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Acute Effects of LSD on Rhesus Monkey Operant Test Battery Performance

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FREDERICK, D. L., M. P. GILLAM, S. LENSING AND M. G. PAULE. *Acute effects of LSD on rhesus monkey operant test battery performance.* PHARMACOL BIOCHEM BEHAV **57**(4) 633–641, 1997.—The acute effects of LSD were assessed in rhesus macaques using behavior in several complex tasks designed to model aspects of time estimation, short-term memory and attention, motivation, learning, and color and position discrimination. The end points monitored included percent task completed, response rate, and accuracy. LSD (0.0003–0.03 mg/kg intravenously) significantly decreased percent task completed and accuracy in the time estimation task at doses ≤0.003 mg/kg, but did not significantly affect response rate in this task at any dose tested. Accuracy in the short-term memory task was significantly decreased at the highest dose tested (0.03 mg/kg), but no other end points were affected in this task. Response rate was decreased in both the motivation and learning tasks at doses (0.01 and 0.003 mg/kg, respectively) lower than those affecting other end points. In the color and position discrimination task, only response rate was affected (0.01 and 0.03 mg/kg). These data demonstrate that in rhesus monkeys, performance of tasks believed to depend on aspects of time estimation and motivation are more sensitive to the acute disruptive effects of LSD than are tasks thought to model learning, short-term memory, and color and position discrimination. © 1997 Elsevier Science Inc.

Monkeys LSD Operant behavior Learning Incremental repeated acquisition Memory Delayed matching-to-sample Time estimation Temporal response differentiation Motivation Progressive ratio Color and position discrimination Conditioned position responding Food reinforcement

THE ERGOT alkaloid lysergic acid diethylamide (LSD) is an indolealkylamine hallucinogen that has been used experimentally in the treatment of mental illness and alcohol/opiate addiction (16) and has been proposed as an animal model for schizophrenia (4). The hallucinogenic actions of LSD are thought to be a result of its agonistic actions at serotonergic (5-HT) receptors, particularly the 5-HT_2 and 5-HT_1A subtypes (30,31,34,41). LSD is presently assigned under Schedule I of the Controlled Substance Act, which is reserved for those drugs believed to have a high potential for abuse and no accepted medical use, but it remains a popular recreational drug among young adults and college students (17).

LSD has been shown to induce stereotypic and abnormal behaviors in rats (6,8,42), cats (14,15), and monkeys (13,35) and to disrupt locomotor activity in several animal species (2,19,32). Although many studies have used operant procedures to elucidate the discriminative stimulus properties of LSD and other hallucinogens, comparatively few have examined the effects of LSD on animals responding under operant schedules to model complex brain functions (e.g., learning, memory, choice discriminations). LSD has been reported to produce prolonged cessation from responding (pausing) in rats responding under fixed-ratio schedules of reinforcement (5,22–24,33). LSD has also been shown to increase response latencies of pigeons in both a time discrimination task (1) and a visual discrimination task (44) at doses that did not affect the accuracy of either discrimination type.

The present experiment assessed the acute effects of LSD

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on rhesus monkey performance in an operant test battery (OTB) devised to permit the simultaneous assessment of several complex brain functions. The behaviors thought to be modeled in the OTB include time estimation, short-term memory and attention, motivation to work for food, learning, and color and position discrimination. The tasks contained in the OTB have been shown to be differentially sensitive to numerous prototypic psychotropic agents [see (26) for an overview], and OTB performance of children and well-trained rhesus monkeys has been shown to be generally indistinguishable (27).

LSD was chosen for this experiment because of its relatively well-characterized mechanism of action at 5-HT receptor sites and to complement the results of recent experiments from this laboratory with methylenedioxymethamphetamine (MDMA) (9,10), a phenalkylamine derivative with mixed stimulant/hallucinogenic properties. LSD doses (0.003–0.3 mg/kg) were chosen based on literature reports and the criteria that the lowest dose produced no observable effects and the highest dose grossly affected performance of most OTB tasks. It was hypothesized that one or more of the behaviors modeled in the OTB would be dependent, at least in part, on the 5-HT system and therefore would be sensitive to the disruptive effects of acute LSD exposure.

METHODS

Subjects

Six male rhesus monkeys (*Macaca mulatta*) between 5 and 12 years of age and weighing 7–10 kg served as subjects. All monkeys had previously been trained to perform the tasks in the OTB for several years and had been used as subjects in previous studies on the acute effects of several psychoactive compounds (7,12,36–39). Animal housing, feeding, and so on were as previously described (37). Briefly, each monkey was individually housed and fed its daily allotment of food immediately after each OTB test session. Water was available ad lib. Animal care and use procedures were in accordance with the American Association for Accreditation of Laboratory Animal Care (AAALAC) guidelines and were approved by the NCTR Institutional Animal Care and Use Committee.

