lower value. The series was also divided on the basis of time and Pearson correlation coefficients calculated on the 16 pairs of values from these first- and last-half transition matrices. These correlations reflect the extent to which home areas or preferred paths are consistent between the first and last halves of the session.

### *Statistical Analyses*

Repeated-measures and mixed-design analyses of variance (ANOVA) were performed for selected variables. Specific comparisons were made by Duncan's multiple-range test. The *F* test (Bruning & Kintz, 1977) was used to determine which groups at which trial blocks contributed to a significant treatment by trials interaction.

## Experiment 1

In Experiment 1, the dose dependency of LSD's effects was examined by the free-exploration test to attempt to distinguish drug effects on activity due to avoidance of novelty from those due to sedation or motor impairments.

### *Procedure*

Sixty animals were randomly assigned to one of six treatment groups receiving 0, 2, 10, 30, 80, or 160 μg/kg LSD. LSD (lysergic acid diethylamide-25, Sandoz or Research Triangle) was obtained from the National Institute on Drug Abuse, Division of Research, and was administered sc (1.0 ml/kg).

### *Results*

*Activity measures.* Doses of 30–160 μg/kg LSD significantly reduced time spent in the novel chamber in a dose-dependent manner. This effect was so marked in the 160 μg/kg group that only half of the animals entered the novel chamber and of those that did enter, only 1 animal spent more than 5 min there; therefore, this group was excluded from all analyses. As shown in Figure 1A, the reduction was most marked in the first 30 min of the session, which resulted in a significant Treatment × Trials interaction, $F(20, 200) = 1.70$, $p < .05$. In contrast, animals treated with 10 μg/kg LSD spent more time in the novel chamber than controls in the first 10-min block ($p < .05$). Doses of 30 and 80 μg/kg LSD also produced an initial reduction in the number of entries into the novel chamber (Figure 1B), which resulted in a signif-

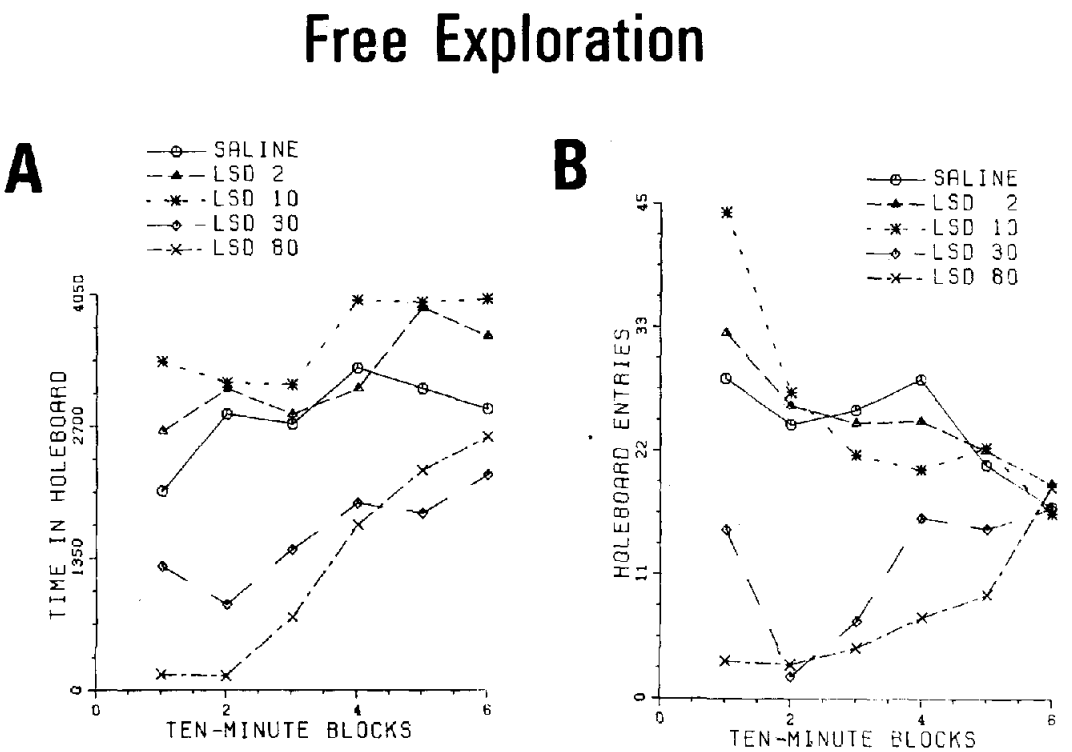


*Figure 1.* Dose dependency of LSD's effect on (A) time spent in the novel hole-board chamber (tenths of a second) and (B) number of entries into the hole-board chamber. (Values are group means per 10-min block; doses are in micrograms per kilogram of body weight. $p < .05$, $F$ test: [A] decrease Block 2 for 30 μg/kg and Blocks 1–4 for 80 μg/kg; [B] decrease Blocks 1–4 30 μg/kg, Blocks 1–5 80 μg/kg.)

icant Treatment × Trials interaction, $F(20, 200) = 4.14$, $p < .001$. Again, the 10 μg/kg group showed the opposite effect, making more entries than controls in the first 10 min of the session ($p < .05$; Figure 2B). Animals treated with 30 or 80 μg/kg LSD also made a greater proportion of repeated entry beam breaks ($M \pm SE$: saline = 0.109 ± 0.006; 30 μg/kg = 0.147 ± 0.014; 80 μg/kg = 0.234 ± 0.042), $F(4, 40) = 7.38$, $p < .001$ ($p < .05$, Duncan's), which indicates a greater amount of vacillatory activity in the entryway.

Although the effects of 30 and 80 μg/kg LSD on time spent in the center of the novel chamber (Figure 2A) paralleled their effects on time spent in the hole board, $F(20, 200) = 2.60$, $p < .001$, the 10 μg/kg dose produced a different profile, significantly increasing time spent in the center for the first 50 min of the session. The 2 μg/kg group did not differ significantly from the control group on any of these measures.

LSD reduced the number of photobeam breaks with the same time course and dose dependency (Figure 2B) as its effect on time spent in the novel chamber (Figure 1A). A similar profile was seen for crossovers, hole pokes, and rearings (Table 1). However, when activity measures were corrected for time spent in the novel chamber (Table 1), it was confirmed that doses of 2–80 μg/kg LSD did not reduce the rate of crossovers or hole pokes but did reduce the frequency of rearings (Table 1). Rats treated with 30 or 80 μg/kg LSD also made relatively more varied than repeated hole pokes ($M \pm SE$ varied/repeated hole pokes: saline = 1.51 ± 0.23; 30 μg/kg = 2.66 + 0.76; 80 μg/kg = 2.69 ± 0.64), $F(4, 40) = 3.88$, $p < .01$, ($p < .01$, Duncan's).