Apparatus

The apparatus has been previously described in detail (37) and consisted of portable primate restraint chairs, sound-attenuated behavioral chambers, operant panels, and computer consoles. The operant or behavioral panels were equipped with three rear-projection press-plates, four retractable levers, six serial position indicator lights, and correct and incorrect response indicator lights. The press-plates, levers, and indicator lights were aligned horizontally, with the press-plates and serial position indicator lights located above the levers. Symbols and colors were projected onto the press-plates from the rear. When operated, both levers and press-plates effected a switch closure. Serial position and correct and incorrect indicator lights were illuminated from behind the panel with various colors. A trough for reinforcer (190-mg banana-flavored food pellet; Bioserv, Inc., Frenchtown, NJ, USA) delivery was centered below the levers.

Operant Schedules

A brief description of the operant tasks contained in the OTB follows. The use and a more detailed description of each task have been reported previously (37), and a diagram of the behavioral test panel was shown in Paule et al. (29).

Motivation task (progressive ratio). Only the far right lever was extended and active. Each monkey was required to increase the number of lever presses made for each subsequent reinforcer. Initially, one or two lever presses (depending on the individual monkey, but the same for each subject every test day) resulted in reinforcer delivery. The number of responses required for the next reinforcer was increased by the initial number of lever presses required for the first reinforcer. Thus, if two lever presses were required for the initial reinforcer, four lever presses were required for the next, then six, then eight, etc. The ratio increments were chosen so that marked periods of pausing or cessation of responding generally occurred during each baseline or vehicle progressive ratio session. This schedule was in effect for 10 min or until 120 reinforcers were earned (although, due to the increasing ratio requirements, no monkey ever earned this number of reinforcers).

Learning task (incremental repeated acquisition). All four levers were extended and active, and the serial position and correct and incorrect response indicator lights were used. Subjects were required to learn or acquire a new sequence of lever presses each test session. The learning task began with the presentation of a one-lever sequence (IRA1). Each response on the correct one of the four levers resulted in reinforcer delivery. After 20 correct, but not necessarily consecutive, response sequences (criterion performance), a 1-min time-out period was followed by the presentation of an "incremented" two-lever sequence (IRA2) in which a response on a different lever was required before a response on the original (IRA1) lever produced a reinforcer. After 20 errorless two-lever sequences (i.e., no errors were made between the first and last correct lever presses of the required sequence), the task was incremented to a three-lever sequence and so on, up to a six-lever sequence or until the allotted task time had elapsed. The serial position indicator lights signalled position in the response sequence, indicating the remaining number of correct responses necessary for reinforcer delivery. Incorrect responses were followed by a 2-s time-out (illumination of the incorrect response indicator light) but did not reset the response requirement; thus, error correction was permitted. Correct responses were followed by illumination of the appropriate serial position indicator light and a 1-s time-out with illumination of the correct response indicator light. This schedule was in effect for 35 min or until 120 reinforcers were earned, whichever occurred first.

Color and position discrimination task (conditioned position responding). Only the three press-plates were used (levers were retracted). At the start of each trial, the center plate was illuminated with either a solid red, yellow, blue, or green color (side press-plates were dark). Subjects continued the trial by making an observing response (a press) to the center plate, after which it was extinguished and the two side plates were immediately illuminated white. If the center plate color had been either blue or green, a response to the right press-plate (white) resulted in reinforcer delivery and initiation of a new trial. If the center press-plate had been either red or yellow, a response to the left press-plate (white) resulted in reinforcer delivery and initiation of a new trial. Responding to the incorrect position initiated a 10-s time-out period followed by the initiation of a new trial. The sequence of color presentation was random. This schedule was in effect for 5 min or until 60 reinforcers were earned, whichever occurred first.

Time estimation task (temporal response differentiation). Only the left lever was extended and active. Subjects were required to hold the lever in the depressed position for a mini-

mum of 10 s but not longer than 14 s. Releasing the lever within the 4-s window resulted in reinforcer delivery. Releasing the lever too early or too late ended the current trial, after which the subject could immediately start another trial. This schedule was in effect for 20 min or until 120 reinforcers were earned, whichever occurred first.

Short-term memory and attention task (delayed matching-to-sample). Only the three press-plates were used (levers were retracted). At the start of each trial, one of seven geometric symbols (the "sample") was projected onto the center plate in a random fashion (side press-plates were dark). To continue the trial, each monkey was required to make an observing response (a press) to the center plate. After the observing response was made, the center plate was extinguished for one of six possible time delays, presented pseudorandomly (2, 8, 16, 32, 48, and 64 s). After each time delay, all three plates were illuminated, each with a different geometric symbol, only one of which matched the sample. A response to the matching symbol resulted in reinforcer delivery and initiation of a new trial with another sample stimulus (presented randomly). A nonmatching response was followed by a 10-s time-out period (all plates darkened) and then initiation of a new trial. This schedule was in effect for 30 min or until 120 reinforcers were earned, whichever occurred first.

Behavioral Testing Procedure

Behavioral sessions lasted approximately 50 min and were conducted daily (Monday–Friday). Monkeys were rotated through nine identical test chambers so that, in general, no monkey was placed in the same chamber on two consecutive test days. OTB schedules alternated daily. For example, if the motivation task (10 min), learning task (35 min), and color and position discrimination task (5 min) were presented on one test day, the time estimation (20 min) and short-term memory and attention task (30 min) were presented the next test day.

Drugs and Dosing Procedure

d-Lysergic acid diethylamide (NIDA, Rockville, MD, USA), was dissolved in bacteriostatic (0.9% benzyl alcohol) saline for a final injection volume of 0.1 ml/kg. The purity of the LSD was determined to be 99.5% by an in-house high-performance liquid chromatographic analysis. Doses of LSD (0.0, 0.0003, 0.001, 0.003, 0.01, and 0.03 mg/kg intravenously) were administered in a randomized order. LSD injections were given on Tuesdays and/or Fridays, and vehicle (saline) injections were given on Tuesdays, Thursdays, and/or Fridays. Testing without prior injection was conducted on Mondays and Wednesdays. Due to the daily alternation of behavioral tasks, all LSD doses were given twice to provide dose–response data for each operant task. Approximately 15 min after injection, each monkey was placed into an operant chamber and the behavioral session began 1 min later.

Behavioral End Points

The end points measured in each task have been described in detail elsewhere (37). Three fundamental measures common to most tasks were monitored: percent task completed (PTC), response rate or latency, and response accuracy.

PTC. The PTC data are measures of a predetermined performance criterion and are functions of both response rate and accuracy. The PTC measure is calculated by dividing the total number of reinforcers earned in a given session by the total number of reinforcers possible and multiplying this quotient by 100. The total number of reinforcers possible for a given task was chosen arbitrarily based on the length and difficulty of the task. The PTC end point is a convenient and comprehensive measure showing intra-animal stability, and it has proven useful for comparing drug effects on performance across tasks.

Response rate and response latency. Response rate for the time estimation and motivation tasks was calculated by dividing the total number of lever presses by the total session time (in seconds). Response rate for the short-term memory, learning, and color and position discrimination tasks was calculated by dividing the total number of responses by the total session time minus time-out and delay periods (in seconds). For the short-term memory and color and position discrimination tasks, mean response latencies were also calculated for both observing and choice responses. If a monkey did not make an observing and/or choice response, a maximum response latency of 300 s was used in the analyses. In addition to overall response rate (collapsed across components) for the learning task, response rates were measured for individual components or levels within the learning task.

Response accuracy. Response accuracy for the color and position discrimination and short-term memory tasks was calculated by dividing the number of correct choices by the total number of trials in a given session and multiplying this quotient by 100. For the time estimation and learning tasks, response accuracy was calculated by dividing the total number of correct lever presses by the total number of lever presses in a given session and then multiplying this quotient by 100. Response accuracy is not applicable for the motivation task.

Other measures. Additional end points that were generally applicable to only one task were also monitored. For the time estimation task, mean duration of lever hold and, for the motivation task, the break point (the magnitude of the last ratio completed for which the monkey earned a reinforcer) were also calculated. Interresponse times (IRTs; from press to press) were recorded for the motivation and color and position discrimination tasks. For the learning task, within-sequence (retention) errors and between-sequence (acquisition) errors were also recorded. Within-sequence errors occur after the subject has entered into a response sequence (made the first correct lever press for that sequence) but before the last correct lever press for that sequence (an exit from that sequence). For example, once the first correct lever of a three-response chain sequence is pressed, a within-sequence error occurs every time an incorrect lever is pressed prior to reinforcer delivery (i.e., completion of the chain). A within-sequence error cannot occur during one-lever sequences. Between-sequence errors occur prior to the first correct lever press (entry) of a particular response sequence.

Statistical Analysis

Only data for those monkeys exhibiting stable performance for the measure of percent task completed after saline (vehicle) injections were included in the statistical analysis. Stable performance was defined as that having a standard error of less than 15% of the mean for the vehicle sessions. During this experiment, all six monkeys exhibited stable baselines for the color and position discrimination, learning, short-term memory and attention, and motivation tasks, and five monkeys had stable baselines for the time estimation task. For a subject's data to be included in the time estimation and color and position discrimination accuracy analyses and the time es-

timation task mean duration of lever hold analysis, a minimum of three trials must have been completed. For inclusion in the short-term memory and learning task accuracy analyses, a monkey must have completed a minimum of 10 trials. For group accuracy in the short-term memory task at specific time delays, significance was assigned to those group means falling outside the 95% confidence intervals constructed from vehicle control observations at each time delay. The overall effect of drug treatments on performance in the various tasks was determined using a one-way repeated-measures analysis of variance. If overall significance was evident ($p < 0.05$), then performance at each dose was compared with vehicle control performance by Bonferroni's (BON) multiple *t*-tests (21).