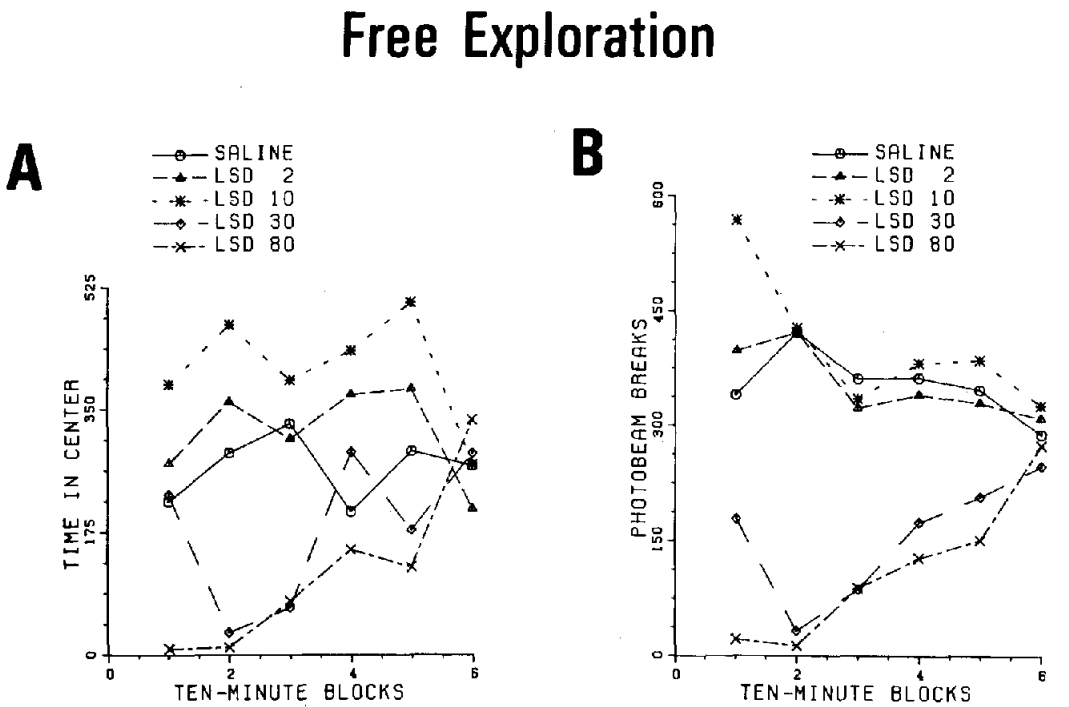


*Figure 2.* Dose dependency of LSD's effect on (A) time spent in the center of the novel hole-board chamber (tenths of a second) and (B) number of photobeam breaks within the hole board. (Values are group means per 10-min block; doses are in micrograms per kilogram of body weight. $p < .05$, $F$ test: [A] decrease Blocks 2 and 3 for 30 μg/kg and Blocks 1–3 for 80 μg/kg; [B] decrease Blocks 2–4 for 30 μg/kg and Blocks 1–5 for 80 μg/kg and increase Block 1 for 10 μg/kg.)

*Locomotor pattern data.* Our previous studies with the free-exploration test (Adams & Geyer, 1982) revealed that normal animals explore the environment in a fairly organized manner, by making a series of excursions (round trips from the home cage to various regions of the novel chamber and back). Within the first 30 min, the control pattern evolves from partial excursions along the walls to full excursions down the center of the hole board. From 30 to 60 minutes, few new routes are seen, and controls begin retracing a few preferred and simple routes, as illustrated in Figure 3. In contrast, during the last 30 min of the session, rats treated with 20–30 μg/kg LSD made more round-about excursions, which were seldom retraced and were punctuated by pauses at seemingly random spots enroute rather than returns to the home cage. As seen in Figure 3, these effects of 30 μg/kg LSD were replicated in the present study. Unfortunately, the marked reduction of time spent in the hole board produced by doses of 80 and 160 μg/kg LSD precluded characterization of their effects on locomotor patterns. Doses of 2 and 10 μg/kg LSD did not significantly alter the spatial patterning of locomotion.

## *Discussion*

The results of Experiment 1 confirmed and extended the previously reported effects of LSD on exploration of a novel chamber (Adams & Geyer, 1982). When rats were allowed to enter and leave a novel chamber at will, LSD produced a dose-dependent reduction of time spent in and number of entries into the novel chamber without an alteration in the overall rate of crossover or hole-poking activity while they were in the chamber. LSD's suppression of exploratory activity was maximal from 10

Table 1
*Effect of LSD on Activity in the Hole Board (Free Exploration)*

| Variable | Dose (in μg/kg) 0 ($n$ = 9) | 2 ($n$ = 10) | 10 ($n$ = 9) | 30 ($n$ = 8) | 80 ($n$ = 9) | $F$ | $p$ |
|---|---|---|---|---|---|---|---|
| **Amount of activity (total counts)** | | | | | | | |
| Crossover | | | | | | | |
| *M* | 1,514 | 1,652 | 1,777 | $784_a$ | $551_a$ | 9.51*** | .001 |
| *SE* | 275 | 194 | 146 | 147 | 129 | 5.13*** | .001 |
| Hole poke | | | | | | | |
| *M* | 125 | 138 | 141 | $47_a$ | $46_a$ | 5.25** | .005 |
| *SE* | 32 | 24 | 19 | 13 | 17 | 1.53 | |
| Rearing | | | | | | | |
| *M* | 87 | 86 | 78 | $32_a$ | $18_a$ | 8.93*** | .001 |
| *SE* | 16 | 14 | 9 | 7 | 6 | 3.94*** | .001 |
| **Rate of activity (counts per minute in hole board)** | | | | | | | |
| Crossover | | | | | | | |
| *M* | 59.4 | 55.5 | 50.4 | 60.0 | 54.0 | 0.30 | |
| *SE* | 6.8 | 5.8 | 5.0 | 9.7 | 6.7 | | |
| Hole poke | | | | | | | |
| *M* | 4.2 | 4.4 | 4.1 | 3.1 | 3.8 | 0.94 | |
| *SE* | 0.6 | 0.5 | 0.6 | 0.3 | 0.4 | | |
| Rearing | | | | | | | |
| *M* | 3.6 | $2.6_a$ | $2.2_a$ | $2.4_a$ | $1.6_a$ | 3.95* | .010 |
| *SE* | 0.4 | 0.5 | 0.3 | 0.4 | 0.2 | | |

*Note.* Means are from total counts or transforms performed on 60 min totals. $F$ ratios shown are for treatment ($df$ = 4, 40) over Treatment × Trials interaction ($df$ = 20, 200). Values with a subscript are significantly different from control values by Duncan's multiple-range test.

to 20 min after test start and was associated with an increase in conflict activity, results suggesting that doses of 30–160 μg/kg LSD extended the initial period of avoidance (neophobia) normally exhibited by rats confronted with a novel environment (Barnett, 1969; Berlyne, 1966; Montgomery, 1955). In contrast, rats treated with 10 μg/kg LSD were more active in the novel chamber during the first 10 min, which suggests that this dose either reduced neophobia or had a slight stimulant action which was not counteracted by the competing tendency to avoid the novel chamber. This same dose dependency (high-dose suppression and low-dose enhancement) was seen for LSD's effect on time spent in the center of the novel chamber. LSD's reduction of rearings appeared distinct from its effect on ambulation and hole poking because it was apparent even at the lowest dose tested (2 μg/kg) and could not be accounted for solely on the basis of LSD's reduction of time spent in the novel chamber.

## Experiment 2

Although the free-exploration test used in Experiment 1 enabled distinctions to be made between reductions in activity due to avoidance of a novel environment and those due presumably to "internal factors" such as sedation, the sampling problems associated with the failure of the rats treated with 80–160 μg/kg LSD to spend a significant amount of time in the novel chamber precluded a thorough characterization of LSD's high-dose effects. Hence, in Experiment 2, the dose dependency of LSD's effects was examined by a modified procedure in which the rats were placed directly into the novel chamber (forced exploration). This procedure also enabled more direct comparisons with the open-field studies in the literature.