RESULTS

Results from the five OTB tasks are summarized in Table 1. Baseline (noninjection) data were not significantly different from those for vehicle injections for any of the behavioral end points monitored (not shown). In Table 1 and all subsequent references, "overall" refers to data collapsed across all time delays in the short-term memory task and across all lever sequence lengths in the learning task. In the time estimation task, mean duration of lever hold includes both lever presses $\geq$2 s in duration and response bursts (<2 s in duration), which are common to this task.

Motivation

In the motivation task, response rates were significantly decreased at $\geq$0.003 mg/kg LSD, whereas break point and PTC were significantly decreased at doses $\geq$0.01 mg/kg. Figure 1 shows the effects of LSD on IRT distributions in the motivation task. The frequency of short IRTs at all LSD doses was considerably lower than the frequency of short IRTs during saline sessions, although this effect was not entirely dose-dependent.

Learning

Overall response rate in the learning task was significantly decreased at $\geq$0.01 mg/kg LSD, whereas overall accuracy and PTC were affected only at the highest dose of LSD tested (0.03 mg/kg). The frequency of retention (within-sequence) and acquisition (between-sequence) errors at the three-lever (IRA3) sequence, which are qualitatively similar to those for other IRA sequences (not shown), are presented in Figs. 2 and 3, respectively. The number and pattern of errors falling outside the 95% confidence intervals constructed from vehicle session data were nearly equal for both within- (retention) and between- (acquisition) sequence error types. Although the overall frequencies of both error types were similar, a higher number of within-sequence errors was noted at the 0.001 dose compared with between-sequence errors at this dose.

Color and Position Discrimination

In the color and position discrimination task, response rate was significantly decreased by LSD at the two highest doses tested (0.01 and 0.03 mg/kg). Although no other end point for this task was significantly affected at any LSD dose tested (see, e.g., IRT distributions shown in Fig. 4), it is clear that ob-

TABLE 1

PERFORMANCE OF RHESUS MONKEYS IN THE OPERANT TEST BATTERY

			Dose of LSD (mg/kg)				
Task	End Point	Saline	0.0003	0.001	0.003	0.01	0.03
Motivation (PR; $n = 6$)	PTC	14.5 ± 1.1	14 ± 5.1	8.5 ± 1.7	9.2 ± 1.6	*3.9 ± 1.6	*4.6 ± 2.7
	PR	2.06 ± 0.29	1.3 ± 0.38	1.02 ± 0.33	*0.97 ± 0.27	*0.034 ± 0.21	*0.37 ± 0.24
	BP	110.2 ± 11.7	79.4 ± 16.2	67.9 ± 16.7	71.6 ± 14.6	*31.5 ± 14.8	*32.1 ± 15.7
Learning (IRA; $n = 6$)	PTC	78.7 ± 4.8	67 ± 12.1	62.1 ± 8.3	64.8 ± 14.4	57.4 ± 12	*34.7 ± 7.6
	Overall RR	1.36 ± 0.22	0.98 ± 0.32	0.94 ± 0.25	1.01 ± 0.23	*0.65 ± 0.16	*0.47 ± 0.22
	Overall ACC	73.4 ± 3.3	68.8 ± 7.2	68.5 ± 3.8	68.7 ± 5.5 (5)	67.1 ± 3.8 (5)	*44.5 ± 5.5 (4)
Color and position discrimination (CPR; $n = 6$)	PTC	97.6 ± 1.1	78.8 ± 9.8	64.2 ± 14.5	70 ± 14.5	68.5 ± 16.2	75.4 ± 13.3
	RR	1.04 ± 0.14	0.85 ± 0.17	0.64 ± 0.18	0.69 ± 0.18	*0.63 ± 0.15	*0.64 ± 0.14
	Observing RL	2.0 ± 0.38	28.3 ± 24.6	15.7 ± 2.2	25.9 ± 19.2	36.5 ± 30.1	41 ± 36.8
	Choice RL	0.40 ± 0.05	0.43 ± 0.06	0.62 ± 0.11	0.51 ± 0.06	0.65 ± 0.17	0.59 ± 0.2
	ACC	97.9 ± 0.44	96.7 ± 1.5	86.4 ± 3.7	84 ± 7.7	84.5 ± 5.8	91.3 ± 5.1 (4)
Time estimation	PTC	39 ± 2.6	26.4 ± 8.8	35.6 ± 6.7	*9.8 ± 6.4	*5.2 ± 4	*0.56 ± 0.5
	RR	0.09 ± 0.009	0.08 ± 0.02	0.09 ± 0.018	0.09 ± 0.041	0.08 ± 0.038	0.04 ± 0.016
	Average hold	9.3 ± 0.83	8.2 ± 0.22	8.7 ± 1	6.9 ± 3.1	4.7 ± 2.3	13.1 ± 11.7 (3)
	ACC	51 ± 6.1	35.6 ± 5.6	42.8 ± 8.2	*18.3 ± 11.5	*11.4 ± 7.2	*2.5 ± 2.4 (3)
Short-term memory and attention ($n = 6$)	PTC	32.5 ± 2.8	23 ± 3.1	26.8 ± 5.1	21 ± 5.2	19.8 ± 5.5	22.9 ± 5.4
	Overall RR	0.26 ± 0.03	0.17 ± 0.04	0.21 ± 0.04	0.10 ± 0.02	0.14 ± 0.04	0.24 ± 0.07
	Observing RL	4.5 ± 0.94	9.4 ± 3	3.4 ± 0.93	10.5 ± 2.6	7.6 ± 4.6	5.2 ± 2.9
	Choice RL	1.6 ± 0.18	3.3 ± 0.82	1.6 ± 0.19	1.8 ± 0.16	6.9 ± 5.5	1.2 ± 0.16
	Overall ACC	79 ± 6.1	69.2 ± 7.2	75.7 ± 6.3	78.8 ± 7 (5)	71.1 ± 6.2 (5)	*57.6 ± 9.6 (4)