### *Procedure*

Sixty rats were randomly assigned to one of six groups ($n$ = 10 per group) to be tested following

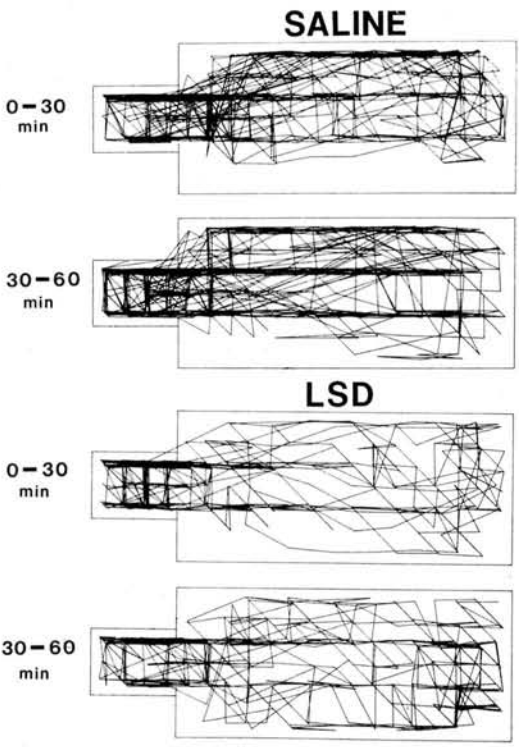


*Figure 3.* Computer-generated plots derived from sequential changes in X-Y position to show the locomotor patterns of rats treated with saline or 30 μg/kg LSD in a free-exploration test.

injection of 0, 2, 10, 30, 80, or 160 μg/kg LSD. An additional 16 animals treated with saline, 30, 80, or 160 μg/kg LSD (4 rats per group) were used for visual observations. The same procedure was followed except that a 15-W red light illuminated the hole-board chamber. Animals were observed through viewing lenses mounted in the lids of the hole board. Events were recorded by an experimenter for a 2-min period every 6 min.

## Results

*Regional analysis.* Doses of 30–160 μg/kg LSD significantly reduced ($p < .05$, Duncan's) the number of entries into the center region ($M \pm SE$ for saline and 30, 80, and 160 μg/kg LSD, respectively: 102 ± 12, 59 ± 7, 50 ± 8, 51 ± 8), $F(5, 53) = 5.83$, $p < .001$. LSD's reduction of time spent in the center of the hole board (Figure 4) exhibited the same temporal distribution and dose dependency that characterized LSD's effect on time spent in the novel chamber in the free-exploration test (Experiment 1); this resulted in a significant Treatment × Trials interaction, $F(25, 265) = 3.69$, $p < .001$.

Doses of 30–160 μg/kg LSD significantly reduced ($p < .01$, Duncan's) the total number of photobeam breaks (Figure 5A) and crossovers (not shown) in the first three 10-min blocks, which resulted in a significant Treatment × Trials interaction, $F(25, 256) = 12.22$, $p < .001$, yet the three high-dose groups did not differ significantly from one another. Doses of 30–160 μg/kg LSD also significantly reduced rearing activity, $F(5, 53) = 18.80$, $p < .001$ ($p < .01$, Duncan's) with a steeper, more linear dose-response curve than that for ambulatory measures (Figure 5B).

Hole-poking activity appeared to be more sensitive to low doses of LSD than was rearing or crossover activity because all doses tested produced a significant decrease, $F(25, 265) = 2.27$, $p < .001$. However, only in the higher dose groups was the reduction in hole pokes specific to the initial portion of the session (Figure 6). As in Experiment 1, doses of 30–160 μg/kg LSD produced an increase in the ratio of varied to repeated hole pokes ($M \pm SE$: saline = 0.44 ± 0.06; 30 μg/kg = 0.94 ± 0.16; 80 μg/kg = 0.89 ± 0.10; 160 μg/kg = 1.20 ± 0.17), $F(5, 53) = 6.67$, $p < .001$, ($p < .01$, Duncan's) due to a proportionately greater reduction of repeated hole pokes.

*Locomotor patterns.* Controls: The locomotor patterns of controls in the forced-exploration test differed slightly from those described for the free-exploration test (Experiment 1). As illustrated in Figure 7, in the absence of a home cage, controls established a home corner (upper left in this example) within the first 30 min of the session. Once established, the controls began to make excursions from the home corner to some remote portion of the chamber and back. The excursions became increasingly more direct, predictable, and of shorter duration as time progressed. By 50 min, most controls had settled fairly permanently in their home corners. Thus, the situation was analogous to the free-exploration test, with "excursions" organized around a home corner in lieu of the home

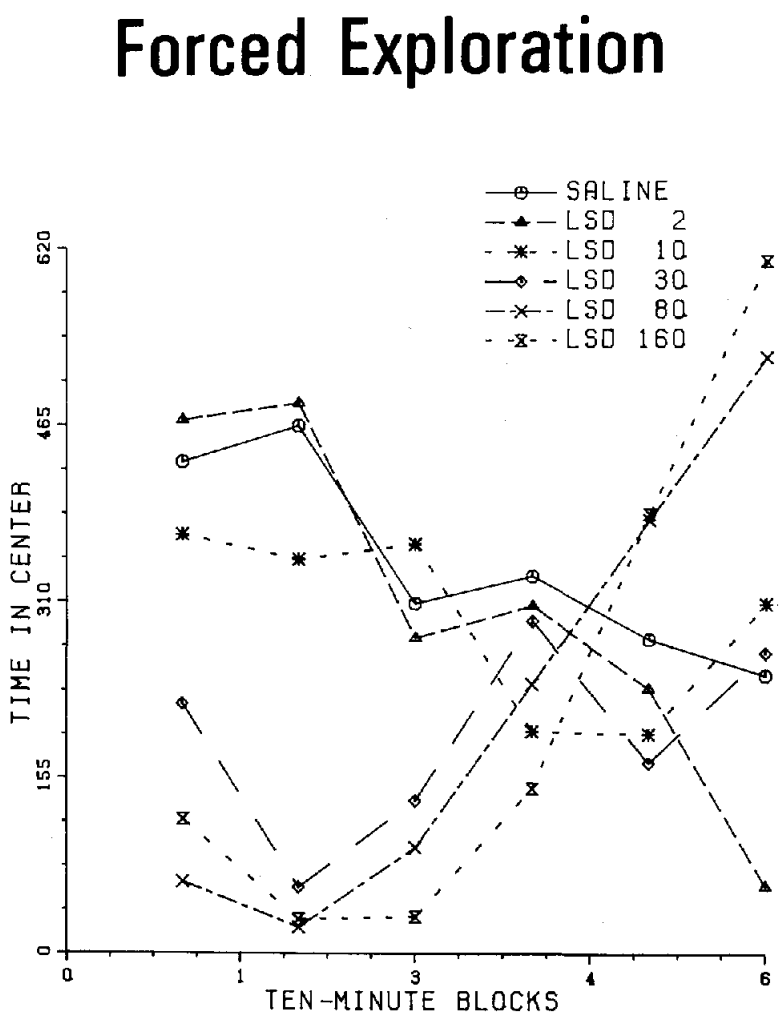


*Figure 4.* Dose dependency of LSD's effect on time spent in the center of the hole board (tenths of a second) in a forced-exploration test. (Values are group means per 10-min block; doses are in micrograms per kilogram of body weight. $p < .05$, $F$ test: decrease Blocks 1–3 for 30 μg/kg; 80 μg/kg, lower Blocks 1–3, higher Block 6; 160 μg/kg, lower Blocks 1–4, higher Block 6.)

cage. Further, whereas in the free-exploration test, the route from the home cage down the center to the rear of the hole board was preferred (Figure 3), in the forced-exploration test, routes along the walls were generally preferred.

30 μg/kg LSD: Video plots revealed an abrupt shift to slower locomotion approximately 7 min after test start in rats treated with 30 μg/kg LSD. The animals began spending a greater proportion of time along the short walls of the chamber, moving back and forth between the corners. Visual observations revealed that this pattern corresponded to the time when rats treated with 30 μg/kg began frequently alternating between normal upright postures and lying or crawling on their bellies. Often the animals would stare at an opposite corner, then crawl toward it, ears erect and twitching, only to halt after going only one third of the way, then backing into the corner while continuing to stare at the far wall. This behavior continued for 20 more min. At 30 min from test start, the rats began to make long traverses along the walls, or

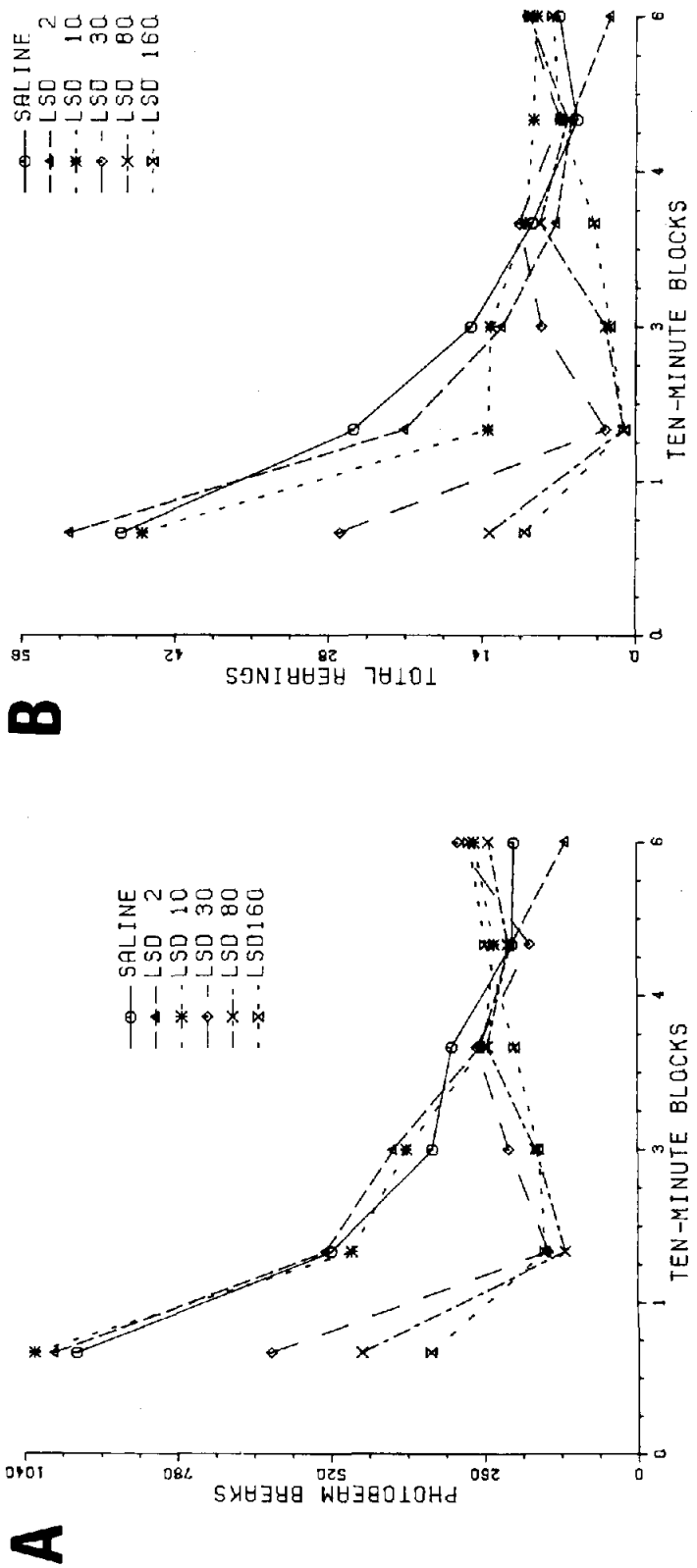


*Figure 5.* Dose dependency of LSD's effect on (A) number of photobeam breaks within the hole board and (B) number of rearings against the walls. (Values are group means per 10-min block; doses are in micrograms per kilogram of body weight. $p < .05$, $F$ test: [A] 30, 80, and 160 μg/kg lower Blocks 1–3.)

# Forced Exploration

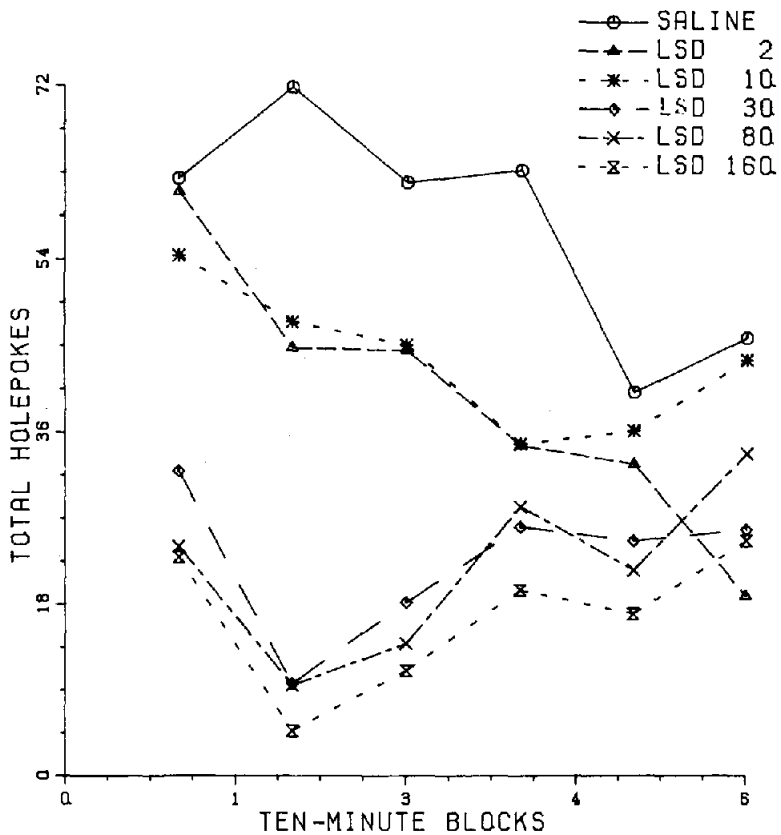


*Figure 6.* Dose dependency of LSD's effect on the temporal distribution of hole poking within the novel chamber. (Values are group means per 10-min block; doses are in micrograms per kilogram of body weight. $p < .05$, $F$ test: lower Blocks 1–6 for 30 and 160 μg/kg, Blocks 1–5 for 80 μg/kg, Blocks 2, 3, 4, 6 for 2 μg/kg, and Blocks 2–4 for 10 μg/kg.)

through the center, along zig-zagging, meandering routes (Figure 7). Note the lack of a preferred route to home for the LSD-treated rat in Figure 7. Many rats treated with 30 μg/kg failed to establish a "home" corner but alternated between stays in the two end-wall regions.