Values reported are means ± SEM. All sample sizes (n) are as indicated except as noted in parentheses. *$P < 0.05$, significant difference from vehicle injection performance. PR, progressive ratio; IRA, incremental repeated acquisition; CPR, conditioned position responding; TRD, temporal response differentiation; PTC, percent task completed; RR, response rate (responses/s); BP, break point; ACC, accuracy; RL, response latency (s).

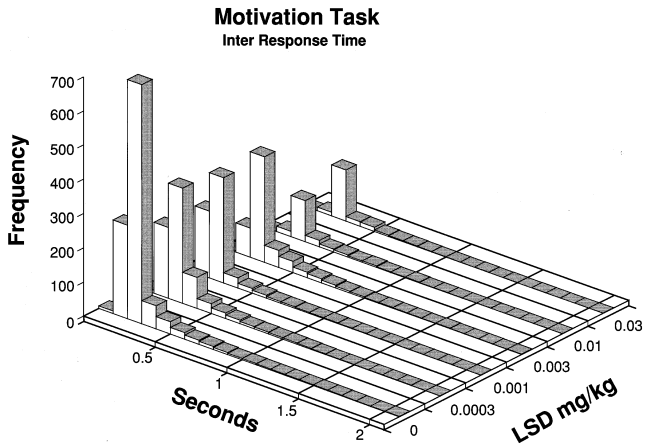

FIG. 1. Interresponse time distributions for the motivation task. Data are means for all six subjects.

serving response latencies (see Table 1) were increased in some subjects at all doses given. However, the large variability in this measure precluded demonstration of statistical significance. Choice response latencies were not similarly affected.

Time Estimation

In the time estimation task, PTC and accuracy were significantly decreased by LSD at doses ≥0.003 mg/kg. Response rate was not significantly affected at any dose tested. There was a trend toward a decrease in the mean duration of lever holds as the doses increased, but the inclusion of response bursts in the calculation of this end point likely masked any affect of the responses of longer duration. Figure 5 presents the effects of LSD on lever hold durations of 2 s or less; lever holds 2–18 s in duration are shown in Fig. 6. Note that the frequency of lever holds in the 10–14-s range was greatly reduced at LSD doses ≥0.003 mg/kg, whereas the frequency of lever holds <2 s in duration increased at the 0.003- and 0.01-mg/kg doses of LSD and remained nearly as high as vehicle levels at the highest dose tested (0.03 mg/kg).

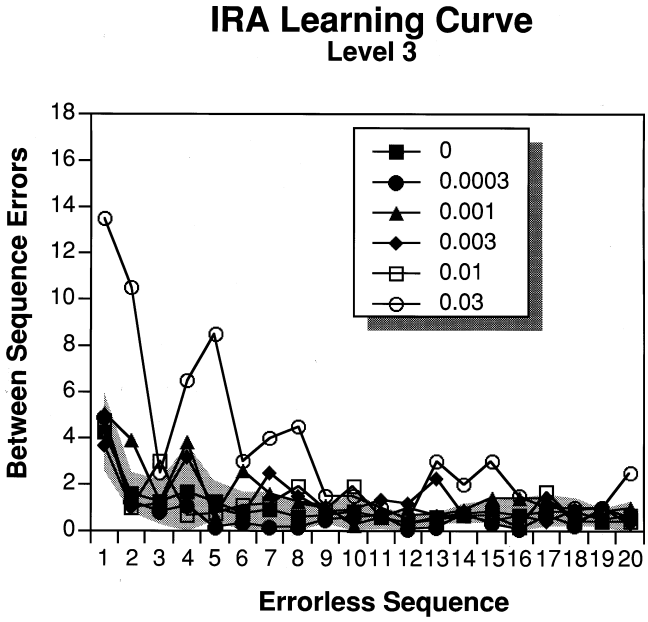

FIG. 2. Effect of LSD on retention (within-sequence) errors in the learning task for three-lever sequences. The shaded area represents the 95% confidence interval constructed from vehicle control sessions.