80 μg/kg LSD: The initial (10-min) period of circling noted in rats treated with saline or 30 μg/kg LSD was extended to 20 min in rats treated with 80 μg/kg LSD (Figure 8). Like the 30 μg/kg group, the abrupt shift from high to low locomotor rate 8 min after test start corresponded to the time when the rats alternated frequently between upright and prone postures. From 20 to 40 minutes, the rats continued to spend a considerable amount of time in the corners or traversing the walls between the front and back regions of the hole board (Figure 8). Visual observations revealed that the rats alternated between walking and crawling on their bellies and appeared to be in a highly alert state; for example, they would begin to walk from a corner down a long wall, stop midway, prick

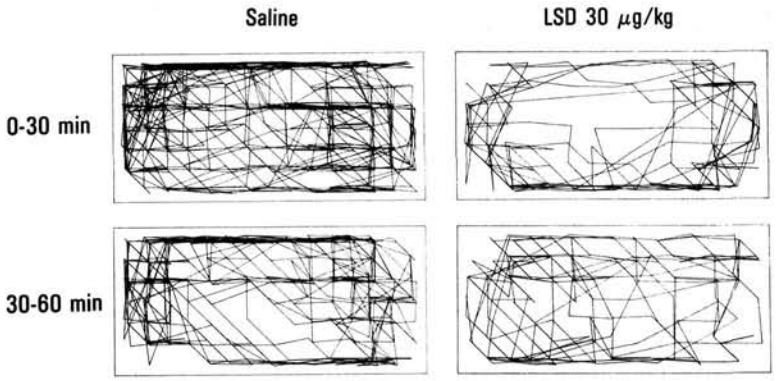


*Figure 7.* Computer-generated plots derived from sequential changes in X-Y position to show the locomotor patterns of a rat treated with saline and one treated with 30 μg/kg LSD (forced-exploration test).

their ears up, sway their heads back and forth, then back into the corner again, and would repeat this sequence 1 min later. From 40 to 60 minutes, excursions through the center appeared for the first time. The most aberrant behavior was observed during this period of time, as illustrated in this excerpt from observation notes (time = 45–47 min):

rat in left rear corner, suddenly sees tail, chases it, rotates 4 times, bites tail, lets go, tail flips around, rat sees tail from other direction, chases it, pounces on tail, jerks head up, walks over to back floor hole, dips head in, jumps back from hole, returns to hole, dips nose into hole, jumps back from hole, sees tail, starts chasing it . . . .

160 μg/kg LSD: For the first 30 min, rats treated with 160 μg/kg LSD alternated between circling the hole board or repeatedly traversing the same set of walls, with pauses (1–2 min) in the corners (Figure 8). From 30 to 40 minutes, traverses through the center appeared, and at 40–60 min abrupt shifts in locomotor rate were seen. Pauses in corners or slow traverses along the walls were interrupted by a series of rapid zig-zagging traverses through the cen-

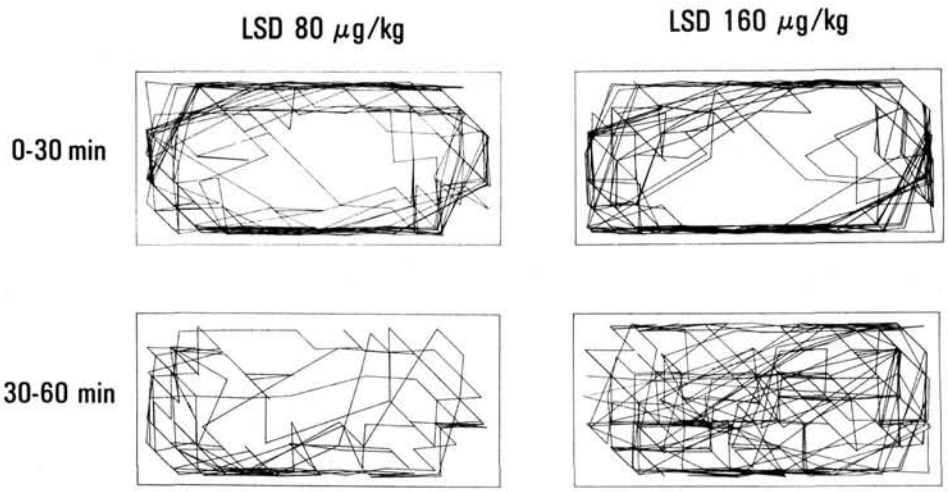


*Figure 8.* Computer-generated summaries of locomotor patterns of two rats, one treated with 80 μg/kg LSD and the other 160 μg/kg LSD.

ter (Figure 8). Like in the 80 μg/kg group, visual observations revealed a great deal of jumping, darting, and pouncing during the last 20 min of the session.

Tests for ataxia: In order to determine whether the crawling behavior observed with doses of 30–160 μg/kg LSD was due to an actual paralysis or muscular hypotonia, some additional rats were used for more rigorous testing. Rats treated with 30 or 80 μg/kg LSD could cling to and locomote about on a vertical wire grid. When tested in the experimental chamber, they would immediately cease crawling and rear up at a suspended food pellet. When the rats were placed in a chamber with a wire mesh floor, they initially exhibited normal locomotion, then began crawling. If a smooth surface was introduced into half of the chamber, they would walk erect each time they encountered the new surface. Even when the situation was reversed, they still crawled on the familiar (smooth) surface and stood erect when they encountered the new (mesh) surface. Thus, although the rats displayed a tendency to crawl, they were capable of standing erect and rearing in order to obtain food or in response to environmental changes.

*Discussion*

*Regional preference.* Thigmotaxis (movement oriented by tactile stimuli provided by contact of vibrissae along vertical surfaces) has been observed for both wild and laboratory rats upon encountering a novel environment, and it is considered to be an important means of guidance and predator avoidance (Barnett, 1963). Thus, one interpretion of LSD's reduction of time spent in the center region is that it reflects a potentiation of the neophobia normally exhibited by rats in a novel environment. Alternatively, LSD could disrupt spatial mapping strategies and cause the rats to rely entirely on thigmotaxis as a means of orienting themselves in space. Although these two possibilities cannot be distinguished on the basis of these data alone, in the previous free-exploration tests (Experiment 1; Adams & Geyer, 1982) several converging measures suggested that LSD's reduction of time spent in the novel chamber reflected a potentiation of neophobia. Therefore, the similar magnitude and time course of LSD's reduction of time spent in the center of the chamber suggest that this might be a comparable measure of the same behavioral dimension. Similarly, LSD's reduction of ambulation and hole poking also appeared to reflect "freezing" responses as opposed to sedation or motor impairments.

Rearing: On the basis of dose dependency and time course, LSD's reduction of rearing activity appears directly related to the abnormal crawling behavior noted in visual observation sessions. The "lability" of this behavior and its influence by sensory stimuli are in agreement with Cunha and Masur's (1978) report that suppression of rearing by 100 μg/kg LSD is immediately reversed by introduction of tones or light to the chamber.

Hole pokes: In addition to LSD's initial suppression of hole poking, LSD produced a preferential suppression of repeated hole pokes—a measure that has been suggested to assay the stereotypy induced by amphetamine (Makanjuola, Hill, Dow, Campbell, & Ashcroft, 1977). According to this model, the present results suggest that LSD reduces perseverative tendencies. However, a more fundamental conclusion is that LSD-treated animals initiate a new behavioral response rather than repeat the last one. A similar phenomenon may underlie the increased frequency of directional changes and failure to repeat old routes which characterize the locomotor patterns of LSD-treated animals.

Locomotor patterns: The increased diversity of locomotor patterns seen previously in free-exploration tests (Experiment 1; Adams & Geyer, 1982) for 30 μg/kg LSD was less obvious in the forced-exploration test because of the greater tendency of LSD-treated animals to avoid the center of the chamber. Nevertheless, from 30 to 60 min, the same types of long meandering excursions were seen in the 30 and 160 μg/kg groups. The increase in the duration of the initial period of circling the chamber paralleled LSD's time course and dose dependency for avoidance of the novel chamber (Experiment 1), a result suggesting that

this behavior reflected thigmotaxis due to enhanced neophobia as opposed to an increase in apomorphine-like stereotypy (cf. Geyer, 1982). At doses of 80 and 160 μg/kg, aberrant behaviors corresponding to the "hallucinatory-like" behaviors reported by others (Hughes, 1973) were seen, though "illusory-like" seems a more appropriate descriptor because the orienting, "attacking," and "escaping" responses always appeared to be triggered by real objects in the environment, such as a floor hole or the animal's own tail.

## Experiment 3

On the basis of the results of Experiments 1 and 2, we hypothesized that both LSD's initial reduction of time spent in the novel chamber in free-exploration tests and its initial reduction of activity and time spent in the center of the hole board in forced-exploration tests reflect a potentiation of neophobia. In order to explicitly test this hypothesis, rats were familiarized with the test chamber prior to drug treatment. Thus, if LSD's suppressant effects were due to an enhancement of rats' normal tendency to avoid novelty, these effects should be diminished in a familiar environment.

### *Procedure*

Thirty-two naive rats were randomly assigned to two groups. Each animal was given three 60-min sessions at 48-hr intervals in the forced-exploration test. Each animal was always tested in the same chamber and at the same time of day. In the third session, rats were treated with saline or 30 μg/kg LSD 10 min prior to testing.

### *Results*

*Activity measures.* As shown in Table 2, rats treated with LSD on their third exposure to the chamber (Day 3) did not exhibit the dramatic reduction of crossover or hole-poking activity that normally occurs from 0 to 30 min on their first exposure to the chamber. Hence, the treatment by trial interaction for these measures was not significant. In contrast, LSD still significantly reduced rearing activity and time spent in the center of the hole board in the first 30 min (Table 2). It should be noted that comparison of activity on the treatment day (3) with the baseline days (1 and 2) revealed no significant effect of LSD on between-sessions habituation (i.e., treatment by day by trial interaction) for any activity measure.

*Locomotor patterns.* LSD also produced a significant alteration in locomotor patterns on Day 3. As in previous tests (Experiments 1 and 2; Adams & Geyer, 1982), LSD-treated animals failed to establish the stereotyped routes of locomotion characteristic of controls. This difference was confirmed statistically by a significant reduction of the correlation between the individ-

Table 2
*Effect of LSD on Activity in a Familiar Environment (Day 3)*

| Variable/treatment | 0–30 min | 30–60 min | $F$ | $p <$ |
|---|---|---|---|---|
| Crossover | | | | |
| Saline | 996 ± 92 | 357 ± 59 | 2.26 | *ns* |
| LSD | 877 ± 75 | 361 ± 67 | | |
| Hole poke | | | | |
| Saline | 86.0 ± 9 | 59.3 ± 14 | 0.08 | *ns* |
| LSD | 66.3 ± 11 | 44.1 ± 9 | | |
| Rearing | | | | |
| Saline | 60.7 ± 9 | 19.9 ± 5 | 8.01 | .01 |
| LSD | 37.4 ± 5* | 20.1 ± 5 | | |
| Time in center | | | | |
| Saline | 1,273 ± 143 | 481 ± 103 | 7.48 | .05 |
| LSD | 841 ± 130* | 655 ± 203* | | |

*Note.* Values are group means ± *SE* of 30 min totals. $F$ ratios are for Treatment × Trials interaction ($df = 1, 30$).
* $p < .05$, $F$ test.

ual transition matrices for 0–30 min versus 30–60 min (mean correlation ± *SE*: saline = 0.703 ± 0.049; LSD = 0.492 ± 0.059), $F(1, 28) = 7.70$, $p < .01$. In addition, whereas controls tended to favor the same locomotor routes on Day 3 as they had on Day 2, LSD-treated animals did not. This group difference was reflected in a significant reduction of the correlation between the individual transition matrices for Day 2 (0–60 min) and those for Day 3 (0–60 min; mean correlation Day 2 × Day 3, ± *SE*: saline = 0.776 ± 0.048; LSD = 0.547 ± 0.080), $F(1, 29) = 5.63$, $p < .05$. Converging evidence for this effect was obtained from the calculation of difference scores for individual animal's *CV*s (a measure of the degree of redundancy in the pattern) between Day 2 and Day 3. All LSD-treated animals showed lower *CV*s on Day 3 than on Day 2, and most controls showed higher *CV*s on Day 3 than on Day 2; this resulted in a significant drug effect for the difference scores (*Mdn*: saline = 0.003; LSD = −0.143; $W = 266.0$, $p < .05$).

### *Discussion*

These results support our original hypothesis (Experiments 1 and 2) that LSD's reduction of ambulation and hole poking in a novel test chamber are reflective of a potentiation of neophobia rather than an impairment of motor functioning. This interpretation is consistent with Montgomery's (1955) observation that the magnitude and duration of initial reductions in exploratory activity are a direct function of the "threateningness" (height, openness, novelty) of a chamber and with Geyer and Light's (1979) results showing that LSD-induced reductions of holepoking are potentiated by vigorous handling and diminished by allowing animals to adapt to a portion of the chamber. A similar dependence of locomotor effects on environmental context has been reported for other hallucinogens (see General Discussion). In contrast, LSD's reduction of rearing is clearly due to some factor other than neophobia because it still occurred in a familiar environment.

The initial avoidance of the center by LSD-treated animals appears to be independent of their familiarity with the test environment. As rats normally tend to avoid open areas (Barnett, 1969), these results suggest that LSD may potentiate agoraphobia (fear of open areas), in addition to its effect on neophobia, as a result of a more general enhancement of responsiveness to aversive or threatening situations.

The fact that LSD's characteristic alteration of locomotor patterns also occurred in a familiar environment provides a clear distinction between LSD's disruption of locomotor patterns and its potentiation of neophobia. Controls exhibit progressively more stereotyped patterns in parallel with their habituation of locomotor rate, so the disruption seen with LSD could indicate a failure of LSD-treated animals to habituate to the myriad stimuli in the environment that presumably elicit exploration (cf. Berlyne, 1960, 1966). Alternatively, an increase in distractibility or altered perception of spatial cues could also explain the seemingly random directional changes and failure to establish simple, consistent excursion routes.

## Experiment 4

One of the most striking features of LSD's effects in humans is the rapidity with which tolerance develops to its psychological effects (Isbell et al., 1956); therefore, a major criterion for validating an analogue model is that the model behavior exhibits tolerance at the same rate and to the same extent to which tolerance occurs for LSD's psychological effects in humans. Because LSD's psychological effects exhibit tolerance 24 hr following a single low (100-μg) dose and complete tolerance after seven daily doses (Isbell, Belleville, Fraser, Wikler, & Logan, 1956), a similar treatment regimen was used in this study.