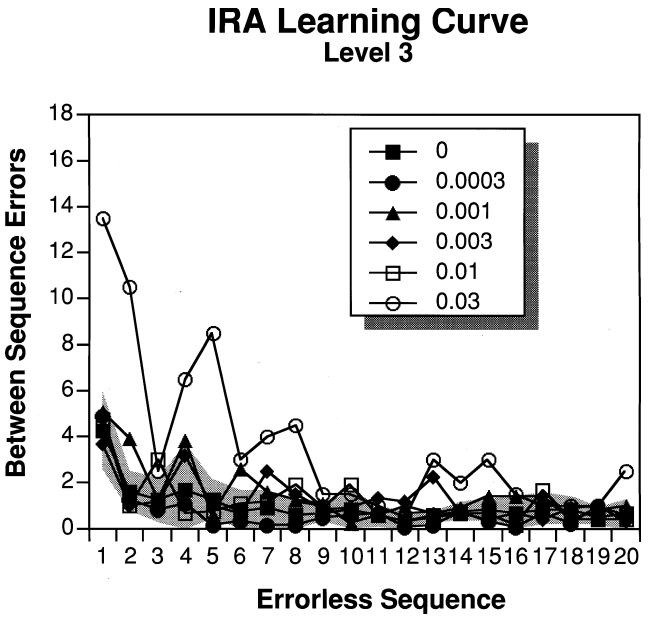

FIG. 3. Effect of LSD on acquisition (between-sequence) errors in the learning task for three-lever sequences. Data are as presented in Fig. 2.

Short-term Memory and Attention

Overall accuracy in the short-term memory and attention task was decreased only at the highest dose tested (0.03 mg/kg

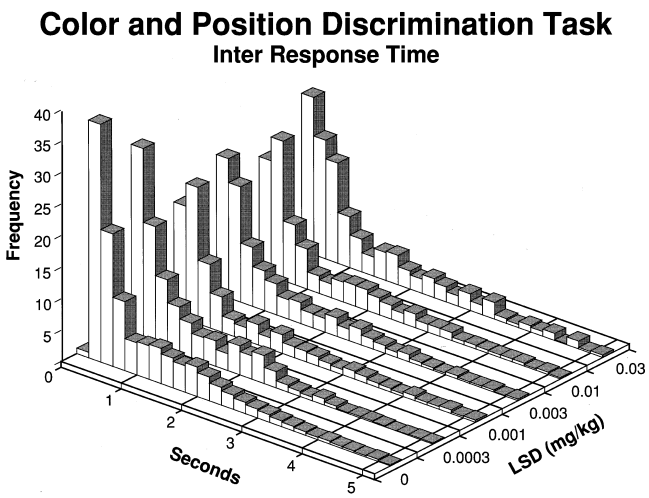

FIG. 4. Interresponse time distributions for the color and position discrimination task. Data are means for all six subjects.

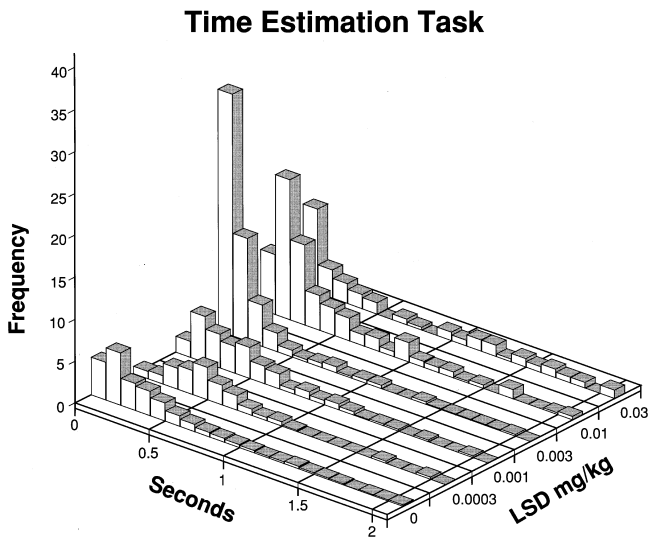

FIG. 5. Effect of LSD on lever holds less than 2 s in duration (response bursts) in the time estimation task. Data are means for five subjects.

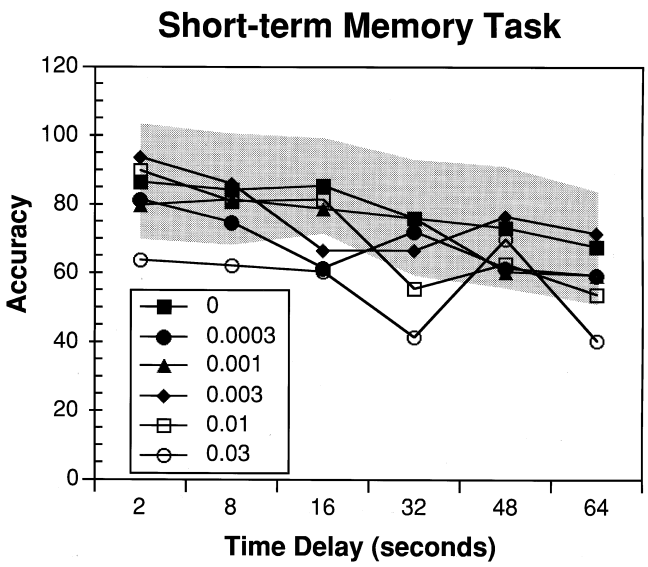

FIG. 7. Effect of LSD on response accuracy (% correct responses) vs. recall delay in the short-term memory task. The shaded area represents the 95% confidence interval constructed from data for vehicle control sessions.