### *Procedure*

Forty-four rats were randomly assigned to one of six groups. All animals received a total of six daily sc injections of saline or drug (five in the animal room and one in the laboratory) prior to testing. Two groups received five daily saline injections (ChrSAL) prior to

Table 3
*Effect of Chronic Treatment on Activity in the First 30 Min*

| Variable | Treatment | | | | | | Analysis of variance | |
|---|---|---|---|---|---|---|---|---|
| | Chrsaline | | ChrLSD | | 24-hrLSD | | Chronic × Acute | 24-hr × Acute |
| | Saline | LSD30 | Saline | LSD30 | Saline | LSD30 | | |
| Crossover | | | | | | | | |
| *M* | 1,085 | 364* | 1,088 | 1,095 | 1,018 | 623* | 5.74† | 3.11 |
| *SE* | 157 | 72 | 122 | 137 | 87 | 35 | | |
| Hole poke | | | | | | | | |
| *M* | 89 | 28* | 103 | 88 | 96 | 47* | 3.91 | 0.16 |
| *SE* | 20 | 9 | 34 | 14 | 18 | 11 | | |
| Rearing | | | | | | | | |
| *M* | 89 | 19* | 95 | 76 | 74 | 39* | 5.72† | 5.62† |
| *SE* | 8 | 6 | 11 | 9 | 7 | 9 | | |
| Center entry | | | | | | | | |
| *M* | 62 | 13* | 64 | 61 | 63 | 26* | 3.73 | 0.52 |
| *SE* | 10 | 3 | 17 | 15 | 8 | 7 | | |

* $p < .05$, (*F* test) for acute LSD effect (difference from control within chronic group).
† $p < .05$.

being tested after either saline ($n = 6$) or 30 μg/kg LSD ($n = 6$). Two groups received five daily injections of 30 μg/kg LSD (ChrLSD) and were then tested after saline ($n = 6$) or 30 μg/kg LSD ($n = 14$). The other two groups received four daily injections of saline then 30 μg/kg LSD on the fifth day (24hrLSD) and were tested after saline ($n = 6$) or 30 μg/kg LSD ($n = 6$).

## Results

*Activity measures.* As summarized in Table 3, rats previously treated with five daily injections of 30 μg/kg LSD (ChrLSD) did not exhibit the initial decrement in crossovers, hole pokes, rearings, or center entries normally seen in response to a 30 μg/kg acute injection (ChrSAL). Rats treated with a single dose 24 hr before testing (24-hrLSD) also exhibited a diminished response to acute LSD, though the diminution was less dramatic than that produced in the ChrLSD group (Table 3).

*Locomotor patterns.* In the ChrSAL group, 30 μg/kg LSD still produced an increased variability of locomotor patterns compared with those of controls (which establish preferred routes of locomotion). This was reflected in the difference scores for the *CV*s from the first to the last 30-min block. Whereas controls invariably exhibited an increase in *CV* from the first to the last half of the session, which resulted in a positive difference score ($M = 0.083$, $SE = 0.10$), LSD-treated animals exhibited a decrease and therefore a large negative score ($M = -0.283$, $SE = 0.18$) which was significantly lower than the score of controls ($U = 2$, $p = .023$, Mann-Whitney *U*).

In contrast, in the ChrLSD group, the locomotor patterns of rats treated with LSD were indistinguishable from those of the controls. The absence of this acute LSD effect in the ChrLSD condition was confirmed by an increase in *CV* from the first to the last half of the session ($M = 0.116$, $SE = 0.07$) which was equivalent to that seen in the controls ($M = 0.120$, $SE = 0.12$; $U = 45$, $p = .837$). Consistent with the other behavioral measures, a single injection of LSD 24 hr prior to testing resulted in partial tolerance to LSD's disruption of locomotor patterns, as revealed by their intermediate *CV* difference score ($M = -0.112$, $SE = 0.07$), which was still significantly lower than that of controls ($M = 0.182$, $SE = 0.08$; $U = 4$, $p = .025$).

## Discussion

All of the behavioral effects of 30 μg/kg LSD exhibited complete tolerance following five daily injections, and partial tolerance 24 hr following a single injection. A

major concern in interpreting the results of chronic drug studies is whether the diminished debilitating effects of the drug reflect pharmacologic tolerance (i.e., reduced sensitivity to the drug at the neural level) or simply reflect behavioral adaptation (learning; cf. Freedman, Aghajanian, & Ornitz, 1958; Murray, Craig, & Fischer, 1977). Because the animals received chronic treatment in small individual home cages and were exposed to the novel chamber only on the test day, there was no opportunity to "learn" (adapt to) the environment; nor could the animals have adapted to the aversive aspects of handling because they were never handled sooner than 8 hr after chronic LSD injection. Thus, the failure of LSD to potentiate neophobia in rats previously exposed to LSD is likely to reflect pharmacological tolerance.

## General Discussion

### *Avoidance of Novel and Open Areas*

The present results demonstrate that the amount of exploratory activity seen in LSD-treated animals is profoundly influenced by the degree of threateningness (novelty, openness) of the environment. Specifically, when rats were tested by placing them directly in a novel chamber, LSD produced a dose-dependent reduction of exploratory activity (Experiment 2) which was not seen when animals were tested in a familiar environment (Experiment 3) and thus indicates that LSD potentiates the normal neophobia exhibited by rats confronted with a novel environment. In a free-exploration test, LSD reduced the time spent in the novel chamber without altering the rate of ambulation and hole poking within the chamber (Experiment 1). In both circumstances, LSD's suppression of exploration was maximal from 10 to 20 min after test start. A previous comparison of 10 and 30-min preinjection intervals (Adams & Geyer, 1982) also indicated that LSD's initial "inhibitory" effects were reflective of potentiated neophobia, because the temporal characteristics of the effect were found to be related to the duration of exposure to the novel chamber rather than the time course of drug action.

In both free- and forced-exploration tests, LSD's initial suppressant effects were best correlated with a reduction of entries into and time spent in the center of the novel chamber. However, as LSD still produced an initial reduction of time spent in the center of a familiar chamber (Experiment 3), LSD may also potentiate agoraphobia (fear of open spaces). The fact that neophobia and agoraphobia are distinguishable, yet are affected by LSD in the same direction, suggests that LSD produces a more general intensification of reactivity to threatening situations. Similar conclusions have been drawn by others (Bridger, Barr, Gibbons, & Gorelick, 1978; Freedman & Halaris, 1978).

In contrast to the higher doses, 10 μg/kg LSD appeared to reduce both neophobia and agoraphobia because, in a free-exploration test (Experiment 1), this dose actually increased the number of entries into and the time spent in the novel chamber in the first 10 min, and increased the time spent in the center region. The observation that low doses of LSD have effects opposite to those of high doses may be related to the fact that low doses of LSD preferentially activate presynaptic "autoreceptors" and cause auto-inhibition of serotonergic (Haigler & Aghajanian, 1973), dopaminergic (Walters, Baring, & Lakoski, 1979), and noradrenergic (Rogawski & Aghajanian, 1979) neurons whereas higher doses have direct postsynaptic actions at the same neurons (Aghajanian, 1981). Thus, reduction of neophobia by 10 μg/kg LSD could reflect reduction of monoaminergic neuronal firing, and potentiation of neophobia by higher doses could be due to a direct agonistic action postsynaptic to these same neurons.

There are innumerable reports of variations in the affective response to LSD in humans which appear to be primarily due to variations in the environmental setting. In novel and/or threatening situations, the primary affectual response induced by LSD consists of anxiety, paranoia, or even terror, whereas in benign situations, anxiety is minimal and euphoria predominates (Bercel, Travis, Olinger, & Dreikurs, 1956; Freedman, 1968; Meyers, Rose, & Smith, 1967). Thus, it appears that the dependency

of LSD's alteration of spontaneous activity of rats on environmental conditions can be most easily analogized to the observation that environmental setting influences the nature of LSD's mood-altering effects in humans.