LSD). Choice and observing response latencies, response rates, and PTC were not significantly affected at any LSD dose tested. Figure 7 presents the effects of LSD on accuracy in the short-term memory and attention task at each time delay. An overall (all delays included) systematic decrease in choice accuracy was observed only at the highest dose (0.03 mg/kg). The decrease in accuracy at the 2-s delay at the highest dose suggests that attentional processes may have been affected, although observing and choice response latencies were not significantly affected.

DISCUSSION

Using the occurrence of a significant disruption in task performance at a dose or doses that did not affect performance of other tasks, the order of OTB task sensitivity (neurobehavioral profile) to the acute disruptive effects of LSD was motivation = time estimation > learning = color and position discrimination > short-term memory. This neurobehavioral profile obtained for LSD is distinguishable from the profiles generated for all other drugs tested in the OTB (amphetamine, atropine, caffeine, chlorpromazine, cocaine, diazepam, marijuana smoke, morphine, MK-801, naloxone, nicotine, pentobarbital, phencyclidine, and Δ-9-tetrahydrocannabinol), including the substituted amphetamine MDMA. The acute disruptive effects of LSD on performance of the OTB time estimation task were highly similar to those effects noted previously for MDMA, whereas the effects of LSD on performance of the other OTB tasks were generally dissimilar to those noted for MDMA (10). In tasks other than the time estimation task, LSD produced a dose-dependent cessation from responding (pausing) but did not affect the correctness of responses that did occur. These data suggest that the expression of behaviors such as time estimation and motivation to work for food may be more sensitive to pharmacological manipulation of 5-HT systems than those behaviors that involve learning, color and position discrimination, and short-term memory and attention.

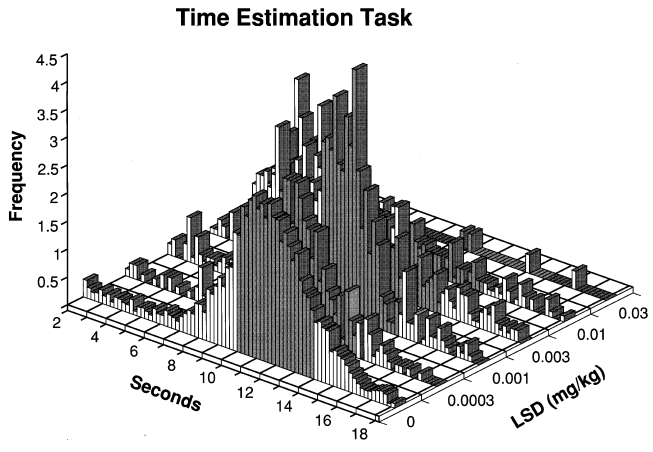

FIG. 6. Effect of LSD on lever holds greater than 2 s in duration in the time estimation task. The more lightly shaded area represents reinforced lever holds.

As mentioned previously, a frequently reported effect of LSD on animals performing fixed-ratio schedules is the occurrence of pausing, i.e., cessation from responding, during portions of the test session. In the OTB motivation task (a progressive ratio schedule of reinforcement), periods of pausing are common during baseline and vehicle test sessions as the ratio size increases for each subsequent reinforcer. Response rate was significantly decreased in this task at 0.003 mg/kg LSD, although break point and percent task completed were not significantly affected at this dose. These results suggest that at this low dose, pausing was not a prominent effect because significant decreases in break point and percent task completed would also have been noted if the decrease in response rate was indicative of an increase in pauses. However, at higher doses, pausing did appear to be evident, as all end

points were significantly decreased. Such LSD-induced pausing likely reflects a decrease in the monkey's motivation to work for food, as LSD and other hallucinogens have been reported to have anorectic effects (43). Additionally, other drugs that facilitate 5-HT neurotransmission (e.g., fenfluramine and dexfenfluramine) are known to possess profound anorectic properties, and it has been reported that the rate-attenuating effects of LSD on FR performance of rats are diminished when the level of food deprivation is increased (18).