*Dose dependency.* In humans, low doses of LSD (<1 μg/kg) have slight stimulant and euphorogenic effects (Hollister, 1968), and the anxiogenic effects emerge at moderate doses (1–2 μg/kg), at which minor perceptual distortions and "elementary hallucinations" (with eyes closed) are seen (Isbell et al., 1956). At higher doses (3 μg/kg or greater), paranoia, true hallucinations, and loss of insight occur. Thus, LSD's potentiation of neophobia in rats at doses of 30–160 μg/kg and reduction at 10 μg/kg roughly correspond to its anxiogenic potency in humans, if species differences in metabolic rate are considered (Freedman & Boggan, 1981).

*Time course and tolerance.* A similar parallel is seen for the time course of LSD's effects. In humans, peak hours for psychological effects correlate well with half-life of LSD in plasma, approximately 4 hr for a dose of 1 μg/kg (Aghajanian & Bing, 1964). As its plasma half-life in rats is 45 min (Freedman & Halaris, 1978), there should be approximately a fourfold difference in time course between the two species. LSD's anxiogenic effects in humans are maximal at 1 hr and still significant, but declining, in the second hour. This time course is consistent with our finding that LSD potentiates neophobia with injections being given from 10 to 30 min prior to testing (Adams & Geyer, 1982). In addition, the time course for tolerance to LSD's potentiation of neophobia in rats paralleled the conditions for tolerance to its psychological effects in humans (Isbell et al., 1956).

*Pharmacological specificity.* Another criterion for determining the relevance of behavioral effects in animals to mental effects seen in humans is that both show the same pharmacological specificity.

Several lines of evidence indicate that LSD's effects on neophobia generalize to other hallucinogens and are not mimicked by nonhallucinogenic congeners. First, as previously mentioned, LSD's suppression of initial hole-poke responding in a simple hole board was shared by both indoleamine (DMT, psilocin) and phenylethylamine (mescaline, 2,5-dimethoxy-4-methylamphetamine [DOM]) hallucinogens. The effect also reliably predicted the hallucinogenic potency of a homologous series of congeners of DOM, with the nonhallucinogenic congeners having no effect (Geyer et al., 1979). File (1977) also reported initial reductions in hole poking in a novel chamber produced by DMT. There are several other reports of DOM and/or mescaline reducing the locomotor activity of rodents in novel settings (Huang & Ho, 1973; Tilson, Baker, Chamberlain, Marquis, & Rech, 1975) but increasing or having no effect on activity in familiar settings (Buxton, 1972; Tilson et al, 1975; Yamamoto & Ueki, 1975). Recent work (Adams & Geyer, 1985), in which the behavioral pattern monitor described here was used, confirmed that both DOM and DMT produce the same initial suppression of exploratory activity and avoidance of central areas as seen with LSD. By contrast, the nonhallucinogenic congener lisuride (Herrmann, Horowski, Dannehl, Kramer, & Lurati, 1977) mimicked LSD's effect only on rearings (Adams & Geyer, in press). Similarly, Shephard, Buxton, and Broadhurst (1982) observed a potentiation of neophobia (inhibition of feeding in a novel setting) by 5-methoxy-N,N-dimethyltryptamine (5-MEODMT) whereas the nonhallucinogenic indoleamine methysergide produced the opposite effect.

### *Suppression of Rearing*

The most consistent and frequently reported effect of LSD on the locomotor activity of rats is suppression of rearing. Doses of 80–500 μg/kg LSD with preinjection intervals greater than 10 min have consistently been shown to suppress rearing (Cunha & Masur, 1978; Dandiya, Gupta, Gupta, & Patni, 1969; Hughes, 1973; Kabes, Fink, & Roth, 1972; Silva & Calil, 1975). The results of Experiments 1 and 3 indicate that LSD's reduction of rearing is unlikely to be due to enhanced responsiveness to threatening stimuli. Rather, the simultaneous use of automated and visual

measures revealed that the reduction of rearing by LSD was related in time course and dose dependency to the abnormal posture (crawling) induced by doses of 30 μg/kg or greater. Several other investigators have observed rats treated with doses of 80–500 μg/kg LSD "crawling around on the floor" (Kabes et al., 1972, p. 83; see also Hamilton, 1960; Winter & Flataker, 1956). Although the "motivation" for this behavior remains unclear, it does not appear to be due to paralysis or loss of muscle tonus (cf. Experiment 2; Winter & Flataker, 1956). As lisuride also suppresses rearing and causes rats to alternate between crawling and walking (Adams & Geyer, in press), LSD's effect on rearing is not a suitable model behavior because it fails to satisfy the criterion of pharmacological specificity.

*Disruption of Spatial Patterns of Locomotion*

The results of Experiment 1 replicated our previous findings of disrupted locomotor patterns in rats treated with 30 μg/kg LSD. In the forced-exploration test, both the 30 and the 160 μg/kg group exhibited randomized patterns (Experiment 2). In both test situations, LSD's disruption of locomotor routes was most obvious during the last half of the session. Evidence for a distinction between LSD's disruption of locomotor patterns and its potentiation of neophobia was revealed by the persistence of LSD's pattern-altering effect in a familiar environment (Experiment 3). Our previous time-course study (Adams & Geyer, 1982) also found that LSD's effect on locomotor patterns reflects a distinct behavioral effect with later onset than its effect on neophobia because rats treated with LSD 30 min prior to testing exhibited lower overall *CV*s (more random patterns) than those treated 10 min prior to exposure. In contrast, the dose-dependent increase in the duration of the initial period of rapid circling exhibited by rats treated with 80 or 160 μg/kg and tested in a novel environment (Experiment 2) is likely to reflect potentiation of neophobia and agoraphobia because it parallels the dose-dependent reduction of time spent in the hole board seen in free-exploration tests (Experiment 1).

The increase in randomness of locomotor patterns produced by LSD may be related to the alterations in sensory responsiveness (e.g., impairment of habituation: Geyer et al., 1978; Key & Bradley, 1960; heightened distractibility: Izquierdo, 1975; Key, 1964a, 1964b) reported by other investigators. These behavioral effects have been suggested as models of the disruption of selective attention produced by LSD in humans (Stoff et al., 1978). Because time-course studies in humans suggest that LSD's perceptual altering effects reflect a secondary phase phenomenon distinct from its anxiogenic effects (Abramson et al., 1955; Salvatore & Hyde, 1956), LSD's disruption of locomotor patterns shows promise as an analogue model. However, further tests of the extent to which this effect generalizes to other hallucinogens, and more extensive time-course studies, are needed to further evaluate this model.

In conclusion, the present results suggest that LSD's suppression of exploration of novel and open areas by rats is due to a potentiation of responsiveness to threatening stimuli. These results, together with our previous findings that a variety of indole- and phenylethylamine hallucinogens share these effects, suggest that enhanced avoidance of novel and central areas may be a useful animal model of hallucinogenic activity. In addition, the effects of LSD on the spontaneous unconditioned behavior of rats, noted here, may well be related to the characteristic effects of hallucinogens in a variety of conditioning paradigms (see Appel, Poling, & Kuhn, 1981; Stoff et al., 1978, for reviews). Although we cannot specify precisely which particular effects on unconditioned responding (e.g., postural changes, enhanced responsiveness to threatening stimuli, attentional alterations) may underlie effects of LSD in various conditioning paradigms, it is clear that such effects could contribute to and perhaps compete with conditioned responses, which would explain deficits such as increased latencies for rope climbing (Freedman et al., 1958; Winter & Flataker, 1956) or "hallucinogenic pauses" during fixed-ratio responding (Freedman, Appel, Hartman, & Molliver, 1964).

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