In the OTB time estimation task, significant decreases in correct lever holds (i.e., those of 10–14 s) were noted at doses of LSD that increased the frequency of response bursts (<2 s) and lever holds of short to intermediate duration (2–6 s). The acute disruptive effects of LSD on monkey performance in this task are similar to those previously observed in this laboratory for MDMA (10), whose acute behavioral effects appear to be similar to both hallucinogens (i.e., 5-HT mediated) and stimulants (i.e., dopamine mediated) (20,40). A decrease in long-duration lever holds, concomitant with an increase in response bursts, was also noted after MDMA administration. Unlike LSD, however, lever holds of intermediate duration were generally not evident after MDMA exposure. Using a different timing procedure, Altman et al. (1) reported no significant effects of LSD on the ability of pigeons to discriminate "long" (5.5-s) vs. "short" (4.5-s) visual stimuli. The temporal discrimination task used by Altman et al. can be thought of as a *time perception* task, in which discrimination of a stimulus duration must be made; the OTB time estimation task can be viewed as a *time production* task, where a response must be emitted for, or at, a relatively fixed time (3). While the dissimilar effects of LSD on the performance of these different types of timing tasks may have been due to species differences, differences in response topography, or other methodological factors, the possibility exists that aspects of time perception and time production are dependent on different CNS domains, perhaps even different 5-HT systems.

Disruption of performance in the OTB learning task occurred only at the higher LSD doses tested and only in the presence of decreases in response rates. Response perseveration did not appear to be a prominent LSD effect, because the frequency of acquisition (between-sequence) errors was no greater than that of retention (within-sequence) errors. Response perseveration, such as that noted after amphetamine administration (28), is characterized by a large increase in between-sequence (acquisition) errors in the absence of similar increases in within-sequence (retention) errors. In the present experiment, LSD caused an approximately equal increase in the number of retention and acquisition errors. Response rate in the learning task was also decreased at a dose that did not significantly decrease overall accuracy in this task. These data indicate that the ability of rhesus monkeys to acquire and retain information is relatively insensitive (and not differentially sensitive) to the acute disruptive effects of LSD. These effects of LSD on learning task performance are generally different from those noted previously for MDMA (10). Although both MDMA and LSD are known to interact with 5-HT systems (21,31,41,43), MDMA has been shown to produce stimulant-like effects on performance of operant procedures [see (11) for review]. In rhesus monkeys, MDMA caused marked increases in acquisition errors relative to retention errors (10), suggesting it had a perseverative effect much like amphetamine.

Response rate in the OTB color and position discrimination task was also significantly decreased by LSD at higher doses, but accuracy (correct discriminations) was not affected. LSD produced large but not statistically significant increases in observing response latencies, whereas choice response latencies were essentially unaffected (see Table 1 for values). Thus, it appeared that in this task, the monkeys would cease responding (pause) for extended periods, but when they did respond they did so rapidly and accurately. These results are consistent with those of Nielsen and Appel (25), who reported that, although LSD significantly decreased responding in pigeons performing a delayed color discrimination task, discrimination accuracy was not affected. West et al. (44) have also reported that LSD decreased response speed in pigeons trained to discriminate white lights of different intensities at doses that did not affect discrimination accuracies.

In the OTB short-term memory and attention task, overall accuracy (percent correct delayed matches) was significantly decreased only at the highest dose tested. Compared with the color and position discrimination and learning tasks, this disruption in accuracy was not associated with decreased response rate. Of particular interest is that, unlike the color and position discrimination task, observing response latencies were not affected by LSD (see Table 1). This is somewhat paradoxical, because the response dynamics of these tasks are very similar. On each trial, a visual stimulus is presented on one of the three press-plate manipulanda and the monkey must acknowledge that the stimulus was observed by making a press to it (the observing response). Thus, a measure of task initiation time is generated for both tasks. The latency to make the observing response was greatly increased by LSD in the color and position discrimination task, but not in the short-term memory task. These paradoxical effects of LSD on observing response latencies in the OTB short-term memory and attention and color and position discrimination tasks may be indicative of selective impairments of specific visual modalities (i.e., color vs. black-and-white or symbol recognition), but such possibilities need further study.

In summary, operant behaviors designed to model aspects of time estimation and motivation were more sensitive to the acute disruptive effects of LSD than were those tasks believed to model learning, short-term memory and attention, and color and position discrimination. The effects of LSD on the OTB time estimation task were qualitatively similar to those noted previously for the hallucinogenic amphetamine derivative MDMA (10), whereas the effects of LSD and MDMA on performance of other OTB tasks were generally dissimilar. These data, along with those previously obtained for MDMA, suggest that time estimation ability is sensitive to pharmacological manipulations of 5-HT systems. The occurrence of pauses during performance of most OTB tasks after LSD administration, in particular the motivation task, suggests that LSD significantly decreased the monkey's motivation to work for food. Although this apparent anorectic effect of LSD resulted in a decrease in the number of reinforcers earned in all OTB tasks, it did not completely abolish responding in any task, and the monkeys were able to correctly perform two of the OTB tasks (learning and color and position discrimination) at doses that significantly decreased response rate. That the monkeys continued to perform the OTB tasks concomitant with a decreased motivation to work for food suggests that monkey OTB performance is not motivated exclusively by food reinforcement.

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